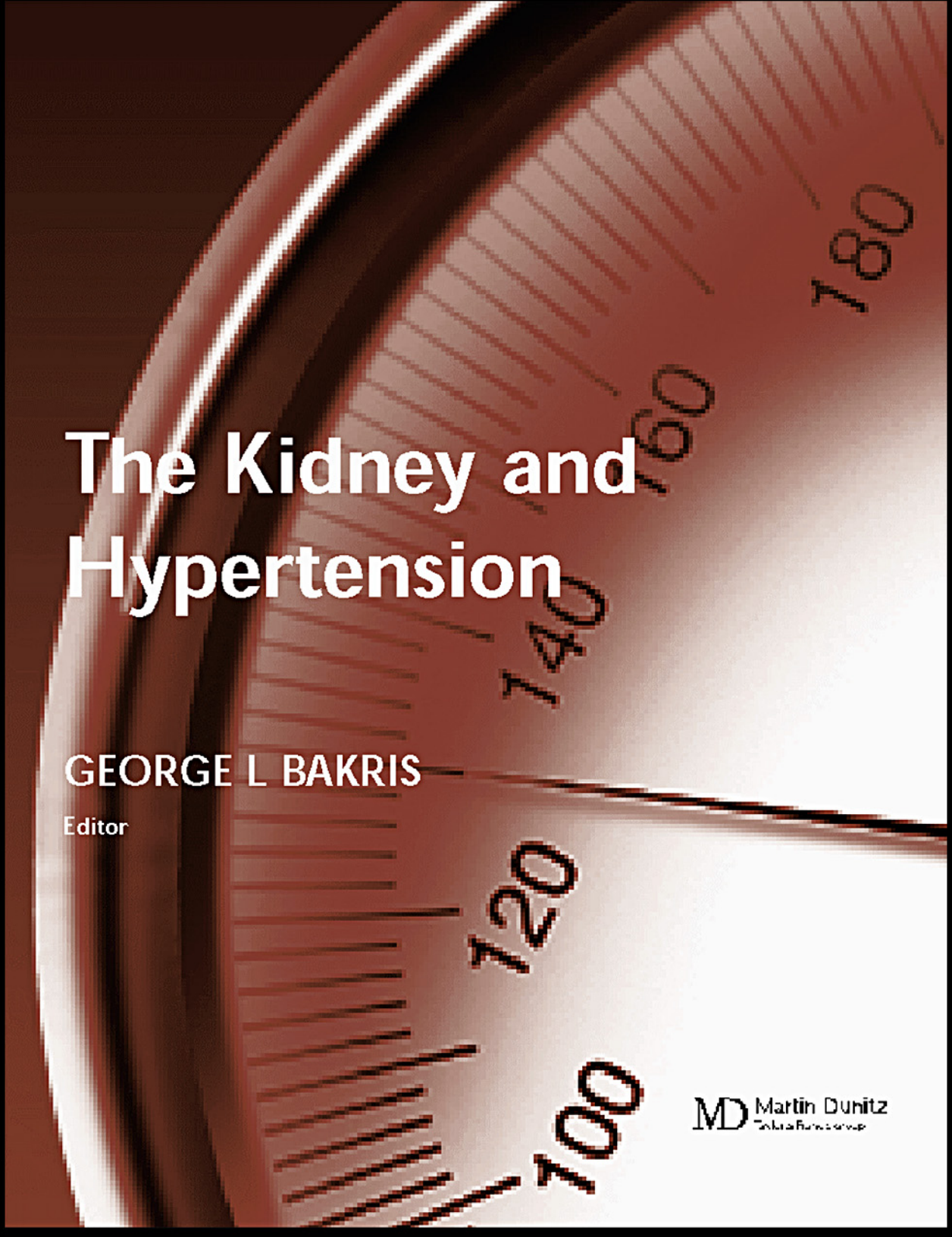

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The Kidney and Hypertension

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Contents

Contributors vii

Preface xi

Assessment and Epidemiology

1 Blood pressure measurement *Clarence E Grim and Carlene M Grim* 3

2 Microalbuminuria/proteinuria: What does it mean? How do you measure it? *George L Bakris* 25

3 Systolic blood pressure in the older patient with kidney disease *Shakaib U Rehman and Jan N Basile* 39

4 When to evaluate for secondary hypertension? *Sandra J Taler and Stephen C Textor* 55

Treatment – General

5 Approaches to maximize cardiovascular risk reduction in people with kidney disease *Sheldon Tobe* 71

6 Approaches to achieve blood pressure goals *Daniel E Hilleman and George L Bakris* 91

7 ACE inhibitors and angiotensin receptor blockers in kidney disease: are we denying protection to patients? *Matthew R Weir* 105

8 Lipid lowering and progression of kidney disease *Robert D Toto* 117

9 Dose adjustment of drugs in kidney disease *Domenic A Sica* 127

10 Hypertensive urgencies *William J Elliott* 139

Treatment – High Risk Groups

11 Diabetes with and without proteinuria *Samy I Mcfarlane, John Shin, Reba Williams and James Sowers* 155

12 Treatment of hypertension in African Americans *Tariq Shafi, Bede Nnolim and John M Flack* 165

13 The kidney and hypertension in South and East Asians *Sunil Nadar and Gregory YH Lip* 175

14 Evaluation and management of hypertensive disorders in pregnancy *Jason G Umans and Lillian J Borrego-Conde* 183

15 Evaluation and management of hypertension in children *Susan R Mendley* 197

16 Blood pressure control in dialysis patients *Aldo J Peixoto* 213

Index 225

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Preface

This book is directed toward expanding the knowledge base of physicians in training, including those in residency and fellowship programs, as well as junior faculty. It was specifically written as a reference book to cover specific and common topics around the area of kidney disease and hypertension seen by the general physician and specialist. All aspects of hypertension are discussed in the context of its contribution to and the genesis of kidney disease.

The book's 16 chapters are written by top authorities in their respective areas. Topics include everything from how to properly measure blood pressure and microalbuminuria to the assessment and treatment of elevated blood pressure in dialysis patients and pregnancy. Half the chapters in this book are dedicated to the reduction of cardiovascular risk in people with kidney disease, since it is the most common cause of death in this cohort. Additionally, since diabetes is the most common cause of kidney failure worldwide, one entire chapter is dedicated to this problem and it is also touched upon in five other chapters with regard to therapeutic interventions.

I trust that you will find this book helpful in understanding basic concepts about hypertension and that it will aid in the management of this disease, so as to maximally reduce both the risk of kidney disease progression and death from cardiovascular disease.

George Bakris
Chicago, June 2003

Section I

Assessment and epidemiology

1

Blood pressure measurement

Clarence E Grim and Carlene M Grim

Introduction • A brief review of your current-blood pressure measurement training and practice • Blood pressure training improves accuracy between observers • A brief history of blood pressure measurement and health risks of high BP Technique and equipment • Testing • Equipment inspection • Blood pressure measurement in the young

The sphygmomanometer is the most important medical instrument you will learn to use in your medical career. UCLA Preventive Cardiology Curriculum: CE Grim, 1991

1. INTRODUCTION

This is perhaps the first time that we are aware of that a text on the diagnosis and treatment of high blood pressure has started off with a chapter on blood pressure measurement. Indeed, many do not discuss clinical blood pressure measurement at all. It is generally assumed that this critical life-saving skill was mastered during basic health care education and is practiced correctly for the rest of a lifetime. However, research has shown that blood pressure measurement is almost never performed according to the guidelines published by the American Heart Association since 1938.[1] We and others believe that a major cause of poor blood pressure control around the world is due to a failure to use accurate blood pressure manometers and to follow established measurement guidelines.

Accurate measurement is important because elevated blood pressure almost never causes symptoms. Therefore, essential hypertension, the most common chronic disease world-wide, can only be diagnosed by accurate measurement. In a book about hypertension and the kidney, accurate measurement is even more important as high blood pressure is often the first sign of kidney disease. Even more important, uncontrolled high blood pressure is the leading cause of progression to renal failure, especially in diabetes. Only careful blood pressure control has been shown to slow the progression to renal failure. Therefore, the key to preventing kidney disease is accurate and reliable blood pressure measurement and management.

Accurate blood pressure measurement is needed to guide therapy for the lifetime of the patient. Lowering unhealthy high blood pressure is one of the most beneficial and cost effective health interventions we have today. Only with accurate blood pressure measurement can the proven benefits of high BP treatment be transmitted to the population. Differences in treated blood pressure as small as 5 mmHg diastolic has been shown to result in 20% fewer deaths, 35% fewer strokes, 20% fewer heart attacks, and 30% less progression to renal failure. In blood pressure measurement, small differences mean a lot.

This chapter first reviews the reader's own training knowledge and practice of blood

pressure measurement and then demonstrates the steps and rational for accurate blood pressure measurement. We also add additional information on the problems of accurate blood pressure measurement in the young and the elderly, a subject that is not commonly covered in standard blood pressure training.

> Health education programs almost never teach blood pressure measurement, according to the American Heart Association guidelines[2]

Although blood pressure measurement is 'taught' in all health schools from medical assistant to medical school, current evidence is that correct measurement techniques, according to the American Heart Association (AHA) guidelines, are almost never practiced.[2] Research suggests this is related to a failure to teach to mastery the knowledge, skills, and techniques needed to obtain a standardized, accurate, and reliable BP reading.[3] We have developed and tested a video-tutored program that teaches the AHA guidelines and tests, to master the knowledge, skills, and techniques required to get an accurate and reliable BP.[4] The program also teaches equipment maintenance and observer quality assurance programs.

At the Medical College of Wisconsin we teach BP measurement the first semester in medical school as our students are quickly moving into clinical experience with preceptors, and once certified they have a skill they can use in this environment. About 30% of entering medical students have previously 'been taught and have taken BPs'. However, in testing over 500 such students we only found that 5% would pass a criterion-based knowledge test of correct BP measurement procedure and practice. A recent report in nurses in practice in Australia show the same problem. None of the 83 volunteers passed a criterion-based test of competency.[5] Thus, in all likelihood your own training has not been up to AHA standards, and the first part of this chapter allows you to first review your current knowledge and practice and then gives details on the proper technique.

One of the aims of this chapter is to first let you quickly review your knowledge base about correct BP measurement and then to update all areas of proper measurement so that the proven benefits of detection and treatment of high BP can be translated to all populations you serve – from the young to the elderly. Failure to follow guidelines can result in errors of up to 100 mmHg in your patient. Understanding the reasons for and following the steps in accurate measurement will, if followed *every time* you measure BP, ensure that your patients and their families are not harmed by poor blood pressure measurement.

The consequences of good blood pressure measurement. Accurate BP measurement is the single most reliable way you have to assess how long your patient will live and what they will likely die from – especially if you or they fail to bring the blood pressure to healthy levels.[13] You and your health care team are in a position to pick up the most common chronic disease killer of adults around the world – an unhealthy high blood pressure. Even an error that results in only a 5 mm too low BP will miss nearly 40% of all hypertensives who will come through your office door. Additionally, nearly all patients with kidney disease have or develop an increase in BP that is unhealthy.

What is high blood pressure? High BP is that level of blood pressure above which 'treatment' makes people live longer and healthier lives by decreasing death and morbidity, having fewer brain/heart adverse events, and less progression to heart/kidney failure. This can only be determined by controlled clinical trails. As discussed in other chapters in this book, the healthy BP in patients with kidney disease is lower than in subjects without kidney disease – especially in a patient with diabetes.

2. A BRIEF REVIEW OF YOUR CURRENT BP MEASUREMENT TRAINING AND PRACTICE

We have found that a few simple questions quickly point out knowledge or practice areas where you or your staff may have forgotten or do not practice *every time* you take a blood

pressure, and may lead to serious errors in the readings you obtain from your patients. Please work through these questions and try to recall how you were first trained and how you practice today. From this information you will be able to quickly identify areas that need to be updated. You should also review and discuss all of these questions with anyone who measures blood pressure for you. In our experience, it is rare for those who measure BP today, to correctly answer all of these questions. Failure to answer *any* of these questions correctly means that you have not mastered all the knowledge, skills, and techniques required to obtain an accurate BP.

- **How do you know the BP device you use every day is accurate and reliable?** All BP devices must be regularly inspected to ensure they are accurate and reliable. The gold standard for accuracy is a mercury manometer. Every practice should have at least one mercury device and most nephrologists rely only on this instrument. Current recommendations are that all non-mercury devices in your setting should be calibrated at least every 6 months. After checking 1200 devices in clinical use in England, Rouse and Marshall suggested that serious errors occur every day in many practices. The authors concluded that medical practitioners who do not calibrate their manometers regularly are guilty of medical negligence.[6]
- **How do you know your (or your staff's) hearing is good enough to be able to accurately identify Korotkoff sounds?** The best way we and others have found is to show a videotape with a series of actual BP examples.[4] You and your staff can determine if you get the same readings when you hear the same sounds and see the same falling column of mercury. Another way is to use a double, or better yet, a triple stethoscope to listen to BP sounds. Trained observers almost always read BPs within 2–4 mmHg of each other. No automated device has been shown to be this accurate. Indeed, no automated instrument has been shown to be as accurate and reliable as a trained medical practitioner using a mercury manometer and a stethoscope.
- **What error is caused by taking BP readings while a patient is sitting on the examining table?** When BP is measured with the subject sitting on the examining table you may overdiagnose high blood pressure. This is because the isometric muscle contraction required when on the edge of the table increases the blood pressure by an average of about 6.5 mmHg diastolic.[8] This will inaccurately increase the number of 'hypertensives' in your practice by about 40%.
- **How do you select the correct cuff for your patient?** Using the wrong cuff can result in errors of up to 20 mmHg systolic and 20 mmHg diastolic. The most reliable way to select the correct cuff is to measure the mid-upper arm circumference (Figures 1.1 and 1.2) and use Table 1.1. This should always be done on the first visit.

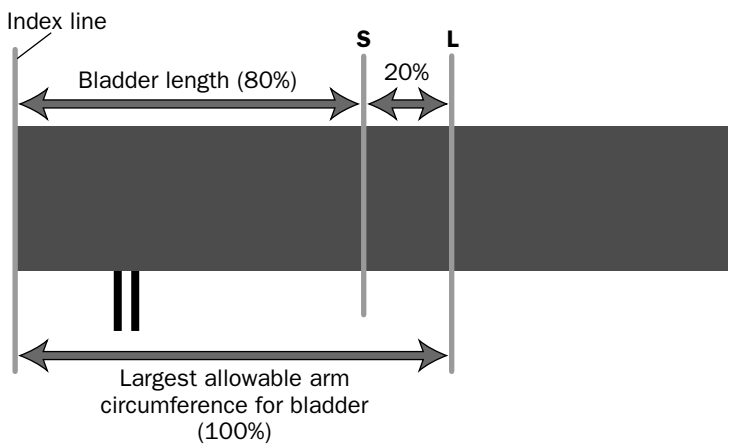

Fig. 1.1 The cuff and arm circumferences. S, smallest arm for this cuff; L, largest arm for this cuff. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

Table 1.1 Blood pressure cuff sizes and arm circumferences recommended by the American Society of hypertension Heart Association Guidelines

Cuff label	*Width (cm)*	*Length (cm)*	*Arm circumference range (cm)*
Child	8	21	16–21
Adult	13	30	27–34
Small adult	10	24	22–26
Large adult	16	38	35–44
Thigh	20	42	45–52

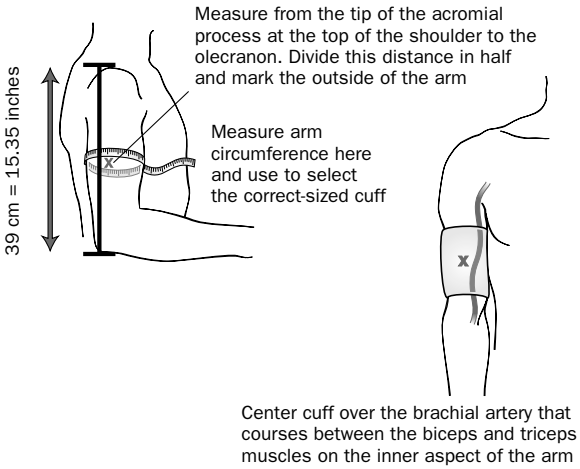

Fig. 1.2 Selecting the most accurate cuff. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

- **When you place the cuff on the arm where does the center of the bladder go?** Many will use the mark on the cuff that indicates 'artery' to locate the artery. However, most cuffs are marked incorrectly. The center of the bladder must go over the brachial artery on the inside of the upper arm (Figure 1.2). Failure to do so will result in a false increase in BP.
- **If you are going to use only one arm to measure the blood pressure which is the best to use?** Most health care staff will state the left arm is preferred. When asked why they may say: 'It is closest to the heart', which is true as the crow flies but not as the blood flows! Indeed, the left arm is much more likely to give you a false low BP than the right arm (Figure 1.3). The correct answer is that at the first visit one should always measure the BP in both arms and then use the arm with the highest blood pressure. Failure to do this can result in errors of up to 100 mmHg.
- **When you seat the patient in a straight-backed chair for measurement or when taking a standing pressure (to screen/diagnose orthostatic hypotension) where do you place the arm to avoid errors due to hydrostatic pressure variations in arm placement?** Many will say that the *antecubital fossa* should be placed so that it is at 'heart level' (i.e. the 4th intercostal space). This is not correct. It is the center of the BP cuff that must be placed at heart level to avoid hydrostatic overestimation of the pressure if the center is *below* the heart level or hydrostatic underestimation of the pressure if the center is *above* the heart level (Figure 1.4). Errors of 10 mmHg can be easily made by failure to pay attention to this detail.
- **How high do you inflate the pressure before you start listening?** Most medical practitioners are trained to go to 200 mmHg or to look at the last blood pressure. However, the correct response is to inflate to 30 mmHg above the palpated systolic BP. Failure to do this will miss the fairly common auscultatory gap and result in errors of up to 40 mmHg.
- **Which part of the stethoscope head should be used to best pick up the low-pitched Korotkoff sounds?** Most use the diaphragm. However, the bell is designed to detect the low frequency sounds. *It is recommended by the AHA*.

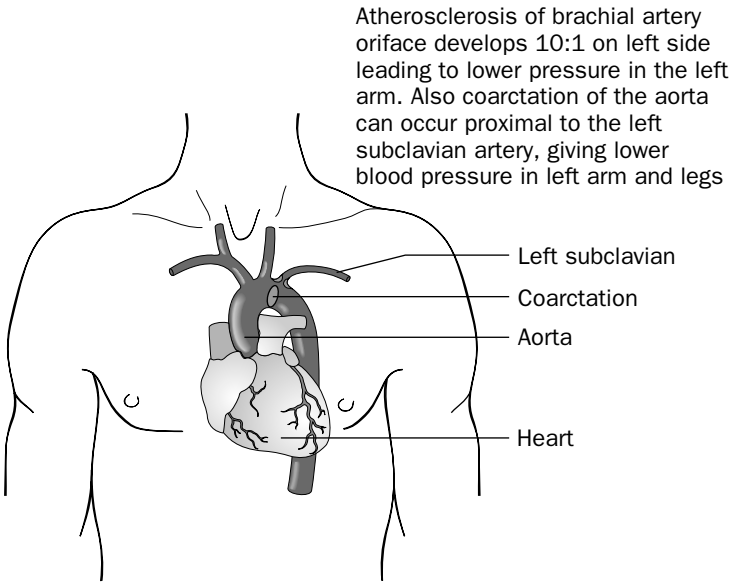

Fig. 1.3 Atherosclerosis and coarctation can affect blood pressure readings. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

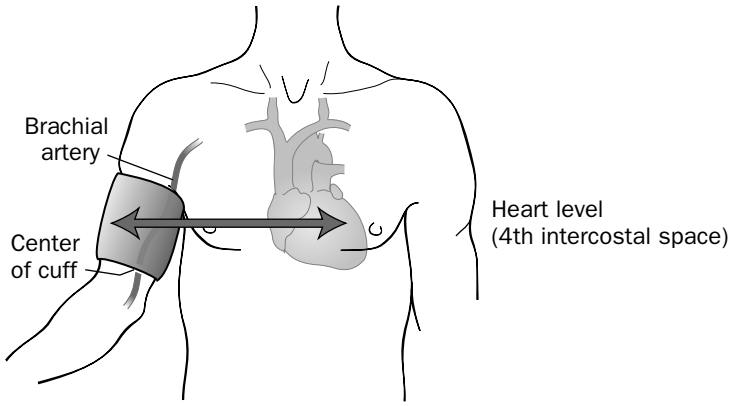

Fig. 1.4 The technique for cuff placement and pulse detection. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

- **How do you know where to place the bell to get the best Korotkoff sounds?** Most just place it under the edge of the cuff. The most accurate sounds are heard directly over the pulse in the antecubital fossa. This is almost always on the inside of the arm just under the biceps tendon. When a standing BP is to be done it is best to mark this site so that it can easily be found on standing.
- **How fast do you deflate the manometer (in mmHg?)** You will be no more accurate than the rate at which you deflate. The most common rate is about 10 mm/second. Watch and time your staff to see how they do this. Those who deflate this rapidly will often record blood pressures that end in zero, such as 130/80, as they cannot read more accurately than 10 mm.
- **Which Korotkoff (K) sound do you (and your staff) use to use to define the systolic blood pressure reading?** If you talk to your staff you will find that some define systolic blood pressure as the first sound they hear. Others may say the first loud sound they hear, and several may say the first really loud sound. Obviously, if they are using different definitions they will get different BPs even if reading the same blood pressure. The correct response is that the systolic blood pressure is defined as the first of at least two regular BP

sounds that are heard. Many practitioners have been trained to use the muffled sounds as the diastolic pressure (K4). This can result in errors of over 10 mmHg for diastolic pressure. Again, *everyone* in your practice must use the same definitions or there will be differences of up 10–40 mmHg just because different definitions are used.

- **Your patient is a 10-year-old boy and his blood pressure averages 120/70 mmHg. Does he have high blood pressure?** Yes, he does. Most practitioners do not know that the diagnosis of high blood pressure in children requires the measurement of height and age and then using a gender-specific table to determine the diagnosis of high blood pressure, as discussed below.
- **Which automatic blood pressure device has been approved for general use in a pediatric population above the age of 3 years?** Despite the fact that automated devices are used extensively in family practice where most children are seen, none of the devices have been proven to be as accurate as a trained medical practitioner using a mercury manometer and a stethoscope. Indeed, the research that has been done suggests that the most commonly used Dinamap device will label 30% of children as having high blood pressure.[9] Automated devices were designed to be used in the operating or recovery room where frequent readings are taken and relatively *large* changes in BP are important. The same can be said for the use of automated devices during dialysis. However, in the clinic you are interested in BP differences as small as 1 mmHg and therefore no current automated device should be used for these decisions.
- **Your patient with renal disease is 75 years old and has a normal EKG, chest x-ray, and echocardiogram and the nurse reports a pressure of over 300 mmHg by palpation. What do you suspect?** This elderly patient probably has Mönckeberg's sclerosis or brachial artery calcification to such an extent that the calcified artery cannot be compressed by the inflated BP cuff – even at 300 mmHg a radial pulse is still palpated.

Table 1.2 Blood pressure readings and comments

Blood pressure	*Comments*
122/74.	Only one reading. AHA and JNC 7 recommend 2–3 readings at all times
170/75, 165/70, 160/65	Blood pressure readings that end in an odd number.[13] AHA guidelines are that BP should be measured to the nearest 2 mmHg
140/80, 150/90, 140/80	Terminal digit bias for 0
146/84, 146/84, 146/84	Failure to take 2nd and 3rd BP and just repeating first reading
188/166, 180/164, 182/162	Failure to pick up an auscultatory gap→ a false high diastolic pressure or a false low systolic pressure

AHA, American Heart Association; JNC, Joint National Committee.

- **Your elderly patient with renal failure, angina, and claudication has a blood pressure of 122/74 in the right arm, 86/50 in the right, but has grade IV hypertensive retinopathy. What do you suspect?** This patient has such advanced atherosclerosis in the right and left arms that BP falls across the stenoses and 'hides' the central aortic pressure of 240 mmHg.
- **As an expert in hypertension and kidney disease you should be able to easily spot the diagnosis of the blood pressure measurement errors when someone else measures blood pressure for you**. What are the likely problems in the BP readings shown in Table 1.2? We recommend that you mask the *Comments* column of the table and try to diagnose treatment errors. When finished,

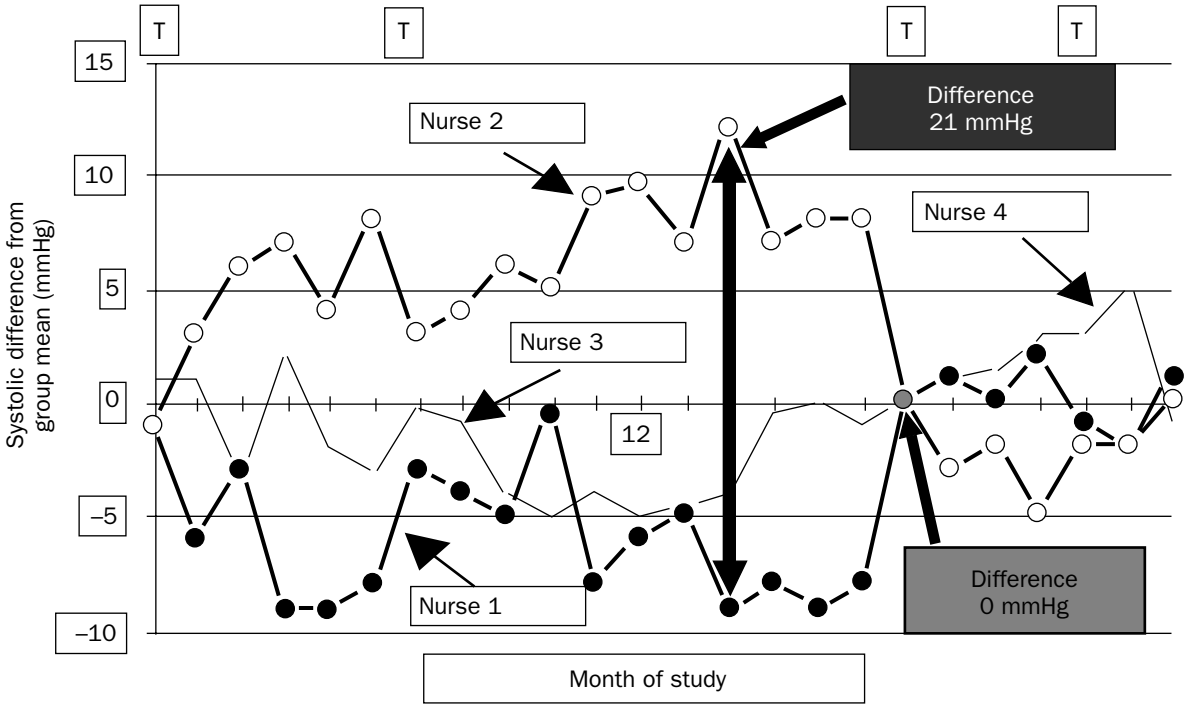

Fig. 1.5 Systolic BP differences between research nurses during a 24 month study: effect of training (T). The months of the study are indicated along the 'o' difference line. Adapted from Bruce et al, J Hypertension 1988[3]

check your diagnosis with the uncovered *Comments* column.

3. BP TRAINING IMPROVES ACCURACY BETWEEN OBSERVERS

One large research study has indicated that even those who have been retrained benefit from repeated reminders of performance standards. The data in Figure 1.5 were collected from trained research nurses during the British Heart Study.[3] At the end of the study, the investigators were interested in the quality of the BPs taken during the two years of the survey. They pooled all BPs taken by all trained nurses and then subtracted this number from the BPs taken by each nurse. The plot is of the difference (and + and – mmHg signs) of the BPs recorded by each nurse by each month of the study. The nurses were trained at the beginning of the study, and the procedure was to be repeated every 6 months, as shown at the top of Figure 1.5 by a 'T'. Note that at the first 'T' the BPs recorded were all very close together. However, over time the BPs recorded by Nurse 1 became consistently lower than those of the other two nurses, and the measurements by Nurse 2 became progressively higher. With the second training the observer differences again narrowed. However, because the training was considered to be tedious and unnecessary by the nurses, it was dropped *until* 18 months into the study. Note that at 14 months into the study the BPs recorded by Nurse 1 and 2 differed by an average of 21 mmHg systolic. After retraining at 18 months the BPs finally became much closer together. Bruce et al. suggest that for research studies, repeated training and testing should be done every few months, but that this would not be practical in routine practice.[3] We disagree. Because major health decisions and treatments are based on readings taken in the clinic, the most rigid quality control should be in place in the day-to-day measurement of BP in the clinic.

4. A BRIEF HISTORY OF BP MEASUREMENT AND HEALTH RISKS OF HIGH BP[11,12]

With the advent of standard methods, it became apparent that elevated BP was an important predictor of premature death and disability in patients who reported feeling ill. One of the first books on this subject was available in 1904, and the authors suggested using only the palpated measurement of systolic pressure. This work was published just one year before Korotkoff published his work on the ausculatory method.[12] The term 'hypertensive cardiovascular disease' was coined by Janeway after following 458 symptomatic patients with a systolic blood pressure greater than 160 mmHg (by palpation) from 1903 to 1912.[13] He noted that 53% of men and 32% of the women had died in this 9 year period, and 50% of those who died had done so in the first 5 years after being seen. Cardiac insufficiency and stroke accounted for 50% of the deaths and uremia for 30%. By 1914, the life insurance industry had learned that even in asymptomatic men the measurement of BP was the best way to predict premature death and disability and all insurance examiners were urged to learn to use this most valuable of medical instruments. In 1913, the chief medical officer of the Northwest Mutual Insurance Company stated: 'No practitioner of medicine should be without a sphygmomanometer. This is a most valuable aid in diagnosis'.[14]

> Standardized BP readings predict premature death and disability and cause of death and disability in asymptomatic persons

Population-wide studies of BP in men and women began in 1948 with the Framingham Heart study. The standardized measurement of BP using the guidelines developed by the American Heart Association demonstrated that cardiovascular risk increased continuously from the lowest to the highest levels of BP and that the systolic BP was the most predictive measure. At least 91% of those who developed heart failure had high BP before they developed overt congestive heart failure.[15] The impact of BP was found to be even more devastating in American blacks in Evans County, Georgion, USA, where 60% of all deaths in black women were attributed to high BP.[16]

These results and the discovery of drugs that lowered BP led to the implementation of large-scale trials in the 1960s, to determine at what level of blood pressure the risks of lowering high BP outweighed the risks of not lowering it. The design and implementation of these trials required ways to ensure that BP would be measured with the same accurate and reliable method by all personnel across several study centers over at least five years. Methods of training during these trials and the National Health and Nutrition Examination Survey (NHANES) population surveys evolved into a standardized training, certification, and quality assurance program that needs to be transferred to the day-to-day practice of medicine if the impressive benefits of these trials are to be conveyed to the general population. We have modeled our video-tutored training and certification program on their experiences.[7] This chapter is based on this training program. It should be remembered that in most of the large-scale trials the difference in BP between the treated and untreated groups over five years was less than 10/5 mmHg. Thus, errors of this magnitude, if too low, will deny the proven benefits of treatment to millions of people who have high BP but who will be advised that their BP is normal.

5. TECHNIQUE AND EQUIPMENT

5.1 Technique

If patients are to benefit from the impressive advances made in the treatment of high blood pressure, the office health care team must have a system that guarantees that the BPs taken follow the steps needed to obtain an accurate and reliable BP. This requires that the personnel who measure BP not only have the knowledge and skills required for accurate BP

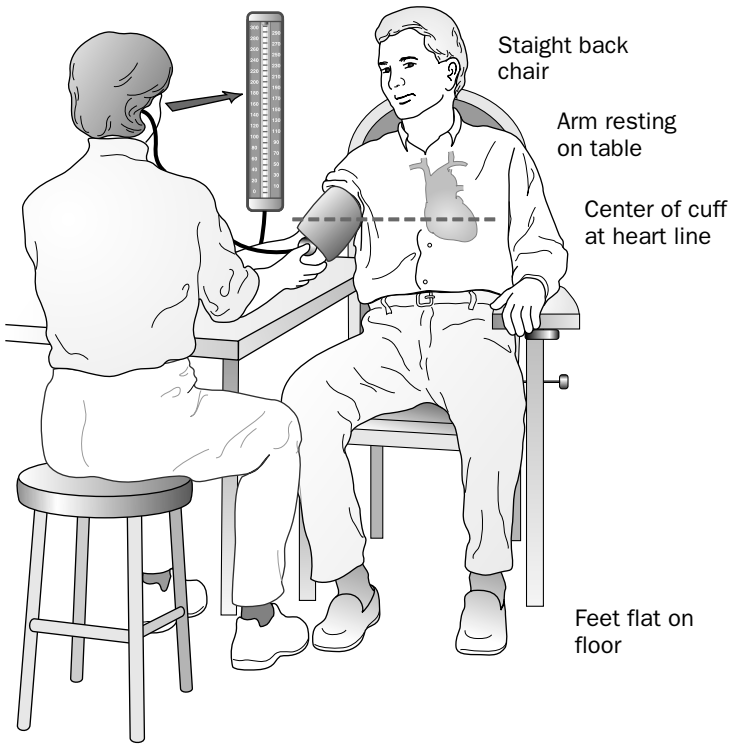

Fig. 1.6 Recording blood pressure. The optimal positions for patient and medical practitioner. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

measurement but also that they actually perform every measurement using correct techniques. In the ideal office for BP measurement, the patient must be seated in a straight-backed chair with arm support on both sides and a stand to support the arm when standing blood pressure is being measured (Figure 1.6). The setting should be quiet and relaxed. Do not measure blood pressure on the examining table, as sitting without back support increases BP by about 6.5 mmHg.[8] The chair should be moveable and a table or desk placed so that BP can be easily measured in both arms. It must be easy to adjust the height of the arm so that the centre of the cuff is at heart level (at the 4th intercostal space, see Figure 1.4). The manometer should be placed so the scale is visible at eye level when the observer is seated. We recommend that the observer is also seated, as this decreases extraneous sounds generated by not being able to rest the observer's arms on the table to minimize muscle noise. You should listen to the sounds in the room to ensure that the heating or air conditioning fans are quiet so that you can hear the soft diastolic sounds. Other sources of noise should also be minimized.

Preparing the patient should be a part of the measurement process. The purpose of preparation is to inquire about, note, and control for factors that cause changes in blood pressure in order to get the best standardized estimate of BP at the time. When possible, apply the cuff and discuss the procedure then leave the patient alone for 5 minutes. If the patient is not wearing a short-sleeved shirt, provide a gown or have them remove their arm from their sleeve, and remind them to wear a loose, short sleeve garment for future readings. Explanation should include how the measurement is performed and that there should be no talking by the patient or the observer during this period. Also tell the patient that at least two readings will be taken. Some patients worry that something is wrong if more that one BP measurement is carried out. The patient is to sit straight *against the back of the chair* with the feet resting flat on the floor and legs uncrossed (see Figure 1.6). The observer

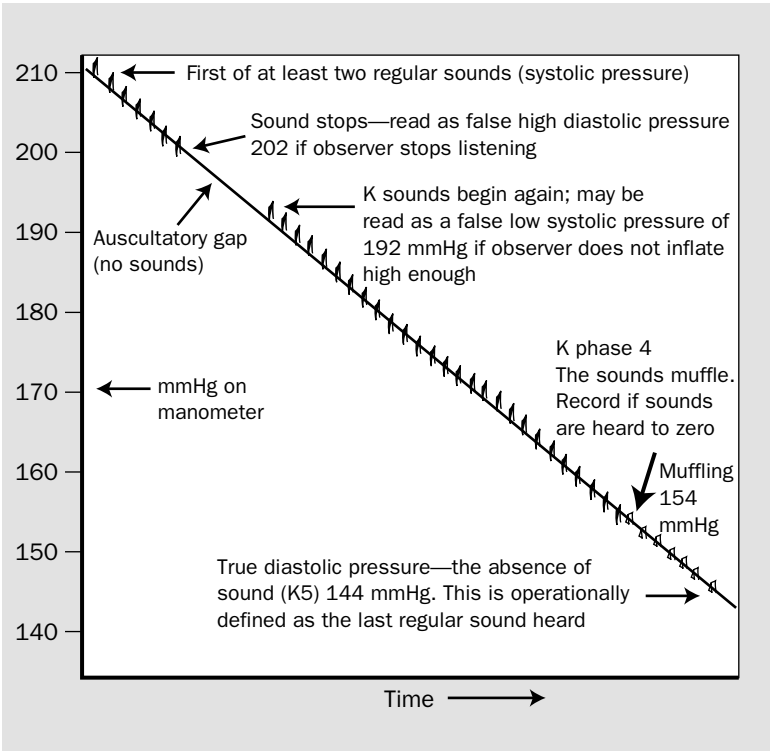

Fig. 1.7 The auscultary gap and Korotkoff (K) sounds.

should also inquire about factors that might affect the blood pressure: pain, tobacco use or caffeine ingestion during the last 30 minutes, over-the-counter medications, full bladder, or strenuous exercise taken earlier.

You and anyone who measures BP for you should have all the required skills, knowledge, and technique. In our testing of experienced observers we have rarely found practitioners who could not hear sufficiently well to identify Korotkoff sounds (Figure 1.7). Others have been found who cannot remember the systolic blood pressure without writing it down. Staff in your setting can be screened for the problems by using our videotaped tests and by multi-stethoscope testing.

5.2 Equipment

5.2.1 The mercury manometer

The mercury manometer is the primary instrument for all blood pressure measurements (Figure 1.8). All those who measure BP with non-mercury devices should have at least one reference mercury gauge available in order to check other devices regularly. The tube containing the mercury needs to be large enough to allow rapid increases and decreases in pressure. The 2 mm graduated markings should be on the tube. The standard glass tube, which can break, should be replaced with either a Mylar-wrapped glass tube or a plastic tube.

5.2.2 The aneroid gauge

The components of the aneroid device comprise a delicate system of gears and bellows that can be easily damaged by rough handling (Figure 1.8). This instrument also develops metal fatigue over time and leads to inaccuracy. Current research suggests that at least 30% of these devices in use are out of calibration and the error is almost always too low.[17] To detect an inaccurate aneroid device, inspect the face for cracks and ensure that the needle is in the zero range. If it is out of this range, it is almost always inaccurate and should be removed from use until recali-

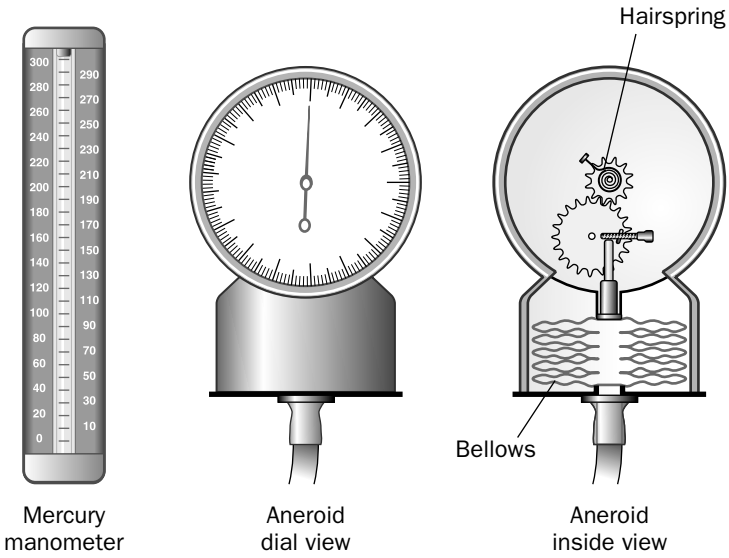

Fig. 1.8 The equipment for measuring blood pressure: mercury manometer and aneroid instrument (dial and internal view). Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

brated. How frequently this device should be checked has not been determined but we recommend every 6 months. The practitioner should realize that once an aneroid device is out of calibration it is difficult to detect the problem without calibrating it against a mercury device. Measurements with an inaccurate device will only be recognized after it has been found to be faulty. In a busy office, this may lead to dangerous mis-measurement until the next inspection is carried out.

The aneroid device must be checked by connecting it to a mercury device with a Y-tube.

- Wrap the cuff around a book or can and inflate to 200 mmHg
- Wait one minute
- Record the pressure
- If it is lower than 170, there is a leak that must be found and corrected. This can be done by inflating to 200 mmHg and then pinching off the tubing to locate the leak. If pinching just before the inflation bulb stops the leak, the leak is in the valve, which can be taken apart and cleaned or replaced. If the leak continues when the tubing is pinched just before the manometer, the leak is in the manometer, and in this case:
  1. Note whether the mercury rises and falls smoothly.
  2. Locate and correct any leaks by replacing the appropriate part, although a leak of <2 mm/second can be tolerated in a pinch, as this is the correct deflation rate.
  3. Date the device to indicate when it was last inspected/repaired
  4. Now reinflate again to 200 mmHg.
  5. Deflate the level in the system and check the aneroid readings against the mercury set at the critical decision points for BP: 180, 160, 140, 130, 120, 110, 100, 90, 80, and 70 mmHg. If the reading differs by more than 3 mmHg at any reading, the aneroid device must be recalibrated by trained personnel or discarded.

5.2.3 The electronic device

Does the electronic device work on this particular patient? Because electronic devices are not accurate on up to 30% of people, verify reading accuracy in each patient using the following protocol:

1. Choose the correct cuff size and center it over the brachial artery.
2. Palpate the pulse in antecubital fossa and place the bell over the point of the strongest pulse.
3. Trigger the automatic device and listen as it records the pressure.

4. Immediately record your pressure readings at K1 and K5, then record and compare the device pressures.

To calibrate an electronic device, replace the aneroid device with the electronic instrument in the Y-system and check the pressure levels registered on the electronic manometer as noted previously. Activate the inflation mechanism and compare the pressure on the digital display with the mercury as above. In some cases you must squeeze the rolled up bladder to simulate a pulsating arm.

The British Medical Association regularly reviews the quality of devices for blood pressure measurement for hospital, clinic, home, and ambulatory measurements. The last review was in December 2001 and shows the dismal state of the market for accurate and reliable devices.[19] It is of interest that no aneroid device has passed the standards set up the US American Association for Medical Instrumentation (AAMI) and the British Hypertension Society. Unfortunately, to be marketed in the United States, devices do not have to meet these standards as they are voluntary. Of the 21 devices that have been formally tested only five have passed UK and US standards. All were manufactured by Omron. The specific ones that passed were HEM-737, HEM-713C, HEM-735-C, HEM-72C, and the HEM-705CP. Of the five devices that have been tested only two have passed the standards: Datascope Accutor Plus and the CAS Model 9010. It is of interest that some of the most widely used devices in hospitals and clinics have failed this objective evaluation. All those who are involved in using electronic devices should keep up to date on the testing results and ensure that devices that are used on their patients should be only those that have regularly passed the required standards. The May 2003 Issue of *Consumer's Reports* reviewed home blood pressure devices.

5.2.3 Calibration of electronic devices

When calibrating a manometer, it is preferable to have two observers to record BP with a double stethoscope, you will then have a more accurate estimate of agreement. Do this at least three times. Compare the average of your readings to those of an aneroid or electronic device. If this differs by more than 4 mmHg, the electronic device should be returned to the manufacturer. If a mercury device is at zero and the column rises and falls rapidly with inflation-deflation, the manometer is accurate (Figure 1.9).

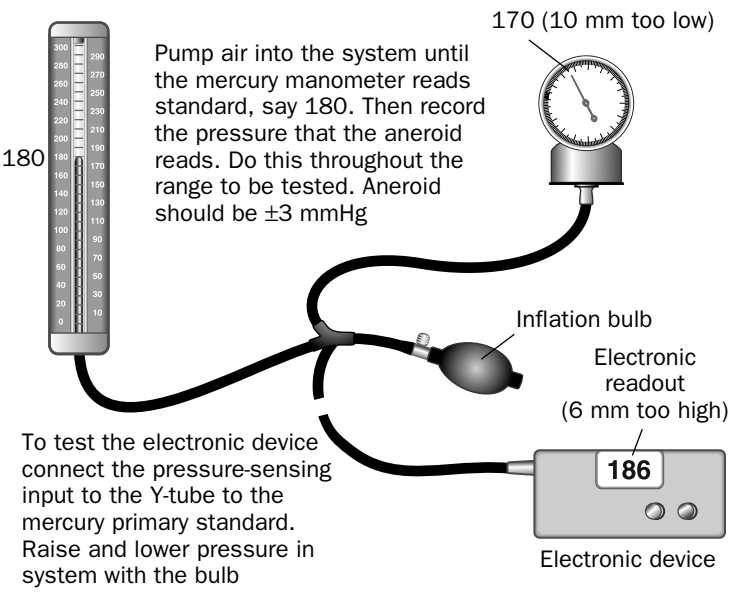

Fig. 1.9 Calibration of the manometer. Mercury, aneroid, and electronic instruments. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

5.2.4 Selecting the most accurate cuff (Figures 1.1 and 1.2)

Measure the arm circumference at the mid-biceps area. Have the patient stand and hold the arm along the side with the forearm flexed at 90 degrees. Place the 0-end of the tape measure at the acromial process at the top of the shoulder and measure to the tip of the elbow (olecranon). Divide this length in half and place a small mark on the lateral biceps area. This mark is used later to speed up location of the brachial artery pulse and to position the cuff. Now let the forearm hang down and measure the circumference of the upper arm in a plane parallel to the floor. The tape should lie against the skin without indenting the skin. This circumference is used to select the correct cuff from those recommended by the AHA. The width of the cuff bladder should encircle at least 40% of the arm and the length of the bladder must encircle at least 80% of the arm. Most cuffs in use are not marked correctly. The correct way to mark the cuff is shown in Figure 1.1.

It is important to mark the BP cuff so that it is used only on arms of the acceptable size for the bladder cuff width (Table 1.1). Blood pressure cuff sizes, arm circumference ranges, and bladder widths and lengths are shown. Many cuffs are not marked at all or are not marked correctly. We recommend doing this measurement yourself and marking the cuff correctly (S = smallest arm for this cuff; L = largest arm for this cuff) (Figure 1.1). Observe where the index line falls when the cuff is placed around the arm. If the index line falls to the right of the L-line when placed on the arm, use a larger cuff. If the index line falls to the left of the S-line use a smaller cuff.

5.2.5 The stethoscope

The bell or low frequency detector of the stethoscope chest piece is designed for the low frequency of Korotkoff (K) sounds and can be placed more precisely over the source of the K sounds. The tubing should be thick and 12–15 inches (30.5–38 cm) in length. For sound transmission, earpieces should be worn in the direction of the ear canal (i.e. toward the patient) (see Figure 1.10).

Sometimes the K sounds may be difficult to hear. There are two methods of making these sounds louder. The first uses the increased flow of blood into an arm which has been rendered transiently ischemic by exercise. To carry out this maneuver inflate the cuff to the maximum inflation level (MIL) and have the patient forcefully open and close their fist 10 times. Then

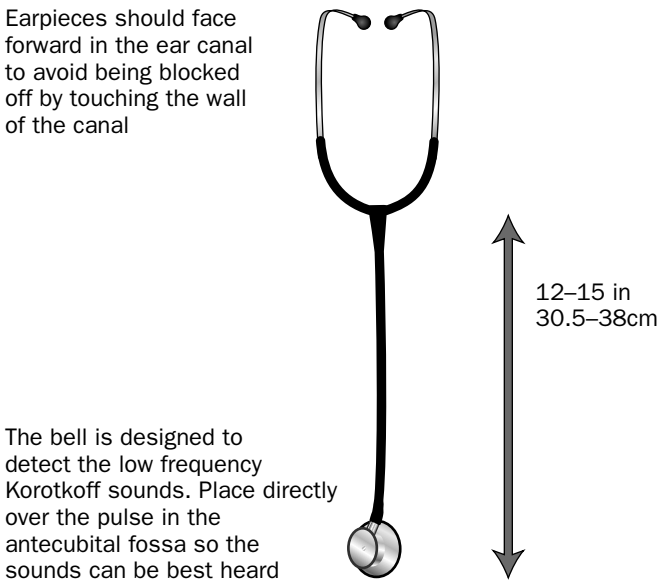

Fig. 1.10 The stethoscope. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

have them relax the hand and measure the pressure in the usual fashion. If this does not work, the next method combines the first with 'draining' the blood out of the arm by holding it straight up over the head for 1 minute, then inflating the cuff another 30 mmHg above the MIL. The arm is then lowered and the fist squeezed 10 times.

5.3 Cuff placement and pulse detection

Palpate the brachial artery in order to place the cuff so it exerts pressure evenly and directly over the artery along the inner surface of the arm. Adjust the arm height so that the center of the cuff on the arm is at heart level (4th intercostal space) (Figure 1.4). If the center of the cuff is above this line the pressure measured will be falsely low. If the center is below this line it will be falsely high. Each 1.3 cm displacement from this point will change pressure + or − 1 mmHg.

For listening to blood pressure sounds, palpate the brachial artery just medial to and usually under the biceps tendon in the antecubital fossa (Figure 1.11). Place the bell of the stethoscope directly over this pulse to get the best Korotkoff sounds. *If you do not feel this pulse do not use this arm. Extending the arm as straight as possible makes the brachial artery easier to feel in the antecubital fossa.*

5.3.1 Determining the maximum inflation level (MIL)

The reason for estimating the palpated systolic pressure and the maximum inflation level (MIL) is to ensure that an auscultatory gap does not give the observer incorrect reading. After a rest period of at least 5 minutes find the MIL. Palpate the radial artery at the wrist (Figure 1.12). Use this pulse to determine when the pressure in the cuff has exceeded the systolic pressure.

1. Inflate the cuff to 60 mmHg, then inflate by 10–15 mm increments until the pulse can no longer be felt. Inflate another 10–15 mmHg and then deflate at 2 mm/second. Note where the pulse reappears as you deflate the cuff. This is the palpated systolic pressure, a good estimate of the true intra-arterial systolic pressure.
2. Release the pressure completely.
3. Add 30 mmHg to the pressure and this is the MIL.
4. Place the bell of the stethoscope over the palpated brachial pulse in the antecubital

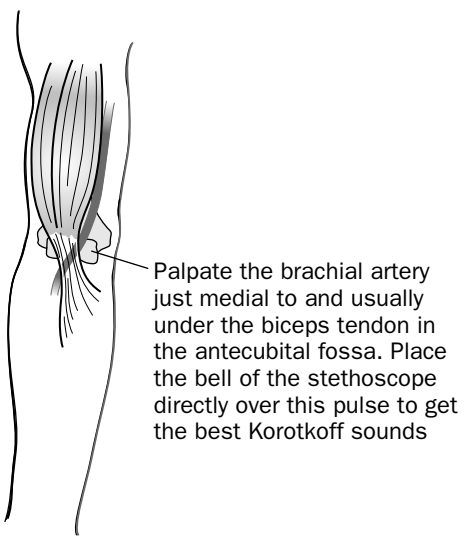

Fig. 1.11 Palpation of the brachial artery to obtain optimal Korotkoff sounds. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

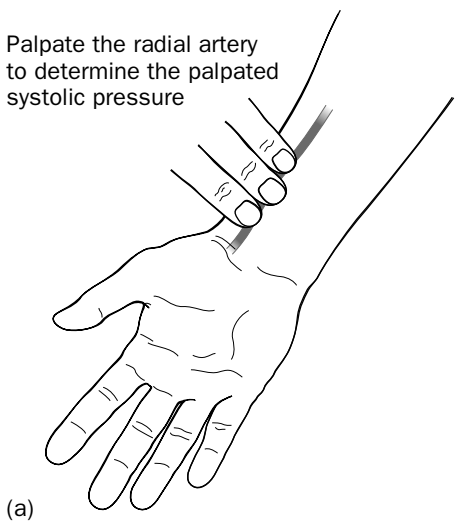

Fig. 1.12 Palpation of the radial artery to obtain systolic blood pressure. Used with permission from Current Medicine, Hollenberg and Braunwald, 2003.[10]

fossa, inflate to at least the MIL, and release the pressure at a steady 2 mmHg per second and record the readings.

5.3.2 Recording blood pressure and the auscultatory gap (Figure 1.7)

To record the reading:

1. Inflate the cuff quickly to the MIL.
2. Immediately begin to deflate at 2 mm/second.
3. Remember the systolic pressure at the point where you hear the first of at least two regular sounds.
4. Repeat this number silently to yourself with each heart beat until you detect the diastolic pressure at the point where the last regular sound is heard.
5. If Korotkoff sounds are heard to zero, repeat the reading and note the K4 or muffling and record all three sounds (e.g. 142/66/0).
6. Record the arm, position, cuff used, and the systolic, and diastolic pressure.
7. Wait one minute. Repeat the reading two more times. Experts recommend discarding the first readings and averaging the last two.

The palpated systolic pressure can be used in environments that are too noisy for hearing Korotkoff sounds. This may be used in an ambulance, a large crowd or in an environment where there is loud music

5.4 Which arm should be used for measuring blood pressure?

At the first visit, blood pressure should be recorded in both arms. This is the only way to avoid missing a large difference between the two arms as the error can be as much as 100 mmHg. In the elderly, the most common cause of a difference is hemodynamically significant atherosclerotic stenosis of the left subclavian artery. In children, the most common reason is coarctation of the aorta (Figure 1.3). In the screening situation where only one side is to be used, the patient should be asked if they know if one arm has a higher BP, and then use that one. Otherwise, use the right arm.

6. TESTING

6.1 Testing for orthostatic hypotension

This should be carried out in any patient who complains of dizziness. With today's medications, excessive falls in blood pressure on standing are uncommon. The procedure is to prepare the patient by telling them what you are going to do. Have them stand up to check the stand you are using to rest their forearm so that in the standing position the center of the cuff is at heart level. Mark the spot where the bell of the stethoscope will go. Now have the subject lie down for 5 minutes (or have them sitting if they have problems getting up from a lying position). You need to time with a stopwatch. Have the patient stand and immediately start the stopwatch. The standard method is to have the patient supine for 5 minutes and then measure the pressure at exactly 1 and 3 minutes after standing. The patient should stand quietly, but be prepared to support them if they faint. At about 30 seconds, inflate to the MIL and begin to deflate so that the first systolic pressure is heard at close to 1 minute as possible. Repeat this at 2.5 minutes to get a 3 minute standing pressure. A drop of 20 mmHg systolic is considered abnormal. If the BP does not drop that much have the patient stand up and down on their toes 10 times. Recheck the BP again. Rarely does standing on toes reveal an exercise hypotension or hypertension.

6.2 Testing observer accuracy with the standardized video-test or triple stethoscope

We have developed a form (Figure 1.13) so that the evaluation of observer accuracy in two circumstances is standardized. For videotape testing, the observers being tested watch a videotape showing 12 examples and the correct answers are then provided.

BP Measurement

GRADING BP ACCURACY AND RELIABILITY

Name _____ Date _____

View the videotape and record your answers in the spaces below.

Example Number		Your answer		T		Correct answer	Difference (record sign [±] of diff.)
Example	Sys	1	2	8	-	126	+2
1	Dias		5	8	-	62	−4
Example	Sys	2	2	0	-	220	0
2	Dias	1	1	0	-	118	−8
Video	Sys				-		
1	Dias				-		
Video	Sys				-		
2	Dias				-		
Video	Sys				-		
3	Dias				-		
Video	Sys				-		
4	Dias				-		
Video	Sys				-		
5	Dias				-		
Video	Sys				-		
6	Dias				-		
Video	Sys				-		
7	Dias				-		
Video	Sys				-		
8	Dias				-		
Video	Sys				-		
9	Dias				-		
Video	Sys				-		
10	Dias				-		
Video	Sys				-		
11	Dias				-		
Video	Sys				-		
12	Dias				-		

(A)

BP Measurement – Quality Assessment

GRADING BP ACCURACY AND RELIABILITY ACCURACY:

Subtract the correct answer from your answer and place this difference (with sign) in the 'Difference' column. Count and record the differences you have from the correct answers in the table below.

Accuracy Table

Range	0	±2	±4	±6	≥±8
Count					

To be graded as accurate you should have at least 22 answers that are ±2 and only 2 can be ±4 mmHg.

ARE YOU ACCURATE? YES NO

If you have answers that are ±8 or greater it is likely that you misread the manometer by about 10 mmHg.

RELIABILITY:

Each of the examples you saw in the standardized video-test was repeated in the sequence. You should be ±2 mmHg in all of the repeat pairs. Complete the table below to assess your reliabilty.

Pair	1 and 11	2 and 8	3 and 10	4 and 7	5 and 9	6 and 12
±2?						

ARE YOU RELIABLE? YES NO

If you are not reliable it is likely you need to read the manometer more carefully or you have a memory problem.

DIRECTION BIAS:

If you read above or below the correct answer, you have direction bias. Record the number of times your answers are above the correct answer (number of +'s) and the number of times you were below the correct answer (number of –'s) in the table below.

+'s =		Least freq. sign =	1	2	3	4	5	6	7
–'s =		Sum of +'s, –'s =	8–10	11–12	13–15	16–17	18–20	21–22	23–24

You should have about 50% +'s and –'s. Enter the sum of +'s and –'s here=_____. If this is ≤ 7, you do not have direction bias. If ≥8, match your sum of +'s and –'s with the cell in the bottom row of the table above. If your least frequent sign is ≤ the value in the cell above it (in the top row) you have direction bias ($P < 0.05$). If you tend to read the systolic too low and the diastolic too high you may have a hearing problem.

TERMINAL DIGIT BIAS:

The last digit of a BP reading should end in an even number if you follow AHA guidelines. Count the number of times your answers ended in 0 and enter it into the 'n' row in the table below under the 0s column. Repeat for 2s, 4s, 6s, and 8s. Any answer ending in an odd number is wrong.

End digit=	0's	2's	4's	6's	8's	odd no.?
n=						
n^2=						

Now square each 'n' and enter it in the n^2= row. Now add the n^2 in this row and enter here Σn^2=_____. If $\Sigma n^2 \geq 161$ you have terminal digit bias ($P < 0.05$). You need to be more careful.

DO YOU HAVE TERMINAL DIGIT BIAS? YES NO

BETWEEN OBSERVER BIAS can be assessed by comparing your answers with others who watched the same video.

(B)

Fig. 1.13 (A) Blood pressure measurement; grading accuracy and reliability. (B) quality assessment.

The form can also be used with a double stethoscope testing method, where the instructor listens with the student and the results are graded in a similar way to the video-test. The form can also be used to assess terminal digit bias on 12 random blood pressure measurements recorded by one observer.

At least annually, all staff who take blood pressure should be:

- observed while taking seated/standing BP and have their technique corrected if needed;
- tested with a multistethoscope for their ability to hear and record the BPs accurately;
- tested with a standardized video-test for accuracy, reliability, terminal digit bias, and direction bias.
- assessed for terminal digit bias in readings taken on 12 previous patients.

Those who make errors should be counseled and retested every month until there is no bias. Those who cannot be certified as being accurate and reliable should not be permitted to measure blood pressure.

7. EQUIPMENT INSPECTION FOR QUALITY ASSURANCE

We recommend that someone in your practice be given the training and responsibility to carry out the regular calibration and quality control so that your patients' blood pressure is always accurate and reliable.

8. BLOOD PRESSURE MEASUREMENT IN THE YOUNG

As in adults, most children with a elevated blood pressure have no symptoms. Therefore, careful BP measurement plays a key role in the health of children by detecting 'silent' diseases. Before the age of 1 year electronic devices are recommended to estimate the systolic BP which is used for classification and detection of gross elevations. After the age of 1 year the auscultatory technique is still the gold standard. This is because no electronic device has the accuracy required for the critical annual BP measurement which will most commonly be used to identify early onset 'essential hypertension'. The technique to be used at age 1 is exactly the same as described above for adults. We recommend three readings at the annual BP screen. Chapter 15 gives details on how to proceed once a BP is found to be above the 95% after several visits (see below).

8.1 What is high blood pressure from age 1 to 18 years?

You have just been given the following readings on a 10-year-old boy: 124/82, 122/84, and 120/78 mmHg. His height is 54.5 inches. Does this boy have a blood pressure level that you should begin monitoring? The average of the last two readings is 121/81.

The definitions of blood pressure in children are shown in Table 1.3.[18] What is different in children is that one must use the child's height to assess if the blood pressure is 'unhealthy'. This is carried out by the following steps:

1. Determine the percentile of the distribution for height for this boy. This boy is 54.5 inches tall. By referring to Table 1.4 it can be seen that his height percentile is 50%. Go to Table 1.5.
2. Now, use this percentile for boys aged 10 to ascertain the corresponding 90% and 95% systolic and diastolic BP levels for him in Table 1.5. These are 115 mmHg and 119 mmHg systolic and 75 mmHg or 80 mmHg for diastolic. Thus, his BP is above the 95% for both systolic and diastolic pressures.

Table 1.3 Classification of blood pressure in children and adolescents, by age, sex, and height

Blood pressure classification	*Systolic and/or diastolic percentile*
Normal	SBP AND DBP below the 90th percentile
High normal[a]	SBP OR DBP equal to or greater than 90th percentile AND less than 95th percentile
Hypertension[a]	SBP OR DBP equal to or greater than the 95th percentile

[a] High normal and hypertension based on at least three separate readings on three separate occasions.

3. He should be seen again in 2 months for a repeat measurement. If persistently above 119/80 mmHg on subsequent visits then the steps recommended in Chapter 9 should be initiated.

SUMMARY

Blood pressure measurement, the most powerful screening test we have to prevent premature death and disability, especially in those with renal disease, is rarely practiced according to standard guidelines. This failure to practice proper technique is almost certainly related to inadequate training when first exposed to blood pressure measurement education activities. This chapter provides a series of questions to establish if the reader's knowledge and practice is up to current standards and reviews how to quickly diagnose poor measurement knowledge and technique in those who measure blood pressure for you.

A review of the key principles of accurate measurement is provided to update your knowledge and skills. Standardized methods for introducing quality control activities in your practice are presented that should enable you to improve the health of the population you serve.

Table 1.4 Heights (inches) for age percentiles

Age (yrs)	*5%*	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*
Females							
1							
2	30.5	31.5	32	33	34	35	35.5
3	33.5	34.5	35.5	36.5	37.5	38.5	39
4	36.5	37	38	39	40.5	41.5	42
5	39	39.5	40.5	42	43	44.5	45
6	41.5	42.5	43	45	46	47.5	48.5
7	44	44.5	46	47.5	49	50.5	51.5
8	46	47	48.5	50	51.5	53	54
9	48	49	50.5	52	53.5	55	56.5
10	49.5	51	52	54	56	57.5	58.5
11	51.5	53	54.5	56.5	58.5	60	61.5
12	54.5	55.5	57	59.5	61.5	63	64
13	57	58	60	61.5	63.5	65	66
14	58.5	59.5	61.5	63	65	66.5	67.5
15	59	60.5	62	63.5	65.5	67	68
16	59.5	60.5	62	64	65.5	67.5	68
17	59.5	61	62.5	64	66	67.5	68.5
Males							
1							
2	31	31.5	32.5	33.5	34.5	35	36
3	34.5	35	36	37	38	39	39.5
4	37	37.5	38.5	39.5	41	42	42.5
5	39.5	40	41	42.5	43.5	45	45.5
6	41.5	42.5	43.5	45	46.5	47.5	48.5
7	44	45	46	47.5	49	50.5	51
8	46.5	47	48.5	50	51.5	53	54
9	48.5	49	50.5	52.5	54	55.5	56.5
10	50	51	52.5	54.5	56	57.5	58.5
11	51.5	52.5	54.5	56.5	58	60	61
12	53.5	55	56.5	58.5	60.5	62.5	63.5
13	56	57.5	59.5	61.5	63.5	65.5	66.5
14	59	60	62	64.5	66.5	68.5	69.5
15	61.5	62.5	65	67	69	71	72
16	63.5	64.5	66	68.5	70	72	73
17	64	65.5	67	69	71	72.5	74

Adapted from the National Center for Health Statistics Growth Charts. Centers for Disease Control 2000.

The early detection of kidney disease hinges on careful standardized blood pressure readings made annually in all members of the population. Once kidney disease has been diagnosed the key to minimizing the progression to renal failure is exquisite blood pressure control. Thus, both detection and treatment of elevated are vital sign to slow or prevent progression of renal disease.

REFERENCES

1. Perloff D, Grim CM, Flack J et al. Recommendations for human blood pressure determination

Table 1.5 Blood pressure levels for the 90th and 95th percentiles of blood pressure for boys aged 1–17 years by percentiles of height

Age (yrs)	Height percentiles[a] BP[b]	Systolic BP (mmHg) 5%	10%	25%	50%	75%	90%	95%	Diastolic BP (mmHg) 5%	10%	25%	50%	75%	90%	95%
1	**90th**	94	95	97	98	100	102	102	50	51	52	53	54	54	55
	95th	98	99	101	102	104	106	106	55	55	56	57	58	59	59
2	**90th**	98	99	100	102	104	105	106	55	55	56	57	58	59	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	**90th**	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	111	112	113	63	63	64	65	66	67	67
4	**90th**	102	103	105	107	109	110	111	62	62	63	64	65	66	66
	95th	106	107	109	111	113	114	115	66	67	67	68	69	70	71
5	**90th**	104	105	106	108	110	112	112	65	65	66	67	68	69	69
	95th	108	109	110	112	114	115	116	69	70	70	71	72	73	74
6	**90th**	105	106	108	110	111	113	114	67	68	69	70	70	71	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	**90th**	106	107	109	111	113	114	115	69	70	71	72	72	73	74
	95th	110	111	113	115	116	118	119	74	74	75	76	77	78	78
8	**90th**	107	108	110	112	114	115	116	71	71	72	73	74	75	75
	95th	111	112	114	116	118	119	120	75	76	76	77	78	79	80
9	**90th**	109	110	112	113	115	117	117	72	73	73	74	75	76	77
	95th	113	114	116	117	119	121	121	76	77	78	79	80	80	81
10	**90th**	110	112	113	115	117	118	119	73	74	74	75	76	77	78
	95th	114	115	117	119	121	122	123	77	78	79	80	80	81	82
11	**90th**	112	113	115	117	119	120	121	74	74	75	76	77	78	78
	95th	116	117	119	121	123	124	125	78	79	79	80	81	82	83
12	**90th**	115	116	117	119	121	123	123	75	75	76	77	78	78	79
	95th	119	120	121	123	125	126	127	79	79	80	81	82	83	83

Table 1.5 ***Continued***

Age (yrs)	Height percentiles[a] BP[b]	Systolic BP (mmHg) 5%	10%	25%	50%	75%	90%	95%	Diastolic BP (mmHg) 5%	10%	25%	50%	75%	90%	95%
13	**90th**	117	118	120	122	124	125	126	75	76	76	77	78	79	80
	95th	121	122	124	126	128	129	130	79	80	81	82	83	83	84
14	**90th**	120	121	123	125	126	128	128	76	76	77	78	79	80	80
	95th	124	125	127	128	130	132	132	80	81	81	82	83	84	85
15	**90th**	123	124	125	127	129	131	131	77	77	78	79	80	81	81
	95th	127	128	129	131	133	134	135	81	82	83	83	84	85	86
16	**90th**	125	126	128	130	132	133	134	79	79	80	81	82	82	83
	95th	129	130	132	134	136	137	138	83	83	84	85	86	87	87
17	**90th**	128	129	131	133	134	136	136	81	81	82	83	84	85	85
	95th	132	133	135	136	138	140	140	85	85	86	87	88	89	89

[a]Height percentile determined by standard growth curves.
[b]Blood pressure percentile determined by a single measurement.

by sphygmomanometry. Circulation 1993; **88**:2460–2470.
2. McKay DW, Campbell NR, Parab A et al. Clinical assessment of blood pressure. J Hum Hypertens 1990; **4**:639–645.
3. Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. J Hypertens 1988; **6**:375–380.
4. Grim CM, Grim CE. A curriculum for the training and certification of blood pressure measurement for health care providers. Can J Cardiol 1995; **11**(Suppl H):H38–H42.
5 Armstrong RS. Nurses' knowledge of error in blood pressure measurement technique. Int J Nurs Pract 2002; **8**:118–126.
6. Rouse A, Marshall T. The extent and implications of sphygmomanometer calibration error in primary care. J Hum Hypertens 2001; **15**(9):587–591.
7. Curb JD et al. Training and certification of blood pressure observers. Hypertension 1983; **5**:610–614.
8. Cushman WC, Cooper KM, Horne RA, Meydrech EF. Effect of back support and stethoscope head on seated blood pressure. Am J Hypertens 1990; **3**:240–241.
9. Park MK, Menard SW, Yuan C. Comparison of auscultatory and oscillometric blood pressures. Arch Pediatr Adolesc Med 2001; **155**:50–53.
10. Grim CE, Grim CM. Accurate and reliable blood pressure measurement in the clinic and home: The key to hypertension control. In: Hollenberg and Braunwald, Eds, Atlas of Hypertension, 4th Edition. Philadelphia: Current Medicine 2003; 325–336.
11. Janeway TC. The Clinical Study of Blood Pressure: A guide to the use of the sphygmomanometer. New York/London: Appleton & Co. 1904.
12. O'Brien ET, Semple PF, Brown WCB. Riva-Rocci centenary exhibition. On the occasion of the 16th Scientific Meeting of the International Society of Hypertension in Glasgow, 23–27 June 1996. J Hum Hypertens 1996; **10**:705–721.
13. Janeway TC. A clinical study of hypertensive cardiovascular disease. Arch Intern Med 1913; **12**:755–798.
14. Fisher JW. The diagnostic value of the sphygmomanometer in examinations for life insurance. JAMA 1914; **63**:1752–1754.
15. Levy D, Larson MG, Vasan RS et al. The progression from hypertension to congestive heart failure. JAMA 1996; **275**:1557–1562.
16. Deubner DC, Tyroler HA, Cassel JC et al. Attributable risk, population risk and population attributable risk fraction of death associated with hypertension in a biracial community. Circulation 1975; **52**:901–908.
17. Bailey RH, Knaus VL, Bauer JH. Aneroid sphygmomanometers: an assessment of accuracy at a university hospital land clinics. Arch Intern Med 1991; **151**:1409–1412.
18. National Heart, Lung, and Blood Institute. Report of the Second Task Force of Blood Pressure Control in Children–1987. Pediatrics 1987; **79**(1):1–25.
19. O'Brien, E. State of the market for devices for blood pressure measurement. Blood Pressure Monitoring 2001; **6**:281–286.

2

Microalbuminuria/proteinuria: What does it mean? How do you measure it?

Jay Garg and George L Bakris

Introduction • Definition and prevalence of microalbuminuria (MA) • Pathophysiology • Clinical applications • Therapeutic intervention • Conclusion • References

1. INTRODUCTION

Based on the data from large single and multicenter clinical trials including the Heart Outcomes Prevention Evaluation (HOPE) study, it is clear that presence of microalbuminuria is a signal from the kidney that cardiovascular risk is increased and that vascular responses are altered. Thus, the presence of between 30 mg/d to 300 mg/d of albumin in the urine is associated with abnormal vascular responsiveness; the result of more advanced atherosclerosis and not necessarily related to presence of hypertension or renal disease. Agents known to reduce the rise in microalbuminuria or actually reduce the level of microalbuminuria, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, HMG-CoA reductase inhibitors, beta-blockers, non-dihydropyridine calcium channel blockers, and diuretics have *all* been shown to reduce cardiovascular mortality and in some cases preserve renal function. This chapter will present data that deal with changes in microalbuminuria in the context of cardiovascular risk reduction and influence on kidney disease.

Microalbuminuria (MA) is defined as the presence of albumin in the urine above the normal range of less than 30 milligrams per day but below the detectable range with the conventional dipstick methodology. Data from several pioneering studies over the last two decades demonstrate that MA is not only a predictor of diabetic complications but also a powerful independent risk factor of cardiovascular disease (CVD).[1–4] Moreover, MA predicts development of ischemic cardiovascular events related to development of atherosclerosis. Numerous clinical studies in persons with both type 1 or type 2 diabetes and MA demonstrate a higher CVD mortality.[5–7] It should be noted, however, that while the contribution of MA as a prognostic indicator of cardiovascular events in people with diabetes is clear, it is still debatable in nondiabetic populations.[8–10]

Newer research has focused on how MA may contribute to the pathogenesis of CVD. This area of research has primarily centered on populations with essential hypertension with or without diabetes. Several pathophysiological mechanisms as to how MA may contribute to the development of atherosclerotic vascular disease have been proposed, however, at the

time of writing, evidence to support one clear mechanism is not available. The currently proposed mechanisms mainly involve local injury to the vascular smooth muscle cells and endothelial cells in the vasculature leading to cell proliferation and increases in vascular permeability (Table 2.1).

2. DEFINITION AND PREVALENCE OF MICROALBUMINURIA (MA)

A consensus conference in 1985 defined MA in persons with diabetes as an abnormal urinary excretion rate of albumin between the range of 20–200 μg/min or 30–299 mg/d.[11] These definitions are still operative today. It is also important to note that the range for the urinary excretion rate of albumin is 25% lower during sleep than during the hours of being awake (15–150 μg/min). This is still the definition used today and is applicable to all people regardless of associated pathological condition. The reason for defining MA in this range, below detection by the routine urine dipstick, is that urinary albumin excretion in this range is associated with much higher cardiovascular mortality rate as well as nephropathy progression among people with type 1 diabetes.[1–9] It should also be noted that this higher incidence of cardiovascular mortality is not similar in the hypertensive nondiabetic populations.[1–8]

Table 2.1 Pathophysiological processes associated with microalbuminuria

Local process

1. Increased intraglomerular capillary pressure
2. Increased shunting of albumin through glomerular membrane pores

Systemic process

1. Activation of inflammatory mediators
2. Increased transcapillary escape rate of albumin
3. Vascular endothelial dysfunction

A high prevalence of MA has been noted in early studies of persons with diabetes.[10–12] Considerably lower percentages, however, have been noted in the more recent larger clinical trials.[13–15] These variations are mostly due to patient selection or inclusion criteria biases, such as the severity of hypertension, age, race, coexisting renal disease, techniques used for detection of MA, sampling size of cohort, day-to-day variability of albumin excretion which lies in the range of 31–52%.

The prevalence of MA in people with type 2 diabetes mellitus is about 20% (range 12–36%) and affects about 30% of people with type 2 diabetes older than 55 years of age.[10,16] The rate of progression to diabetic nephropathy in affected people with type 2 diabetes is 5%/year and 7.5%/year among those affected with type 1 diabetes.[3,4] Subsequent chronic renal failure occurs at 1% annually in type 2 diabetes patients and the risk for those with type 1 diabetes approaches 75% after 10 years.[7,17]

The prevalence of MA ranges from 5% to 40% among nondiabetic persons with essential hypertension. The reason for this high variability in MA prevalence among those with essential hypertension relates to both duration of blood pressure control as well as associated lipid abnormalities, especially low-density lipoprotein (LDL) levels. A recent analysis of the baseline data from the African–American Study of Kidney (AASK) Disease Trial illustrates this point. In this trial of 1097 African American people with hypertension and no diabetes, the strongest predictor of albuminuria at baseline was the level of LDL cholesterol.[18] Moreover, a recent meta-analysis of small clinical studies has documented decreases in MA when HMG-CoA reductase inhibitors are used to lower LDL levels.[19] A second related predictor was the duration of hypertension. In this way, MA may be a barometer of how well blood pressure has been controlled over time, much like HbA_{1c} is used to assess glucose control. This may be a valid assertion, since blood pressure reduction with all agents except dihydropyridine calcium antagonists, central antagonists and peripheral sympathetic blockers, reduce albuminuria.[20]

3. PATHOPHYSIOLOGY

The exact pathophysiology as to how MA contributes to or accelerates the atherosclerotic process is uncertain. The current understanding, however, suggests that mechanisms of vascular injury associated with MA are different between those with and without diabetes who also have hypertension.[17,21,22] People with MA have an elevated transcapillary escape rate of albumin, regardless of whether they have type 1 or type 2 diabetes. These individuals also have clusters of other metabolic and non-metabolic risk factors associated with CVD development. These risk factors include an elevated blood pressure, dyslipidemia, and insulin resistance.[11,13,15,23] All of these factors contribute to the genesis of atherosclerosis. Collectively, these risk factors have been put together and called Syndrome X since they frequently cluster in certain individuals. More recently, some authors have suggested that MA be added as a fifth element to the metabolic components of Syndrome X.[24]

In persons with MA who do not have diabetes, generalized vascular leakiness is caused by alterations in the extracellular matrix. This contributes to the development of endothelial dysfunction that ultimately promotes the atherosclerotic process.[17,25] Defective endothelial permeability permits lipid influx into the vessel wall causing atherosclerotic changes (Figure 2.1). In many acute and chronic illnesses, MA is associated with increased vascular permeability as the final common pathway through various mediators, some of which are complement activation, macrophage, neutrophil, and endothelial stimulation from diverse inflammatory insult.[21]

In addition to this systemic process, individuals with type 2 diabetes manifest local

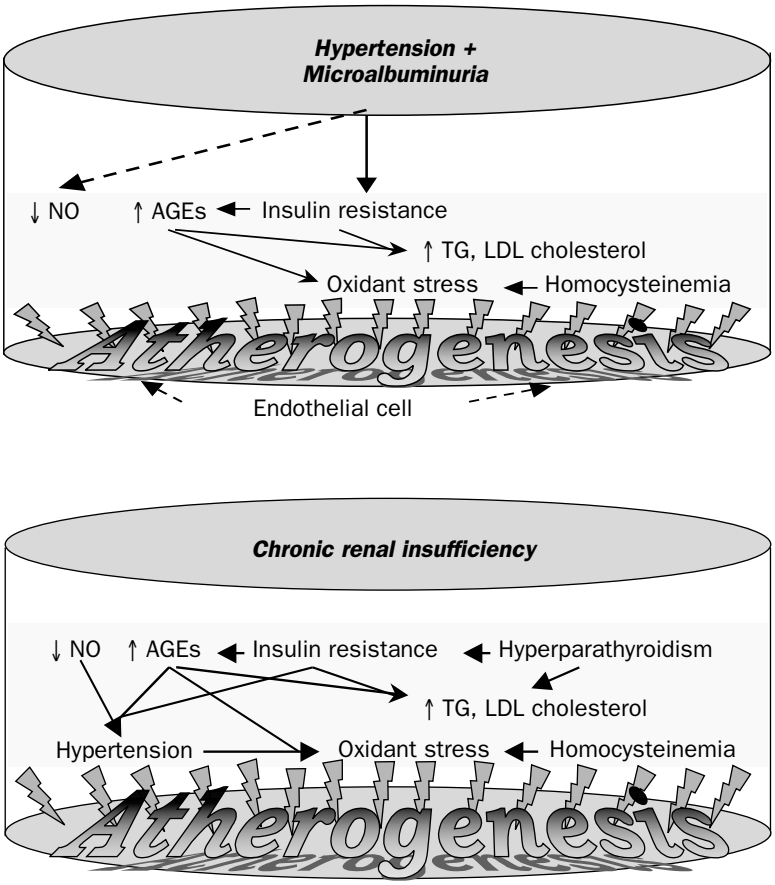

Fig. 2.1 Factors that interact to produce and worsen atherosclerosis in people with renal disease. NO, nitric oxide; AGEs, advanced glycosylation endproducts;

injury at the level of the glomerular membrane that eventually leads to worsening of generalized vascular leakiness through increased albumin production secondary to renal losses.[17,26] This is likely a spectrum of local to generalized vascular dysfunction. It is, however, difficult to predict whether people with type 2 diabetes will express one form of dysfunction versus the other. This may explain the different course of diabetic renal diseases between the two types of diabetes. People with either type of diabetes share early local structural changes in the kidney and vasculature, such as mesangial cellular hypertrophy and thickening of glomerular and tubular cells.

The single most significant determinant that initiates the development of diabetic vasculopathy as well as nephropathy is the resultant advanced glycosylation end-products and related moieties that are created by hyperglycemia.[8,25,26] Along with hyperglycemia, an increase in intraglomerular capillary pressure in the kidney and systemic hypertension are common in this setting. These further contribute to renal and vascular demise and act a bit like adding 'gasoline to an already burning fire'.

The role of albumin in the pathogenesis of vascular disease, however, may be quite different between the diabetic and nondiabetic hypertensive person. First, albumin is present in a glycated state in people with diabetes. The glycation of albumin transforms it into an antigenic-like molecule that initiates a variety of cellular and immune relations, such as activating polymorphonuclear leukocytes. Second, direct injury of the glomerular membrane by advanced glycosylation end-products in the person with diabetes, results in a loss of glomerular membrane size selectivity.[8] This loss at the level of the cell membrane, in turn, contributes to increased leakiness of the cellular membrane and, hence, increases albuminuria.

Additional studies provide evidence to support the concept that glycation of albumin generates a molecule that is associated with generation of reactive oxygen species.[25,27] These oxygen and hydroxyl radicals cause injury to epithelial cells (glomerular membrane), vascular smooth muscle cells, and mesangial cells. Advanced glycosylation end-products chelate with proteins on the glomerular membrane to neutralize the negative charge present. This induces a loss of charge sensitivity and results in an increased leakiness of both vascular and renal cell membranes in individuals with diabetes. In the kidney this process not only affects the glomerular membrane but also the mesangial matrix proteins.[28] These changes in membrane proteins subsequently contribute to increases in MA over time as well as development of nephropathy in people with diabetes.

3.1 Comorbid conditions associated with MA

MA reflects widespread vascular disease and is associated with the presence of unfavorable risk profile and target organ damage especially in people with diabetes (Box 2.1). This section will cover the major risk factors for CVD in the context of MA.

3.1.1 Hypertension

Several studies have shown that the amount of MA present in a given person is proportional to the severity of systolic, diastolic, and mean blood pressure (BP) elevation as measured by either clinic or 24 hour ambulatory BP monitoring.[29,30]

Box 2.1 Factors known to influence the development of microalbuminuria

1. Increased body mass index
2. Increased blood pressure (systolic, diastolic, mean)
3. Altered lipid levels
4. Insulin resistance (hyperinsulinemia)
5. Smoking
6. Salt sensitivity
7. Elderly
8. Endothelial dysfunction

This observation is further corroborated by the results of a clinical study of 787 untreated patients with MA and essential hypertension. This study agreed with the findings of previous investigators and showed that patients with MA had higher BP levels.[13] An interesting finding in this study was that even borderline levels of MA, those in the range of 28–30 mg/d, were associated with higher diastolic and mean BP readings than normoalbuminuric hypertensive subjects. Another Italian population study with 1567 participants revealed that there was an 18 mmHg higher systolic BP in the group of nondiabetic people with MA than in those without MA.[15] Moreover, the men with MA in this trial showed a higher relative risk of having an elevated systolic BP compared to the women with MA.

Circadian BP abnormalities, as seen in nocturnal non-dippers who are known to be at higher risk for CVD, have also been described in people with MA.[31,32] Moreover, the timing of when hypertension occurs or becomes pronounced in people with either type 1 or type 2 diabetes with MA is different.[17] Taken together, these studies all support the concept that the level of MA reflects the duration of blood pressure control as well as lipid abnormalities, two major components of the 'metabolic syndrome' (see below). Hence, the degree of MA may serve as an indicator of BP and lipid control as does the HbA_{1c} for glucose control.

In type 1 diabetes, hypertension is not a prominent clinical feature when MA is present but becomes significantly elevated (both systolic BP and diastolic BP) when overt nephropathy develops. In contrast, BP (mainly systolic) is already elevated when MA becomes manifest in type 2 diabetes. Thus, MA is not reflective of the duration of BP control in people with type 2 diabetes.

3.1.2 Hyperinsulinemia

Reaven and coworkers have evolved the term the 'metabolic syndrome' after they pointed out that insulin resistance and compensatory hyperinsulinemia form a common denominator between cardiovascular risk factors (hypertension, obesity, hyperinsulinemia, and glucose intolerance) and the development of CVD.[33] Recent data support the notion that MA may represent an independent manifestation, possibly constituting the fifth element, of this cardiometabolic syndrome.[34]

The defect in insulin action is linked to urinary albumin excretion in both diabetes and in people without diabetes but with hypertension. The mechanism of this link between insulin action and MA, however, remains largely speculative.[29] Three hypotheses have been proposed to link these processes: (1) the cosegregation theory; (2) the causal relationship theory; and (3) the final products of same pathogenetic factor theory. A discussion of each of these hypotheses is beyond the scope of this chapter; however, the reader is referred to Pontremoli (1996) for more information.[30] Briefly, all of these theories note that people with diabetes who have both hypertension and MA show a greater abnormality of glucose intolerance and lipid metabolism. Both hyperinsulinemia and MA have been shown to increase CVD risk in people who do not have diabetes. Moreover, simultaneous occurrence of the aforementioned conditions in nondiabetic subjects identifies a group of people with an increased risk for CVD occurrence.[35]

3.1.3 Endothelial dysfunction

The endothelium that is composed of endothelial cells produces components of the extracellular matrix and a variety of proteins that play an important role in vascular and renal function. An impairment of normal endothelial antithrombotic and vasodilatory properties is a main factor in atherogenesis.[26] Thus, it has been proposed that defective endothelial permeability may be the origin of MA in the general population, in those with essential hypertension, and among those with diabetes.

Although endothelial dysfunction is not a discrete entity, several experiments and observation suggest that endothelial dysfunction may represent a common pathway for macro- and microvascular diseases.[21] Endothelial dysfunction seems to play a key role in the (nondiabetic) glomerulosclerosis and atherosclerosis.

Increased permeability of the endothelium allows atherosclerotic lipoprotein particles (oxidized low-density lipoprotein and others) to penetrate into the large vessel wall and promote development of atherosclerotic plaques (Figure 2.1).[22,26] This increase in vascular permeability coupled with beta-receptor hyporesponsiveness causes impaired insulin action by preventing insulin-mediated skeletal muscle vasodilation that compromises insulin-induced glucose uptake.

MA is also associated with biochemical indices of endothelial dysfunction, such as increased von Willebrand factor (vWF) and increased platelet adhesiveness. There are two ways to assess endothelial dysfunction in humans; those that can either be measured by elevated endothelial dependent regulatory mediators or by those that can be impaired by endothelial-dependent vasodilation.[26]

Clausen et al. did an elegant study to demonstrate that there is endothelial-dependent vasodilation in subjects with MA. They compared the dilatory capacity of the brachial artery in 19 volunteers with MA but less than 150 μg/min and without clinically evident atherosclerotic disease to a control group of clinically healthy participants with normoalbuminuria (MA $< 6.6\mu$g/min). They found that flow-associated dilatation and nitroglycerine-induced dilation were significantly impaired in subjects with MA as compared to subjects with normoalbuminuria.[38]

In conclusion, endothelial dysfunction seems to play a key role in (nondiabetic) glomerulosclerosis, MA genesis, insulin sensitivity, and atherosclerosis. Relevance of these biochemical markers in the development of endothelial dysfunction requires further investigation. In this ultra-microstructural molecular science age, endothelial cell dysfunction should be considered as 'micro' target organ damage rather than a marker of target organ damage or merely associated with target organ damage.

3.1.4 Dyslipidemia

A number of studies have shown an increased association between patients with MA and abnormalities in serum lipoproteins. These lipid abnormalities include a low high-density lipoprotein (HDL) level as well as high values for low-density lipoprotein (LDL), total triglycerides, and increased levels of lipoprotein (a). In a cross-sectional analysis of 1160 type 1 diabetic subjects in the Diabetes Control and Complications Trial (DCCT), progressive increases in albuminuria were associated with elevations in proatherogenic intermediate-density lipoproteins and small dense LDL particles.[39] In addition, among both diabetic and nondiabetic patients with essential hypertension, MA is associated with increased serum total cholesterol and reduced serum HDL cholesterol.[13,15,29,40,41] The most consistent association between lipoprotein abnormalities and MA is with a low HDL. This suggests that clearance of LDL cholesterol may be as important as lower levels of this lipoprotein subfraction to avoid cellular injury. Thus, the apparent association between microalbuminuria and cardiovascular disease may be related to this adverse risk factor profile. Of note, however, is that a higher prevalence of MA was not observed in people with homozygous familial hypercholesterolemia who develop severe premature atherosclerosis and CVD.[42]

Clusters of other atherogenic risk factors with MA may suggest atherogenic vascular damage. In one report of 680 patients with or without diabetes, the presence of hyperhomocysteinemia, a known risk factor for atherosclerosis, was significantly associated with microalbuminuria, independent of type 2 diabetes or hypertension.[43] The association of MA with an abnormal prothrombotic profile may not be surprising since some conditions like endothelial dysfunction is hypothesized as a common contributing factor in the pathogenesis of both MA and atherosclerosis.[8,22] Dyslipidemia is evident at the onset of MA in people with diabetes and accelerated processes of nephropathy. Intervention to improve the abnormal lipid profiles delays or halts this atherosclerotic process.[44] Italian population data in 1567 participants showed a relative risk for the presence of MA in men and women of 2.25 and 2.10, respectively, in those with a 1.0 mmol/L

(40 mg/dL) higher plasma cholesterol level.[15] However, the Copenhagen Heart Study did not reach the same conclusion.[14]

4. CLINICAL APPLICATIONS

The presence of MA may have limited diagnostic value since it represents a very sensitive but disease-nonspecific nature of vascular permeability.[22] However, it has several applications in many other clinical situations. These applications include risk assessment, prognostic implications, disease severity evaluation, and can be a marker of target-organ damage from CVD (Box 2.2).

4.1 Vascular risk assessment

Since Yudkin et al.[1] reported that MA was a predictor of vascular disease in nondiabetic subjects, several population-based studies have shown an association between the increased urinary albumin excretion and several established adverse cardiovascular risk profiles, such as increased serum lipid levels, body mass index, uric acid, blood pressure, insulin levels, smoking, male gender, and left ventricular mass.[13,15,49,50] It is very well established that people with MA and type 2 diabetes have much higher rates of atherosclerotic vascular disease than those without MA.[17,51] Conversely, in populations of type 1 diabetes, MA heralds more progression to end-stage renal disease with less atherosclerotic heart disease.[4,7]

Screening for MA (spot urine for albumin/creatinine) is a relatively inexpensive procedure to identify the patients who have target organ injury, endothelial injury or CVD.[8,9,34] Routine assessment of MA in diabetic patients is well advised but in the general population, as in people with hypertension without diabetes, its utility is still debatable. In part, this is due to the relatively low prevalence of MA in the nondiabetic population and uncertainty of the significance of its modification in these groups.[24,34] However, targeting high-risk patients may be of greater value.

Box 2.2 Current clinical applications of microalbuminuria

1. Vascular risk assessment
2. Disease severity assessment
3. Prognostic implications
4. Marker of target-organ damage

4.2 Prognostic implications

If MA is associated with a higher risk of cardiovascular disease events and poorer prognostic value or at least hypertensive target organ damage or diabetic complications it should be more common in such subjects. Systematic overviews of the literature support the observation that MA is more common in such groups.[10,13,15,24] MA is a strong predictor of mortality (in both total and CVD-related) and CVD among people with type 1 diabetes, type 2 diabetes, and those with hypertension without diabetes.[5,6,23,35] Among over 9000 participants in the HOPE trial, the presence of microalbuminuria was associated with an increased relative risk of the primary aggregate end-point (myocardial infarction, stroke, or cardiovascular death) in those with and without diabetes (1.97 and 161, respectively).[52] In addition, a previous meta-analysis showed that the overall odds ratio is 2.4 for total mortality and 2.0 for CVD morbidity and mortality in type 2 diabetes.[10]

Other studies observed that subjects with MA and type 2 diabetes have approximately a total mortality of 8% and CVD mortality 4% annually. These values are up to four times higher compared to patients without MA.[3,17] Total and cardiovascular mortality was twice as high in people with type 1 diabetes who had MA compared to subjects without MA.[53]

MA is not only a concomitant indicator of early target-organ damage associated with CVD but was also associated with increased coronary morbidity and mortality in the nondiabetic population. Agrawal et al. reported a significantly higher prevalence of coronary

artery disease, stroke, and peripheral vascular disease among people with MA.[49] The prevalence of CVD was 31%, 6%, and 7%, respectively, in nondiabetic hypertensive subjects compared to 22%, 4%, and 5% without MA. However, others have contradicted this association of MA with CVD mortality and target organ damage. In a prospective follow-up study of over 300 treated hypertensive men extending for an average of 3.3 years, Agewall et al. showed no increased risk of CVD morbidity and mortality.[54] These investigators did find, however, that although target-organ damage was more common among patients with MA than those without it, macroalbuminuria and not MA showed prognostic value.

5. THERAPEUTIC INTERVENTION

The merits of normalizing or reducing the level of MA in diabetic subjects are unquestionable but there are still several unanswered questions in nondiabetic patients.[34,55] There are well established renoprotective and cardiovascular-protective effects of lowering MA in diabetic patients with antihypertensive regimens containing either angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), or non-dihydropyridine calcium channel blockers. Low protein diets and glycemic control also preserve renal function and prevent nephropathy in the very early stages of the renal disease but not once renal dysfunction is present (i.e. serum creatinine > 1.3 mg/dL).[56–61] The effects of glucose control and low protein diet are partially independent of blood pressure reduction.

Some studies have also demonstrated the efficacy of treatment by reversal or reduction of urinary albumin loss in normotensives as well as in controlled hypertensive diabetics with MA even without altering blood pressure or blood glucose control.[62] However, treatment of hypertension is very important for kidney function among diabetics. This is probably best exemplified by the UKPDS trial.[59] In this trial, blood pressure control yielded a relatively greater benefit over glucose control in those people with type 2 diabetes and nephropathy (Figure 2.2). The most effective and consistent results for preservation of renal function and reduction of cardiovascular events is treatment of blood pressure to levels below 130/80 mmHg in people with either renal insufficiency or diabetes.[62,63]

The bulk of evidence supports the concept that an ACEI or ARB should be part of the antihypertensive cocktail used to lower pressure to such levels in these populations. This primarily relates to the observations that ACEIs markedly attenuate mesangial matrix expansion in models of diabetes and prevent development of atherosclerosis in cholesterol-fed

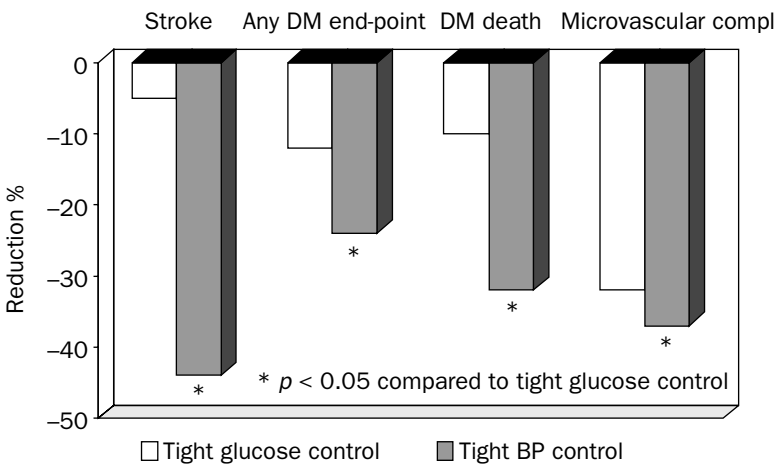

Fig. 2.2 Comparative Impact on cardiovascular risk reduction between tight glucose control (achieved HbA_{1c} ~ 7.8%) and tight blood pressure control (achieved BP ~ 144/82 mmHg). *Note*: Both groups had risk reduction from baseline. DM, diabetes mellitus; compl, complement.

rabbits. These agents also prevent glomerulosclerosis despite poor glucose control.[65] ACEIs attenuate the rise in MA as well as normalize kidney size and prevent renal death.[56,63,66] The benefits of an ACEI have been seen in both normotensive and hypertensive type 2 diabetics. In one study of normotensive type 2 diabetics, the plasma creatinine concentration and rate of protein excretion remained stable after treatment with an ACEI for five years.[56] By comparison, placebo-treated patients had a 13% rise in plasma creatinine concentration, a 2.5-fold increase in mean protein excretion (from 123 mg/d to 310 mg/d) and a higher rate of progression to overt proteinuria (42% vs 12% in the ACEI group) during this period. These differences were maintained at 7-year follow-up.[67] Another study noted similar findings in hypertensive type 2 diabetics with microalbuminuria. Over a 3 year period, administration of an ACEI was associated with less progression to overt proteinuria (7% vs 21% in a placebo-treated group) and a slower rate of rise in the plasma creatinine concentration.[68] Therefore, this class of antihypertensive agents has compelling indications to be used in the treatment of hypertension in people with diabetes and MA.[55]

A long-term randomized clinical trial was recently completed that evaluated the effect of ACEIs on subjects with diabetes. The substudy of the Heart Outcomes Prevention Evaluation (HOPE), the microalbuminuria, cardiovascular, and renal outcomes, MICRO-HOPE, looked at whether the addition of the ACEI ramipril to the current regimen of high-risk patients with diabetes mellitus can lower the risk of cardiovascular events and the risk of overt nephropathy in patients with MA. Out of 3577 participants with diabetes randomized to ramipril or placebo, 1140 of them were considered to have MA. Ramipril lowered the risk of the primary outcome (myocardial infarction, stroke, or cardiovascular death). Of 295 participants who developed an albumin/creatinine ratio of more than 36 mg/mmol, 117 (7%) participants on ramipril and 149 (8%) on placebo developed overt nephropathy [RR 24% (3–40); $p = 0.027$]. Ramipril lowered the risk of overt nephropathy in participants who did and did not have baseline MA and led to a lower albumin/creatinine ratio.[69]

ACEIs also may modify cardiovascular risk factors in other ways, specifically by improving dyslipidemia. In the study of normotensive type 2 diabetics noted above, the plasma total cholesterol concentration fell from 245 mg/dL to 232 mg/dL (6.4–6.0 mmol/L) after five years of ACE inhibition versus an increase from 246 mg/dL to 259 mg/dL (6.4–6.7 mmol/L) in the placebo group. There was a correlation between the increases in lipid levels and albuminuria in placebo-treated patients, suggesting that some factor lost in the urine may contribute to lipid metabolism.[70]

A separate issue is whether agents that inhibit the renin-angiotensin-aldosterone system (RAAS), such as ACEIs, ARBs, and beta-blockers, are effective as preventive therapy in normotensive, normoalbuminuric patients with type 2 diabetes. Based on data from clinical trials, they all appear to be effective, especially ACEIs and ARBs.[71–74] In the largest study of either ARBs or ACEIs, 590 such patients were randomly assigned to either irbesartan (150 mg/d or 300 mg/d) or placebo and then followed for two years. The primary end-point was the time from baseline to first detection of overt nephropathy (urine albumin excretion $> 200\ \mu g/min$ and at least a 30% increase from baseline on two consecutive visits). This end-point occurred with significantly higher frequency in the placebo group compared to irbesartan (14.9% vs 9.7% and 5.2% with 150 mg and 300 mg of irbesartan). This benefit was not related to significant differences in blood pressure.[74]

6. CONCLUSION

Over the last few decades, our understanding of the epidemiology, pathophysiology, and clinical significance of microalbuminuria (MA) among diabetics, essential hypertensives, and the general population has deepened. MA is associated with a higher prevalence of diabetic complications, metabolic and nonmetabolic risk factors, target organ damage, as well as adverse cardiovascular disease in both diabetic

Table 2.2 Summary of the current state of knowledge regarding microalbuminuria

Hypertension

1. Microalbuminuria is *NOT* predictive of hypertensive renal disease development.
2. There are data on the differential effects of antihypertensive drugs on microalbuminuria in the context of cardiovascular outcomes. ACEIs show greater cardiovascular risk reduction and are the best tolerated compared to other agents.
3. Microalbuminuria *IS* indicative of a history of poor blood pressure control and presence of left ventricular hypertrophy.

Diabetes

1. Microalbuminuria *IS* predictive of a higher probability of cardiovascular morbidity and mortality.
2. Microalbuminuria *IS* predictive of progressive renal disease.
3. Microalbuminuria reduction after achievement of BP goal (<130/80 mmHg) *IS* predictive of a good renal outcome.

and nondiabetic people with essential hypertension. Many studies indicate that routine measurement of MA and treatment should be employed in diabetic patients.[55] However, the long-term significance of MA and the efficacy of specific treatment in nondiabetic hypertensives as well as the general population need further investigation before routine measurement of MA can be advocated. Lastly, the choice between an ACEI and ARB in patients with MA is uncertain because both appear to be renoprotective,

Table 2.2 summarizes current knowledge about microalbuminuria at the time of writing.

REFERENCES

1. Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in non-diabetic subjects. Islington Diabetes Survey. Lancet 1988; **2**:530–533.
2. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Microalbuminuria as predictor of increased mortality in elderly people. BMJ 1990; **300**:297–300.
3. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984; **310**:356–360.
4. Viberti GC, Hill RD, Jarrett RJ, et al. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982; **1**:1430–1432.
5. Viberti GC, Yip-Messent J, Morocutti A. Diabetic nephropathy. Future avenue. Diabetes Care 1992; **15**:1216–1225.
6. Stephenson JM, Kenny S, Stevens LK, Fuller JH, Lee E. Proteinuria and mortality in diabetes: the WHO Multinational Study of Vascular Disease in Diabetes. Diabet Med 1995; **12**:149–155.
7. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T. The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. Diabet Med 1995; **12**:482–487.
8. Bakris GL. Microalbuminuria: prognostic implications. Curr Opin Nephrol Hypertens 1996; **5**:219–223.
9. Gosling P. Microalbuminuria and cardiovascular risk: a word of caution. J Hum Hypertens 1998; **12**:211–213.
10. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med 1997; **157**:1413–1418.
11. Bigazzi R, Bianchi S, Campese VM, Baldari G. Prevalence of microalbuminuria in a large population of patients with mild to moderate essential hypertension. Nephron 1992; **61**:94–97.
12. Mogensen CE, Poulsen PL. Epidemiology of microalbuminuria in diabetes and in the background population. Curr Opin Nephrol Hypertens 1994; **3**:248–256.

13. Pontremoli R, Sofia A, Ravera M et al. Prevalence and clinical correlates of microalbuminuria in essential hypertension: the MAGIC Study. Microalbuminuria: A Genoa Investigation on Complications. Hypertension 1997; **30**:1135–1143.
14. Jensen JS, Feldt-Rasmussen B, Borch-Johnsen K et al. Microalbuminuria and its relation to cardiovascular disease and risk factors. A population-based study of 1254 hypertensive individuals. J Hum Hypertens 1997; **11**:727–732.
15. Cirillo M, Senigalliesi L, Laurenzi M et al. Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. Arch Intern Med 1998; **158**:1933–1939.
16. Mimran A, Ribstein J, DuCailar G, Halimi JM. Albuminuria in normals and essential hypertension. J Diabetes Complications 1994; **8**:150–156.
17. Schmitz A. Microalbuminuria, blood pressure, metabolic control, and renal involvement: longitudinal studies in white non-insulin-dependent diabetic patients. Am J Hypertens 1997; **10**:189S–197S.
18. Bakris GL, Randall O, Rahman M et al. for the AASK Study Group. Associations between cardiovascular risk factors and glomerular filtration rate at baseline in The African American Study of Kidney Disease (AASK) Trial. J Am Soc Nephrol 1998; **9**:139.
19. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int 2001; **59**:260–269.
20. Tarif N, Bakris GL. Preservation of renal function: the spectrum of effects by calcium-channel blockers. Nephrol Dial Transplant 1997; **12**:2244–2250.
21. Gosling P. Microalbuminuria: a marker of systemic disease. Br J Hosp Med 1995; **54**:285–290.
22. Jensen JS. Renal and systemic transvascular albumin leakage in severe atherosclerosis. Arterioscler Thromb Vasc Biol 1995; **15**:1324–1329.
23. Panayiotou BN. Microalbuminuria: pathogenesis, prognosis and management. J Intern Med Res 1994; **22**:181–201.
24. Alzaid AA. Microalbuminuria in patients with NIDDM: an overview. Diabetes Care 1996; **19**:79–89.
25. Mogyorosi A, Ziyadeh FN. Update on pathogenesis, markers and management of diabetic nephropathy. Curr Opin Nephrol Hypertens 1996; **5**:243–253.
26. Stehouwer CD, Lambert J, Donker AJ, van Hinsbergh VW. Endothelial dysfunction and pathogenesis of diabetic angiopathy. Cardiovasc Res 1997; **34**:55–68.
27. Yaqoob M, McClelland P, Patrick AW et al. Evidence of oxidant injury and tubular damage in early diabetic nephropathy. QJM 1994; **87**:601–617.
28. Shikata K, Makino H, Sugimoto H et al. Localization of advanced glycation endproducts in the kidney of experimental diabetic rats. J Diabetes Complications 1995; **9**:269–271.
29. Bigazzi R, Bianchi S. Microalbuminuria as a marker of cardiovascular and renal disease in essential hypertension. Nephrol Dial Transplant 1995; **10**:10–14.
30. Pontremoli R. Microalbuminuria in essential hypertension – its relation to cardiovascular risk factors. Nephrol Dial Transplant 1996; **11**:2113–2115.
31. Bianchi S, Bigazzi R, Baldari G, Sgherri G, Campese VM. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. Am J Hypertens 1994; **7**:23–29.
32. Redon J, Liao Y, Lozano JV et al. Ambulatory blood pressure and microalbuminuria in essential hypertension: role of circadian variability. J Hypertens 1994; **12**:947–953.
33. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; **37**:1595–1607.
34. Lydakis C, Efstratopoulos A, Lip GY. Microalbuminuria in hypertension: is it up to measure? J Hum Hypertens 1997; **11**:695–697.
35. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. Hyperinsulinemic microalbuminuria. A new risk indicator for coronary heart disease. Circulation 1995; **91**:831–837.
36. Stehouwer CD, Nauta JJ, Zeldenrust GC et al. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet 1992; **340**:319–323.
37. Pedrinelli R, Giampietro O, Carmassi F et al. Microalbuminuria and endothelial dysfunction. Lancet 1994; **344**:14.
38. Clausen P, Jensen JS, Jensen G, Borch-Johnsen K, Feldt-Rasmussen B. Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. Circulation 2001; **103**:1869–1874.
39. Sibley SD, Hokanson JE, Steffes MW et al. Increased small dense LDL and intermediate-density lipoprotein with albuminuria in type 1 diabetes. Diabetes Care 1999; **22**:1165.

40. Groop PH, Viberti GC, Elliott TG et al. Lipoprotein(a) in type 1 diabetic patients with renal disease. Diabetes Med 1994; **11**:961–967.
41. Bianchi S, Bigazzi R, Campese VM. Microalbuminuria in essential hypertension: significance, pathophysiology, and therapeutic implications. Am J Kidney Dis 1999; **34**:973–995.
42. Zouvanis M, Raal FJ, Joffe BI, Seftel HC. Microalbuminuria is not associated with cardiovascular disease in patients with homozygous familial hypercholesterolaemia. Atherosclerosis 1995; **113**:289–292.
43. Hoogeveen EK, Kostense PJ, Jager A et al. Serum homocysteine level and protein intake are related to risk of microalbuminuria: the Hoorn Study. Kidney Int 1998; **54**:203–209.
44. Keane WF. Lipids and progressive renal failure. Wien Klin Wochenschr 1996; **108**:420–424.
45. Yudkin JS. Microalbuminuria: a genetic link between diabetes and cardiovascular disease? Ann Med 1992; **24**:517–522.
46. Dudley CR, Keavney B, Stratton IM, Turner RC, Ratcliffe PJ. U.K. Prospective Diabetes Study: XV.: Relationship of renin-angiotensin system gene polymorphisms with microalbuminuria in NIDDM. Kidney Int 1995; **48**:1907–1911.
47. Marre M, Bernadet P, Gallois Y et al. Relationships between angiotensin I converting enzyme gene polymorphism, plasma levels, and diabetic retinal and renal complications. Diabetes 1994; **43**:384–388.
48. Pontremoli R, Sofia A, Tirotta A et al. The deletion polymorphism of the angiotensin I converting enzyme gene is associated with target organ damage in essential hypertension. J Am Soc Nephrol 1996; **7**:2550–2558.
49. Agrawal B, Berger A, Wolf K, Luft FC. Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension. J Hypertens 1996; **14**:223–228.
50. Winocour PH, Harland JO, Millar JP, Laker MF, Alberti KG. Microalbuminuria and associated cardiovascular risk factors in the community. Atherosclerosis 1992; **93**:71–81.
51. Deckert T, Kofoed-Enevoldsen A, Norgaard K et al. Microalbuminuria. Implications for micro- and macrovascular disease. Diabetes Care 1992; **15**:1181–1191.
52. Gerstein HC, Mann JF, Yi Q et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001; **286**:421–426.
53. Messent JW, Elliott TG, Hill RD et al. Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: a twenty-three year follow-up study. Kidney Int 1992; **41**:836–839.
54. Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. Am J Cardiol 1997; **80**:164–169.
55. Bennett PH, Haffner S, Kasiske BL et al. Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. Am J Kidney Dis 1995; **25**:107–112.
56. Ravid M, Savin H, Jutrin I et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993; **118**:577–581.
57. Consensus development conference on the diagnosis and management of nephropathy in patients with diabetes mellitus. American Diabetes Association and the National Kidney Foundation. Diabetes Care 1994; **17**:1357–1361.
58. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; **329**:977–986.
59. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; **317**:703–713.
60. Bakris GL, Williams B. Angiotensin converting enzyme inhibitors and calcium antagonists alone or combined: does the progression of diabetic renal disease differ? J Hypertens Suppl 1995; **13**:S95–S101.
61. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; **329**:1456–1462.
62. Sano T, Kawamura T, Matsumae H et al. Effects of long-term enalapril treatment on persistent micro-albuminuria in well-controlled hypertensive and normotensive NIDDM patients. Diabetes Care 1994; **17**:420–424.

63. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2001; **24**(Suppl 1):S33–S43.
64. Bakris GL, Williams M, Dworkin L et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000; **36**:646–661.
65. Gaber L, Walton C, Brown S, Bakris G. Effects of different antihypertensive treatments on morphologic progression of diabetic nephropathy in uninephrectomized dogs. Kidney Int 1994; **46**:161–169.
66. Bakris GL, Slataper R, Vicknair N, Sadler R. ACE inhibitor mediated reductions in renal size and microalbuminuria in normotensive, diabetic subjects. J Diabetes Complications 1994; **8**:2–6.
67. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med 1996; **156**:286–289.
68. Lebovitz HE, Wiegmann TB, Cnaan A et al. Renal protective effects of enalapril in hypertensive NIDDM: role of baseline albuminuria. Kidney Int Suppl 1994; **45**:S150–S155.
69. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000; **355**:253–259.
70. Ravid M, Neumann L, Lishner M. Plasma lipids and the progression of nephropathy in diabetes mellitus type II: effect of ACE inhibitors. Kidney Int 1995; **47**:907–910.
71. Ravid M, Brosh D, Levi Z et al. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1998; **128**:982–988.
72. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998; **317**:713–720.
73. Mogensen CE, Neldam S, Tikkanen I et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000; **321**:1440–1444.
74. Parving HH, Lehnert H, Brochner-Mortensen J et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001; **345**:870–878.

3

Systolic blood pressure elevation in the older patient with kidney disease

Shakaib U Rehman and Jan N Basile

Introduction • The importance of systolic hypertension • isolated systolic hypertension (ISH) • Treatment of hypertension in the elderly is beneficial • The approach to the elderly hypertensive with renal insufficiency • Strategies for slowing progressive renal failure in patients with hypertension Selection of antihypertensive drugs • The j-curve phenomenon • Conclusion • References

1. INTRODUCTION

The elderly, defined as individuals 65 years of age and older, represent the most rapidly growing segment of the population. Accounting for 13% of the United States population in 1990, they are expected to account for 20% of the population by the year 2040. The percentage of those over age 85 is projected to reach 16 million over the same time period.[1] More than 50% of the population older than 60 years of age have hypertension, defined as a systolic blood pressure (SBP) $>$ 140 mmHg and a diastolic blood pressure (DBP) $>$ 90 mmHg, approaching 75% in those over age 75 (Table 3.1).[2] Of the 50 million hypertensives in the United States, only 1 out of every 4 have their blood pressure controlled (i.e. $<$ 140/90 mmHg). Control rates are even worse in the elderly[3] (Figure 3.1). A recent trial found that only 7% of hypertensive patients 65 years of age and older enrolled in a large Health Maintenance Organization were on treatment and had their blood pressure controlled to $<$ 140/90 mmHg.[4] Many cardiovascular risk factors including obesity, sedentary lifestyle, hyperlipidemia, diabetes, and left ventricular hypertrophy remain more common among the elderly with hypertension than among those of younger age. These are well known to the practicing physician. What is not as well appreciated is that over 6 million Americans are estimated to have abnormally high serum creatinine and are at risk for progressive nephropathy.[5] Current estimates predict as many as 600 000 Americans will develop end-stage renal disease (ESRD) by the year 2010.[6]

The kidney and hypertension are closely related. Up to 85% of patients with kidney disease have hypertension and hypertension contributes to the progressive decline in renal function. The elderly continue to have a much higher morbidity and mortality in those with underlying renal disease than their middle-aged and younger counterparts. In addition, analysis of recent trials suggest that renal functional decline significantly influences cardiovascular prognosis. A 24 hour urine sample should be collected in which both creatinine and albumin are detected to evaluate the adequacy of the collection. Nephropathy is diagnosed by either an

Table 3.1 Prevalence (%) of hypertension by age, gender, and ethnicity in the US, 1988–91: NHANES III

	Males			*Females*		
Age (yrs)	*African American*	*Causcasian*	*Mexican American*	*African American*	*Causcasian*	*Mexican American*
18–29	6.4	3.3	3.4	2.3	1.0	0.9
30–39	22.5	13.2	7.6	11.2	6.9	4.4
40–49	35.2	22.0	24.8	33.2	11.3	10.5
50–59	53.3	37.5	38.4	47.8	33.0	28.8
60–74	71.2	51.1	44.3	73.9	50.0	53.0

Hypertension was defined as an average systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg, and/or current antihypertensive drug treatment. NHANES, National Health and Nutrition Examination Service. Adapted from Whelton. Med Clin N Am 1997.[53]

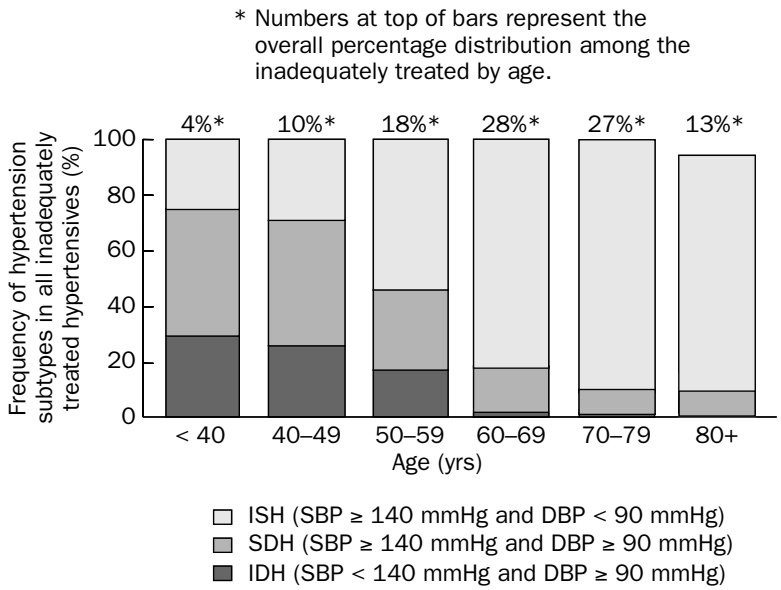

Fig. 3.1 Distribution of hypertension subtype in the inadequately treated population by age: NHANES III. Adapted from Franklin et al.[56]

increase in serum creatinine, or an increase in urinary albumin excretion. When the amount of protein excreted is greater than 30 mg but below 300 mg per gram of creatinine in a spot urine sample or 30–300 mg of albumin in a 24 hour sample, microalbuminuria is diagnosed. When there is more than 300 mg of albumin excreted, macroalbuminuria is detected (Table 3.2). These abnormalities in renal function, including the presence of microalbuminuria, are potent predictors for the future development of ESRD,[7] as well as cardiovascular disease and mortality in those with and without hypertension (Figures 3.2, 3.3, Box 3.1).[8,9] In the Heart Outcomes Prevention Evaluation (HOPE) trial, the development of renal insufficiency

Table 3.2 Testing for proteinuria/albuminuria

Category	*24 h collection (mg/24 h)*	*Timed collection (μg/min)*	*Spot collection (μg/mg creatinine)*
Normal	<30	<20	<30
Microalbuminuria	30–300	20–200	30–300
Clinical albuminuria	>300	>200	>300

Positive reaction requires 2 of 3 specimens collected within 3–6 month period to be abnormal. Exercise within 24 h, infection, fever, congestive heart failure (CHF), marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion. Adapted from American Diabetes Association (ADA). Diabetes Care 2000; **23**(Suppl 1):S32–S42.[54]

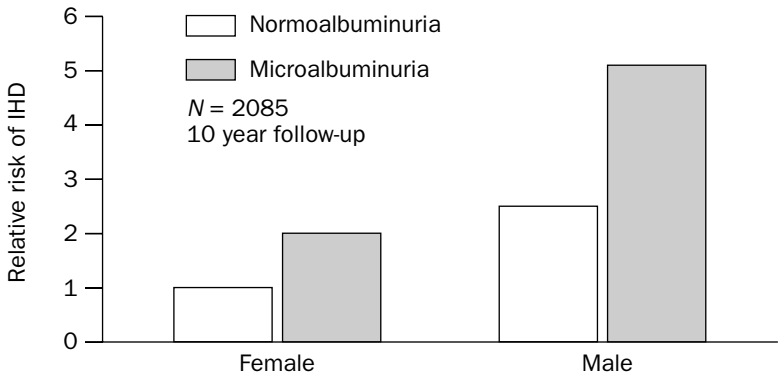

Fig. 3.2 Microalbuminuria and ischemic heart disease risk. Adapted from Borch-Johnsen et al.[57]

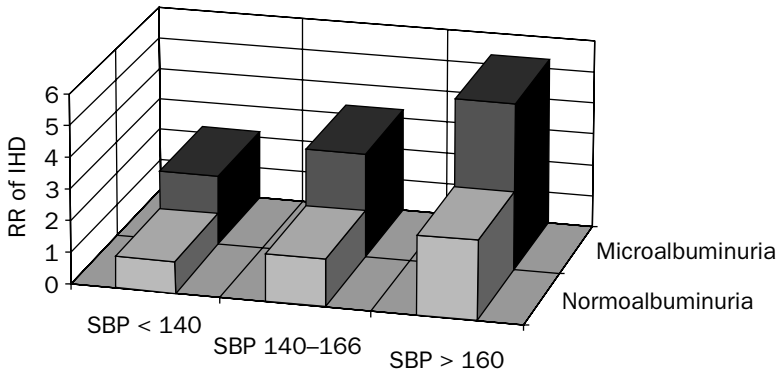

Fig. 3.3 Microalbuminuria and ischemic heart disease (IHD) risk. RR, relative risk; SBP, systolic blood pressure. *N* = 2085 10 yr follow-up. Adapted from Borch-Johnsen et al.[57]

was associated with a two fold greater risk of cardiovascular death, all cause mortality, and hospitalization for heart failure when compared to those with normal renal function (Figures 3.4 and 3.5).[8] Accordingly, antihypertensive therapy should aim to stabilize renal function and reduce proteinuria for renal as well as cardiovascular benefit.

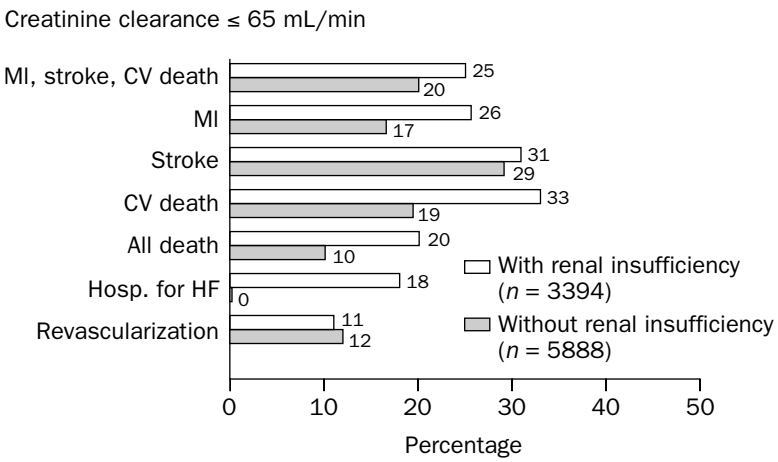

Fig. 3.4 HOPE: Risk reduction in patients with and without renal insufficiency. MI, myocardial infarction; CV, cardiovascular; HF, heart failure. Adapted from Mann et al.[8]

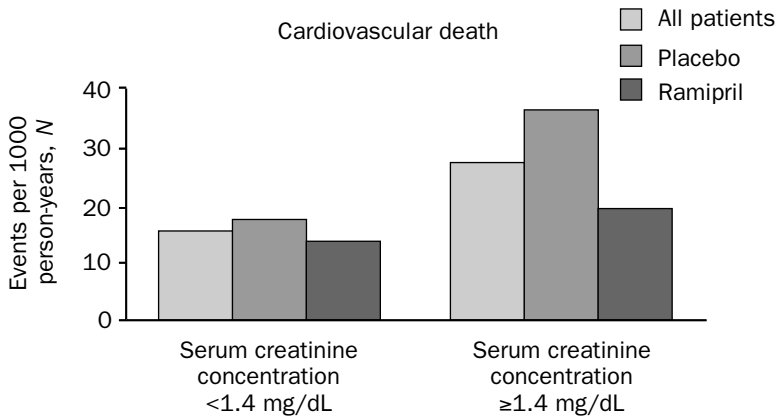

Fig. 3.5 Renal insufficiency is a determinant of cardiovascular outcomes: HOPE. Adapted from Mann et al.[8]

Box 3.1 Albuminuria

- Associated with myocardial infarction and stroke
- Reflects endothelial damage
- Part of the cardiometabolic syndrome
- Progression of micro- to macroalbuminuria predicts progression of renal disease

Microalbuminuria: 30–300 mg/day

2. THE IMPORTANCE OF SYSTOLIC HYPERTENSION

Hypertension in the elderly confers a three- to fourfold increased risk for cardiovascular disease when compared to younger individuals. It remains a significant risk factor for the progression to more severe hypertension. Hypertension also increases the risk for stroke, congestive heart failure, coronary heart disease, end-stage renal disease (ESRD), and overall mortality.[10]

In younger populations, elevations in DBP and SBP are both independently associated with an increased risk for cardiovascular and renal disease. Once we reach age fifty, however, elevation in SBP confers a greater risk for cardiovascular disease (Figures 3.6 and 3.7)[11–13] and remains a greater predictor of ESRD than DBP in younger men. In the Multiple Risk Factor Intervention Trial (MRFIT), men 35–57 years of age, showed a greater risk for ESRD for each increment of SBP when compared to DBP (Figure 3.8).[14] Elevation in SBP remains a potent predictor for the development of ESRD at all

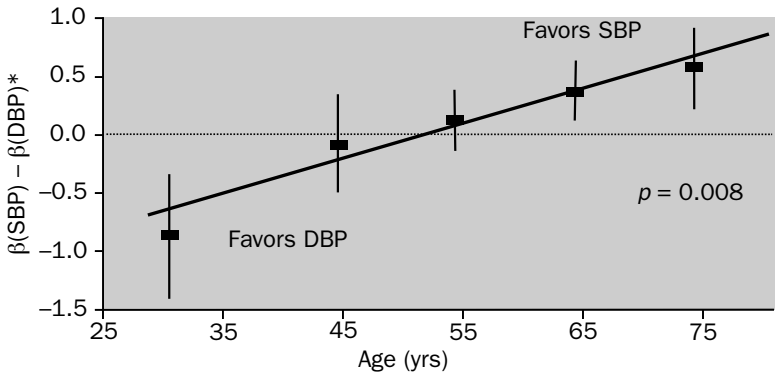

Fig. 3.6 Relative importance of DBP and SBP as predictors of CHD as a function of age. * The difference between SBP and DBP proportional hazard regression coefficients, i.e. β(SBP) – β(DBP), was estimated for each age group. DBP, diastolic blood pressure; SBP, systolic blood pressure; CHD, coronary heart disease. Adapted from Franklin et al.[58]

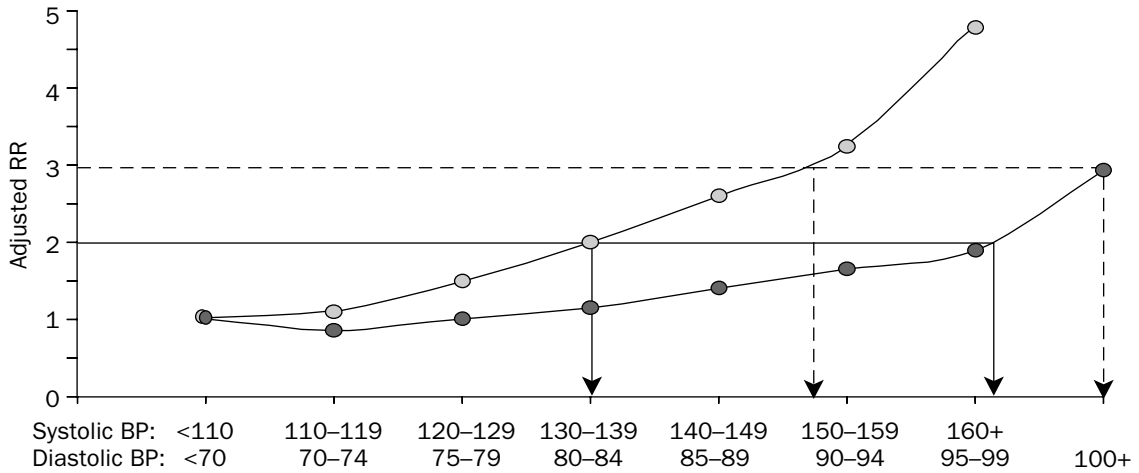

Fig. 3.7 Age-adjusted risk of cardiovascular mortality by SBP and DBP in men screened: MRFIT. Adapted from National High Blood Pressure Education Program Working Group.[59]

ages, although for the same degree of SBP elevation, it is associated with a threefold greater risk in African Americans when compared to whites (Figure 3.9).[15]

SBP is easier to determine and also allows more appropriate risk stratification than DBP. In a recent analysis of the Framingham Heart Study, knowing only the SBP correctly classified the stage of blood pressure elevation in 99% of adults over the age of 60. Knowing only the diastolic BP allowed 66% to be correctly classified.[16] As vascular compliance is reduced around age 60, SBP continues to be directly associated and DBP inversely associated with the risk of cardiovascular and renal disease. Accordingly, the pulse pressure (SBP-DBP) is a stronger predictor of overall risk than either SBP or DBP alone.[16,17] In a cross-sectional analysis of nondiabetic men and women 45–64 years of age, an increasing pulse pressure was a strong predictor for the development of microalbuminuria and reduction in creatinine clearance (Figure 3.10).[18]

A near linear relationship exists between achieved systolic blood pressure with antihypertensive therapy and yearly rate of loss of

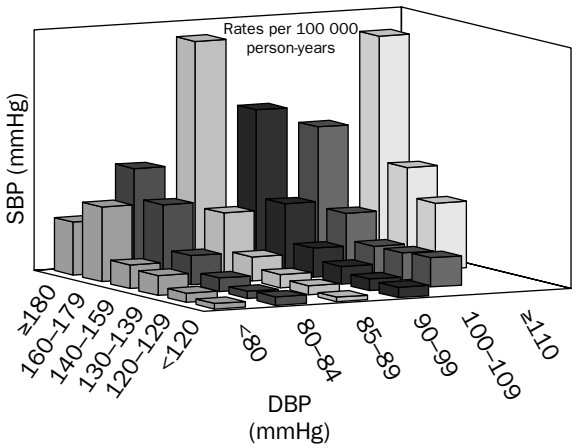

Fig. 3.8 Blood pressure and all cause ESRD rates: MRFIT trial. Adapted from Klag et al.[14]

renal function in diabetic and nondiabetics with renal disease. As the SBP approaches 130 mmHg, the GFR decline approaches that of normal aging (Figure 3.11).[19] Furthermore, the Modification of Diet in Renal Disease (MDRD) study demonstrated the importance of BP control to lower levels than normally achieved in those with renal disease and proteinuria. Subjects with more than 1 gram and especially those with 3 grams or more of protein excretion per day demonstrated substantial benefits when achieving a blood pressure of <125/75 (Figure 3.12).[20] Based on the above information, in an effort to reduce the risk of both cardiovascular and renal disease, the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of

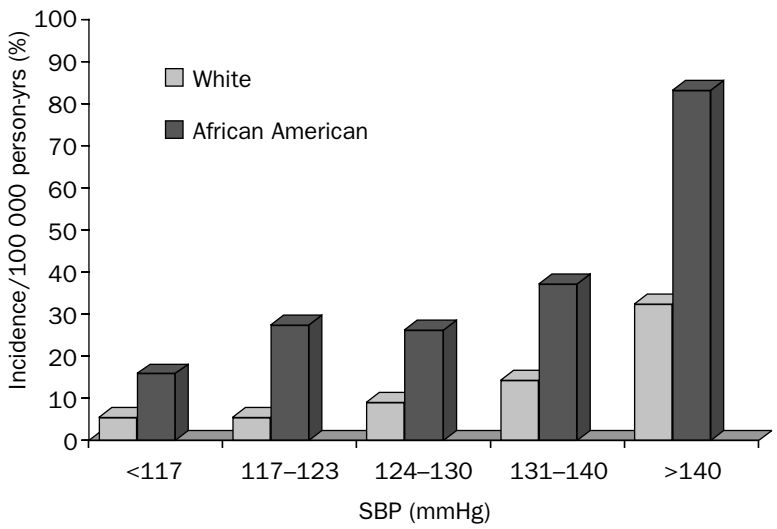

Fig. 3.9 Systolic blood pressure, ethnic group, and age-adjusted incidence of all cause renal disease. Adapted from Klag et al.[15]

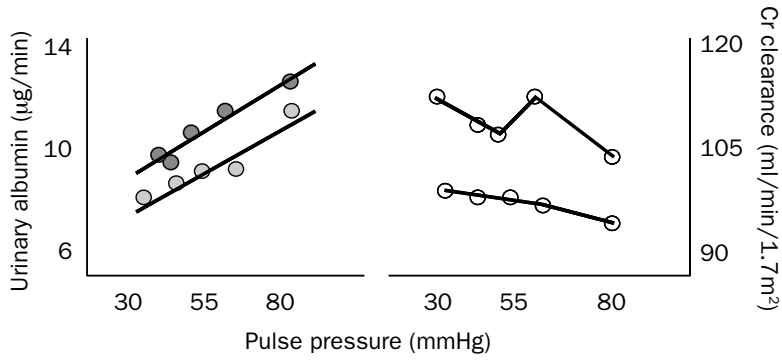

Fig. 3.10 Pulse pressure, microalbuminuria, and renal function. Cross-section of nondiabetic men (677) and women (890), aged 45–64. Adapted from Cirillo et al.[18]

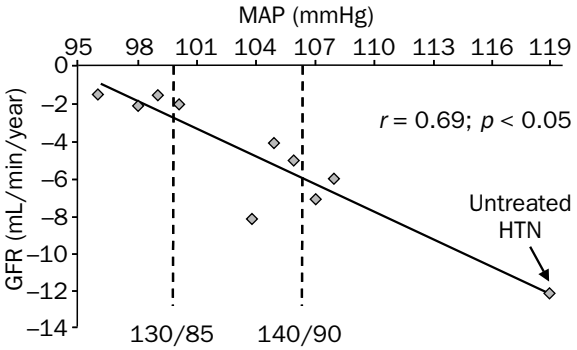

Fig. 3.11 Relationship between achieved blood pressure and GFR decline. Nine clinical trials of diabetic and nondiabetic nephropathy. GFR, glomerular filtration rate; HTN, hypertension. Adapted from Bakris et al[46] and Bakris.[19]

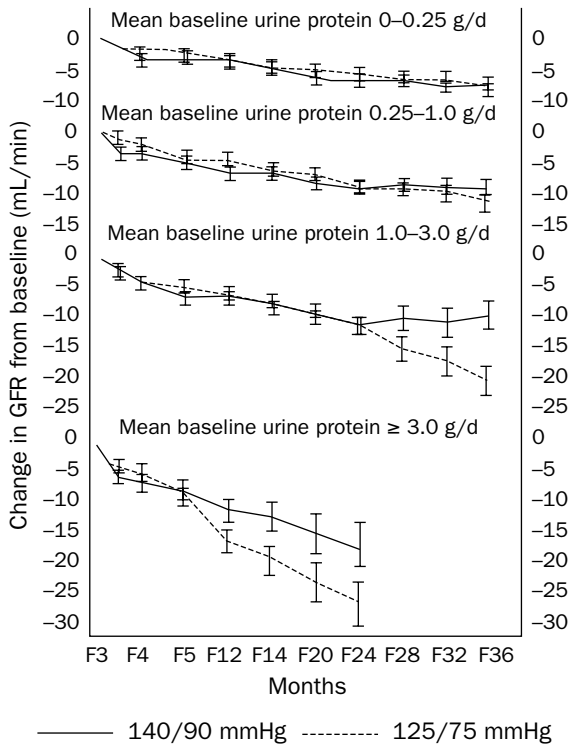

Fig. 3.12 Lower blood pressure goals preserve renal function in those with > 1 gram proteinuria: MDRD. Adapted from Klahr et al.[20]

Hypertension continues to recommend achieving a SBP of <140 mmHg as the minimum goal of therapy, to <130 mmHg in those with renal insufficiency.[3]

3. ISOLATED SYSTOLIC HYPERTENSION (ISH)

Isolated systolic hypertension (ISH) is defined as a SBP ≥ 140 mmHg and a DBP < 90 mmHg. It represents the most common form of hypertension in the older individual and its prevalence increases with age; two-thirds of individuals 60 years of age and older, and three-fourths of those over 75 years of age have ISH.[21] Stage 1 ISH (SBP 140–159 mmHg, DBP < 90 mmHg) is present in 27% of the population older than age 60, whereas stage 2–3 ISH (SBP ≥ 160 mmHg, DBP < 90 mmHg) affects 10% of this population (Figure 3.13).[22] The remainder has combined systolic/diastolic or rarely diastolic-only hypertension. Persons with stage 2–3 ISH are at greater risk of developing cardiovascular and renal disease than those with stage 1 ISH.

4. TREATMENT OF HYPERTENSION IN THE ELDERLY IS BENEFICIAL

Several large, prospective, clinical trials in the elderly were conducted in the 1980s. Involving subjects at least 60 years of age with elevations in DBP, treating to a goal of <90 mmHg lessened the risk of cardiovascular morbidity and mortality with an even greater benefit in reducing stroke and stroke-related mortality (Figure 3.14).[23–26]

Several more recent randomized controlled trials have confirmed the value of treating Stage 2 or greater ISH. In these trials, there was an associated 35–40% reduction in stroke, 50% reduction in heart failure, 30% reduction in coronary events, and a 10–15% reduction in mortality (Table 3.3). In order to achieve this benefit, SBP was reduced at least 20 mmHg from baseline and to <160 mmHg.

In the Systolic Hypertension in the Elderly Program (SHEP),[27] a diuretic beta-blocker based regimen reduced first stroke by 36% ($p = 0.0003$) and coronary events by 27% ($p<0.05$). Heart

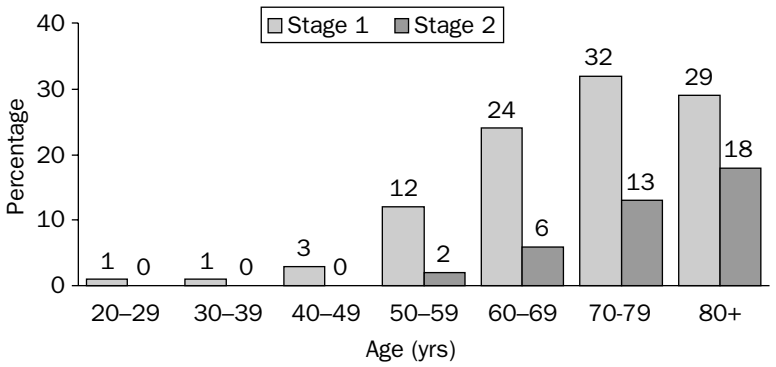

Fig. 3.13 Prevalence of systolic hypertension. Adapted from Cushman et al.[22]

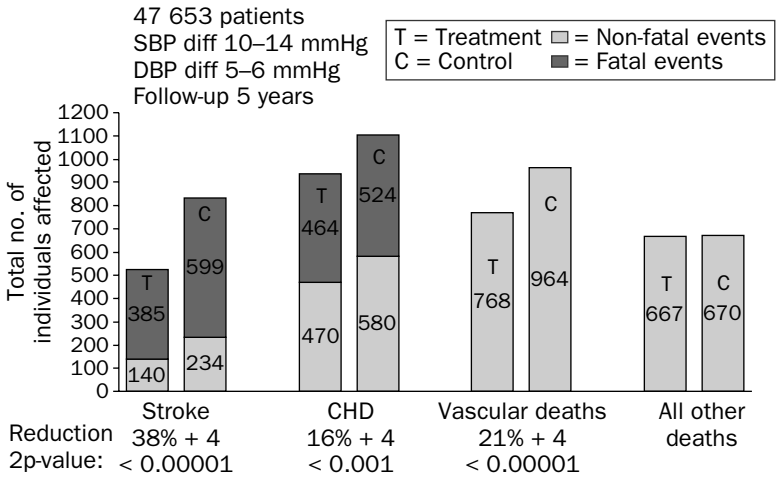

Fig. 3.14 All randomized trials of antihypertensive treatment. Adapted from MacMahon and Rodgers.[60]

failure was reduced by 49% ($p<0.001$) with an 81% reduction ($p = 0.002$) in participants with either a history of or evidence of a prior myocardial infarction on the electrocardiogram.[28] The reduction in cardiovascular events was present even in patients aged 80 years or older ($p<0.01$). In the 583 SHEP patients with type 2 diabetes, major cardiovascular disease events were reduced by 34%.[29] While those with the highest serum creatinine levels (1.4–2.4 mg/dL) had cardiovascular events reduced by 41% ($p = 0.02$), the benefit was lost if the potassium level was not kept above 3.5 mg/dL.[30,31]

In 1997, the Systolic Hypertension in Europe (Syst-Eur) Trial reported results from a randomized, placebo-controlled trial of 4695 Europeans 60 years of age or older with SBP 160–219 mmHg and DBP less than 95 mmHg (European definition of ISH). Patients were randomized to the moderately long-acting dihydropyridine calcium antagonist, nitrendipine, 10–40 mg/d, with the addition of enalapril 5–20 mg/d, and hydrochlorothiazide 12.5–25 mg/d, if necessary, or matching placebos. Active treatment reduced stroke by 42% ($p = 0.003$) and all cardiovascular events by 31% ($p<0.001$). Reductions in heart failure (29%) and myocardial infarction (30%) were not statistically significant.[32]

A meta-analysis of eight placebo-controlled trials in the elderly with ISH, which included a total of 15 693 patients 60 years of age and older and followed for an average of 3.8 years found that active treatment reduced coronary events by 23%, stroke by 30%, cardiovascular death by 18%, and total death by 13%.[33] Although most of these trials were performed in patients over 60 years of age, a recent meta-analysis supports the benefit of antihypertensive therapy even in

Table 3.3 Reduction in major cardovascular events in placebo-controlled trials of systolic hypertension

	SHEP	*STOP*	*MRC Elderly*		*Syst-Eur*
No.	4736	1627	4396		4695
Age (yrs)	≥ 60	70–84	65–74		≥ 60
BP (mmHg)	160–219/<90	180–230/90–120	160–209/<115		160–219/<95
Initial active drug	Chlorthalidone	HCTZ/amiloride or β-blocker	HCTZ/amiloride	Atenolol	Nitrendipine
Stroke reduction (%)	36 †	47 †	31 †	17	42 †
CHD reduction (%)	27 †	13	44 †	+1	30
HF reduction (%)	49 †	51 †	NR	NR	29
CVD reduction (%)	32 †	40 †	35 †	2	31 †
Mortality reduction (%)	13	43 †	19	+7	14

SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Older Persons with Hypertension; MRC Elderly, Medical Research Council trial of treatment of hypertension in older adults; Syst-Eur, Systolic Hypertension in Europe Study; BP blood pressure; HCTZ, hydrochlorothiazide; CHD, coronary heart disease; HF, heart failure; NR, not reported; CVD, cardiovascular disease.
† Significant reduction
Adapted from Cushman WC, Cardiol Clin 1999.[62]

patients over 80 years of age, as the oldest of the elderly seem to benefit the most from active treatment.[34]

5. THE APPROACH TO THE ELDERLY HYPERTENSIVE WITH RENAL INSUFFICIENCY

While several trials have included elderly individuals, no clinical trial has specifically studied renal function in the elderly as its primary end-point. In a *post-hoc* analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril, an angiotensin-converting enzyme inhibitor (ACEI), substantially reduced the risk of cardiovascular morbidity in patients with renal insufficiency (Box 3.1, Figure 3.4).[8] It was equally safe in those both with and without mild renal insufficiency and was stopped no more often than placebo in those with underlying renal disease.

The African-American Study of Kidney disease (AASK), the largest trial ever conducted in nondiabetic African Americans with hypertensive nephrosclerosis, enrolled patients up to age 80 with renal insufficiency and at least 300 mg of protein/d. Those treated with the ACEI, ramipril, had a 36% slower rate of renal disease progression and a 48% reduction for the triple-composite end-point of deterioration in renal function, ESRD, or death when compared to the group randomized to the calcium channel blocker, amlodipine. This occurred despite similar BP control in both groups (Figure 3.15).[35]

6. STRATEGIES FOR SLOWING PROGRESSIVE RENAL FAILURE IN PATIENTS WITH HYPERTENSION

Blood pressure impacts on the rate of progression of kidney disease with a nearly linear relationship between elevation in blood pressure and the rate of decline in renal function. Current recommendations state that BP

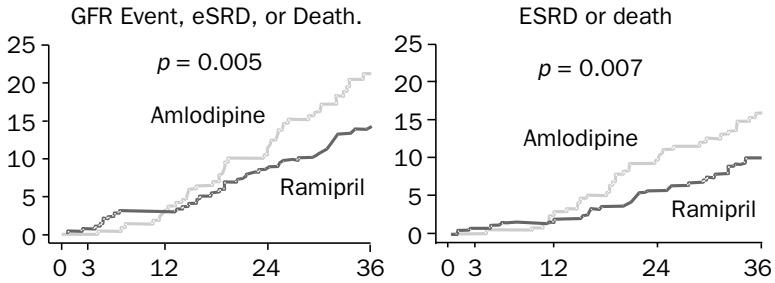

Fig. 3.15 Hypertension renal progression secondary end-point: AASK. Cumulative incidence of renal events and death (%). Adapted from Agodoa et al.[35]

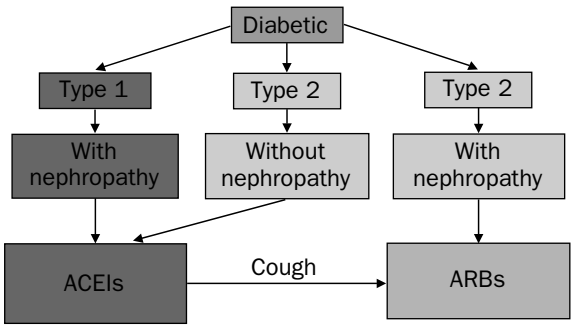

Fig. 3.16 ACEI vs ARB treatment approach. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.

should be reduced to <130/80 mmHg in those with diabetes, renal insufficiency, or heart failure (Box 3.2).[3] In experimental models of kidney disease, angiotensin II is an important mediator of glomerular hypertension. Evidence from clinical trials support recommendations to use ACEI or angiotensin II receptor blocking (ARB) therapy in patients with diabetic and nondiabetic renal disease. In those with type 1 diabetes and nephropathy, ACEI therapy improves renal outcome,[36] while in those with type 2 diabetes and nephropathy, ARB therapy has been shown to improve renal outcome (Figure 3.16).[37,38] In those with nondiabetic renal disease, an ACEI has more evidence for improving renal outcome (Table 3.4, Figure 3.17).[39,40] Regardless of the initial drug used, in those with diabetes or renal disease, multiple antihypertensive drugs will often be required to effectively control blood pressure to the recommended goals (Figure 3.18).

7. SELECTION OF ANTIHYPERTENSIVE DRUGS

Today, clinicians have many drug classes available to effectively lower blood pressure. In the elderly patient with renal disease, manifested by an elevation in serum creatinine or the presence of micro-or macroalbuminuria, ACEI and ARB therapy slow the progression of renal disease more effectively than other antihypertensive drug classes. Furthermore, in a recent prespecified subgroup analysis of the Losartan Intervention for Endpoint Reduction (LIFE) trial, losartan-based therapy was superior to beta-blocker based therapy in patients with ISH and left ventricular hypertrophy. Involving 14% of the entire cohort (mean age of 70 years) over 4.7 years of follow-up, a 25% reduction in the combined end-point of cardiovascular death, acute myocardial intarction, and stroke occurred in the once-daily losartan group. Of note, hydrochlorthiazide was added in almost all patients, including those on either losartan or atenolol.[41]

Accordingly, in the elderly patient with systolic hypertension at risk for or with underlying renal disease recommendations include (Figure 3.19):

1. An ACEI or ARB as first-line therapy. The addition of a thiazide diuretic will often be required. (Thiazide and not loop diuretics should be used as long as the serum creatinine is <1.8). Diuretics are particularly effective at enhancing the BP response of the elderly and African American to both ACEI and ARB therapy. Although often used together, it remains unclear if the combination of an ACEI and ARB provides additional long-term renoprotection. Without trial-based evidence to support the use of an ACEI and ARB together, a

Box 3.2 Strategies for slowing progressive renal failure in patients with hypertension

- BP should be reduced to 130/80 mmHg with whatever antihypertensive therapy is necessary to achieve the target BP.
- Antihypertensive drug recommendations for patients with hypertension and renal disease:
  – Most important: lower BP to goal.
  – Multiple antihypertensive drugs may be needed.
  – Impressive results have been achieved with ACE inhibitors (ACEIs) in type 1 diabetic nephropathy, proteinuria >1 g/d, and renal insufficiency and with angiotensin II receptor blockers (ARBs) in type 2 diabetics with nephropathy.

Adapted from JNC VI. Arch Intern Med 1997;[3]
Brenner et al. N Engl J Med 2001;[37]
Lewis et al, The Collaborative Study Group, N Engl J Med 2001.[38]

Table 3.4 ACEIs demonstrate renal benefits

Study population	*Drug*	*Dosage*	*Renal benefit*	*Study duration*
Nondiabetic				
AIPRI[55]	Benazepril	10 mg/d	$p < 0.001$	~3 yrs
REIN[7]	Ramipril	1.25–5 mg/d	$p < 0.004$	~3.5 yrs
AASK[35]	Ramipril	2.5–10 mg/d	$p < 0.005$	~3.5 yrs

ACEIs, angiotensin-converting enzyme inhibitors.

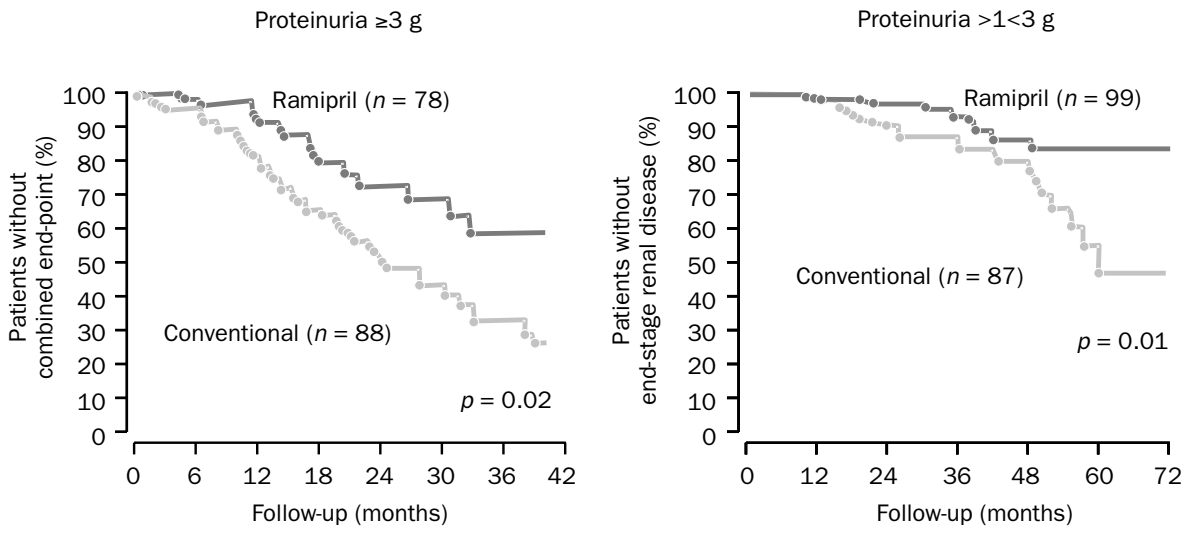

Fig. 3.17 Effect of ACEIs in nondiabetic nephropathy. ACEIs, angiotensin-converting enzyme inhibitors. GISEN Group. Adapted from Ruggenenti et al.[61]

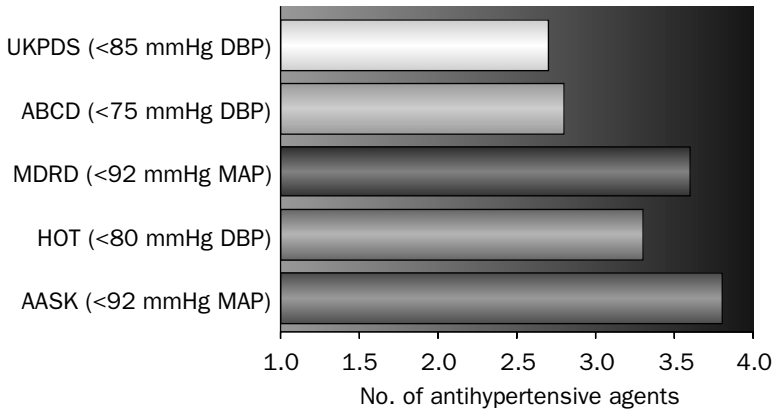

Fig. 3.18 Average number of antihypertensive agents needed to achieve DBP goals. DBP, diastolic blood pressure; MAP, mean arterial pressure. Adapted from Bakris et al.[46]

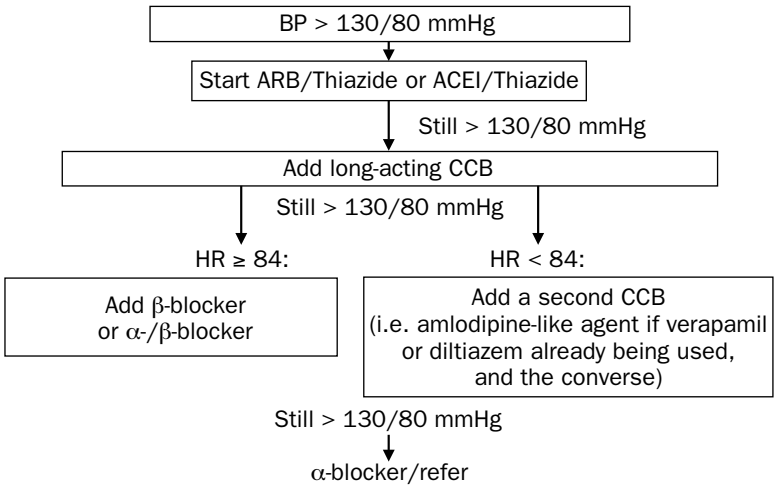

Fig. 3.19 Algorithm for elderly patients with nephropathy. Adapted from Bakris et al.[46]

diuretic should be added to the ACEI or ARB first, before the two are used together.

2. The addition of a calcium channel blocker (CCB) will often be required. The dihydropyridine (DHP) and non-dihydropyridine (non-DHP) CCBs have different effects on proteinuria, despite similar BP-lowering effects. Both non-DHP CCBs, verapamil or diltiazem, in combination with an ACEI, result in a twofold greater reduction in proteinuria in the diabetic with nephropathy than either agent alone.[42] Whether a long-acting CCB of the DHP class, which is evidence-based in ISH, or non-DHP class, which has greater antiproteinuric effects, should be used first, is controversial.[43] The beneficial effect of the non-DHP on protein excretion may be minimized when the DHP is combined with an ACEI.[44] If the goal is to minimize proteinuria, then a non-DHP CCB should be used. If protein excretion is normal and BP reduction is the goal, either CCB class will be effective.
3. Beta-blocking drugs lower BP. In the United Kingdom Prospective Diabetes Study (UKPDS), atenolol was found to slow the progression of proteinuria and renal disease in subjects with type 2 diabetes.[45] Preliminary reports from the AASK trial also suggest that the beta-blocker, metoprolol, was more effective than the DHP-CCB, amlodipine. As recently recommended by the National Kidney Foundation, based on observational data from the Framingham Heart Study, when the baseline heart rate is greater than 84 beats per minute, a beta-

blocker should be used before a CCB.[46] As the combination of a beta-blocker and a non-DHP CCB may produce excessive negative inotropic and chronotropic effects, they should be used together cautiously, if at all.

4. Alpha-blocker therapy can also be used as an additive agent in the elderly patient at risk for or with renal disease. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), there was a 25% greater cardiovascular event rate as well as a twofold greater risk of heart failure in the group randomized to doxazosin when compared to the diuretic chlorthalidone. Accordingly, alpha-blocker therapy should be used as an additive strategy and not as initial monotherapy in the treatment of the elderly hypertensive.[47] With the high prevalence of benign prostatic hypertrophy (BPH) in the elderly, however, the additive use of an alpha-blocker will often be required.

The recently completed ALLHAT trial, compared the ACEI lisinopril, the CCB amlodipine, and the diuretic chlorthalidone, in 42 448 high-risk hypertensives. It has been shown that all three drugs are equally effective in preventing cardiovascular mortality.[48] Secondary analysis of the effects of these initial strategies on renal function in the more than 15 000 diabetics, African Americans, and women is anxiously awaited.

8. THE J-CURVE PHENOMENON

There has been disagreement among clinicians on how low the diastolic blood pressure (DBP) can be lowered, especially in the elderly and those with pre-existing ischemic heart disease. Elderly hypertensives are thought to be at a higher risk of having a coronary event if DBP is lowered too far.[49,50]

Although achieving a BP of $< 140/90$ mmHg reduces the risk of vascular disease, the J-curve hypothesis proposes that an increased risk of cardiovascular events in elderly hypertensives results from lowering DBP below a certain critical value. Suggested only by observational and retrospective studies, prospective data validating this hypothesis is lacking. The Hypertension Optimal Treatment (HOT) trial is the only prospective study to test this hypothesis and neither proved nor disproved it.[51] A retrospective analysis of the SHEP trial, however, suggested that in the few patients whose DBP was lowered to <55 mmHg, there was no benefit in outcome when compared to the placebo group. Although there is no evidence that renal outcome is negatively affected, caution should be exercised when lowering DBP to less than 55 mmHg when treating older individuals with ISH.[52]

9. CONCLUSION

Hypertension is a major risk factor for the elderly and confers considerable morbidity and mortality. With the marked growth of the elderly in the United States and the world, practitioners will continue to see an expanding older hypertensive population. Treatment of hypertension substantially lowers cardiovascular events, including strokes, myocardial infarctions, heart failure, and cardiovascular and total mortality. These are well known to the practicing physician. What is not as well appreciated is that the elderly are at risk for progressive nephropathy and they continue to have a much higher morbidity and mortality when underlying renal disease is present than their middle-aged and younger counterparts. With over 6 million Americans estimated to have an abnormally high serum creatinine level, more and more Americans will develop end-stage renal disease by the year 2010.

Drug therapy should be considered if systolic blood pressure is persistently greater then 140 mmHg or diastolic blood pressure is 90 mmHg or higher. The starting dose of medication should be one-half that used in younger patients to account for slower metabolism in the elderly. In the elderly hypertensive patient with renal disease, which is often secondary to diabetes, ACEI or ARB therapy with or without a diuretic should be initially used. Blood pres-

sure should be reduced to <130/80 mmHg. There is, at present, no evidence to support the use of an ACEI + ARB together. A calcium channel blocker of either the non-DHP or DHP class can be used if the pulse is <84 whereas a beta-blocker can be used when the pulse is above that value. Alpha-blocker therapy can be used as additive therapy to further reduce blood pressure.

REFERENCES

1. Ooi HL, Cileman PL, Duggan J et al. Treatment of hypertension in the elderly. Curr Opin Nephrol Hypertens 1997; **7**:504–509.
2. Burt VL, Whelton P, Roccella E et al. Prevalence of hypertension in the U.S. adult population: Results from the third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995; **25**:305–313.
3. Chobanian AV, Bakris GL, Black HR et al. The seventh report of the National Committee on Prevention, Detection Evaluation and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003; **289**:2560–2571.
4. Barker WH, Mullooly JP, Linton LP. Trends in hypertension prevalence, treatment, and control in a well-defined older population. Hypertension 1998; **31**:552–559.
5. Jones CA, McQuillan GM, Kusek JW et al. Serum Creatinine Levels in the US Population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 1998; **32**:992–999.
6. US Renal Data System (USRDS). 2001 Annual Data Report. National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases 2001.
7. GISEN Group. Randomized placebo-controlled trial of ramipril on decline in glomerular filtration rate of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1997; **349**:1857–1863.
8. Mann JFE, Gerstein HC, Pogue J et al. on behalf of the HOPE Investigators. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomization trial. Ann Intern Med 2001; **134**:629–636.
9. Ruilope LM, Salvetti A, Jamerson K et al. Renal function and intensive lowering of blood pressure in the hypertensive subjects of the Hypertension Optimal Treatment (HOT) Study. J Am Soc Nephrol 2001; **12**:218–225.
10. Savage PJ, Pressel SL, Curb JD et al. for the SHEP Cooperative Research Group: Influence of long-term, low-dose diuretic-based antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension. Arch Intern Med 1998; **158**:741–751.
11. Applegate WB. The relative importance of focusing on elevations of systolic vs diastolic blood pressure. Arch Intern Med 1992; **152**:1969–1971.
12. Mann SJ. Systolic hypertension in the elderly. Arch Intern Med 1992; **152**:1977–1984.
13. Kannel WB, Dawber TR, McGee DL. Perspectives on systolic hypertension: The Framingham study. Circulation 1980; **61**:1179–1182.
14. Klag MJ, Whelton PK, Randall BL et al. Blood pressure and end-stage renal disease in men. N Engl J Med 1996; **334**:13–18.
15. Klag MJ, Whelton PK, Randall BL et al. End-stage renal disease in African-American and white men. 16-year MRFIT findings. JAMA 1997; **277**:1293–1298.
16. Lloyd-Jones DM, Evans JC, Larson MG et al. Differential impact of systolic and diastolic blood pressure level on JNC-VI staging. Hypertension 1999; **34**:381–385.
17. Franklin SS, Khan SA, Wong ND et al. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999; **100**:354–360.
18. Cirillo M et al. The GUBBIO Study Collaborative Research Group. Kidney Int 2000; **58**:1211–1218.
19. Bakris GL. Maximizing cardiorenal benefit in the management of hypertension: Achieving blood pressure goals. J Clin Hypertens 1999; **1**:141–148.
20. Klahr S, Levey AS, Beck GJ. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994; **330**:877–884.
21. Izzo J, Levy D, Black HR. Clinical Advisory Statement. Importance of systolic blood pressure in older Americans. Hypertension 2000; **35**:1021–1024.
22. Cushman WC, Crespo CJ, Roccella EJ. The prevalence of stage 1 and stage 2+ isolated systolic hypertension in the United States (1988–1994). Circulation 1998; **97**:825 (Abstract).

23. VA Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: III. Influence of age, diastolic pressure, and prior cardiovascular disease: Further analysis of side effects. Circulation 1972; **45**:991–1004.
24. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program: II. Mortality by race, sex and age. JAMA 1979; **242**:2572–2577.
25. The Management Committee, Australian National Blood Pressure Study. Treatment of mild hypertension in the elderly. Med J Aust 1981; **2**:398–402.
26. Amery A, Birkenhager W, Brixco P et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. Lancet 1985; **1**:1349–1354.
27. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991; **265**:3255–3264.
28. Kostis JB, Davis BR, Cutler JA et al. for the SHEP Cooperative Research Group: Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1997; **278**:212–216.
29. Curb JD, Pressel SL, Cutler JA et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. JAMA 1996; **276**:1886–1892.
30. Pahor M, Shorr RI, Somes GW et al. Diuretic-based treatment and cardiovascular events in patients with mild renal dysfunction enrolled in the Systolic Hypertension in the Elderly Program (SHEP). Arch Intern Med 1996; **158**:1340–1345.
31. Franse LV, Pahor M, Di Bari M et al. Hypokalemia associated with diuretic use and cardiovascular events in the systolic hypertension in the elderly program. Hypertension 2000; **35**:1025–1030.
32. Staessen JA, Fagard R, Thijs L et al. for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators: Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; **350**:757–764.
33. Staessen JA, Gasowski J, Wang JC et al. Risk of untreated and treated isolated systolic hypertension in the elderly: Meta-analysis of outcome trials. Lancet 2000; **355**:865–872.
34. Gueyffier F, Bulpitt C, Goissel JP et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomized controlled trials. INDANA Group. Lancet 1999; **353**:793–796.
35. Agodoa,L, Appel L, Bakris G et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis. A randomized controlled trial. JAMA 2001; **285**:2719–2728.
36. Lewis E, Hunsicker L, Bain R, Rohde R. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; **329**:1456–1462.
37. Brenner B, Cooper M, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes and mortality in patients with type 2 diabetes and nephropathy: Results of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study. N Engl J Med 2001; **345**:861–869.
38. Lewis E, Hunsicker L, Clark W, for The Collaborative Study Group: Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to Type 2 diabetes. N Engl J Med 2001; **345**:851–860.
39. GISEN Group: Randomized placebo-controlled trial of ramipril on decline in glomerular filtration rate of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1997; **349**: 1857–1863.
40. Jafar T, Schmid C, Landa M. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med 2001; **135**:73–87.
41. Kjeldsen S, Dahlof B, Devereux R et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: A Losartan Intervention For Endpoint Reduction (LIFE) Substudy. JAMA 2002; **288**:1491–1498.
42. Bakris GL, Mangrum A, Copley JB et al. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. Kidney Int 1998; **54**:1283–1289.
43. Maki DD, Ma JZ, Louis TA et al. Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med 1995; **155**:1073–1080.
44. Ruggenenti P, Perna A, Benini R et al. Effects of dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibition, and blood pressure control on chronic, non-diabetic

nephropathies. J Am Soc Nephrol 1998; **9**: 2096–2101.
45. Holman R, Turner R, Stratton I et al. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998; **317**: 713–720.
46. Bakris GL, Williams M, Dworkin L et al. Preserving renal function in adults with hypertension and diabetes: A consensus approach. Am J Kidney Dis 2000; **36**:646–661.
47. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2000; **283**:1967–1975.
48. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. JAMA 2002; **228**:2981–2997.
49. Fang J, Madhavan S, Cohen H, Alderman H. Isolated diastolic hypertension: A favorable finding among young and middle-aged hypertensive subjects. Hypertension 1995; **26**:377–382.
50. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. Lancet 1987; **1**:581–583.
51. Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. Lancet 1998; **351**:1755–1762.
52. Somes G, Pahor M, Shorr RI, Cushman WC, Applegate WB. The role of diastolic blood pressure when treating isolated systolic hypertension. Arch Intern Med 1999; **159**:2004–2009.
53. He J, Whelton PK. Epidemiology and prevention of hypertension. Med Clin N Am 1997; **81**: 1077–1097.
54. American Diabetes Association (ADA). Standards of medical care for patients with diabetes mellitus. Diabetes Care 2000; **23**(Suppl 1):S32–S42.
55. Maschio G, Alberti D, Janin G et al. Effect of angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Insufficiency Study Group. N Engl J Med 1996; **334**:939–945.
56. Franklin SS, Jacobs MJ, Wong ND et al. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. Hypertension 2001; **37**:869–874.
57. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S et al. Urinary albumin excretion. An independent predictor of ischemic heart disease. Arterioscler Thromb Vasc Biol 1999; **19**:1992–1997.
58. Franklin SS, Larson MG, Khan SA et al. Does the relation of blood pressure to coronary heart disease change with aging? The Framingham Heart Study. Circulation 2001; **103**:1245–1249.
59. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. Arch Intern Med 1993; **153**:186–208.
60. MacMahon S, Rodgers A. The effects of blood pressure reduction in older patients: an overview of five randomised controlled trials in elderly hypertensives. Clin Exp Hypertens 1993; **15**:967–978.
61. Ruggenenti P, Perna A, Gherardi G et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999; **354**:359–364.
62. Cushman WC. Hypertension in the elderly. Cardiol Clin 1999; **17**:79–92.

4

When to evaluate for secondary hypertension?

Sandra J Taler and Stephen C Textor

Introduction • Definition of secondary causes of hypertension • Historical features • Physical findings • Laboratory abnormalities • Clinical syndromes • How to evaluate for secondary hypertension • Summary • References

1. INTRODUCTION

Management of hypertension remains among the most common office problems confronting physicians. Recent trends emphasize the need to simplify diagnostic evaluation and to restrain the costs associated with laboratory investigation of high blood pressure. As a result, most hypertensive patients receive treatment without extensive investigation to exclude secondary causative factors. The purpose of this chapter is to examine when to expand a basic evaluation further to identify 'secondary causes' of hypertension. Most commonly this applies to patients who fail to reach goal blood pressures. Although secondary hypertension is infrequent, identifying a treatable secondary cause of hypertension can improve patients' lives enormously.

It is important to emphasize that most hypertensive patients have essential hypertension, even those with 'resistance' to antihypertensive drugs. Current guidelines from the Joint National Committee outline basic laboratory tests to be obtained before treatment. These include a complete blood count, serum sodium, potassium, creatinine, fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, urinalysis, and 12-lead electrocardiogram (Table 4.1).[1] These measures focus upon target-organ injury or associated comorbid disease risk, such as diabetes mellitus. To a limited extent, these data provide baseline information regarding potential hazards of drug therapy (e.g. hypokalemia and/or renal dysfunction). Secondary mechanisms of hypertension including renal artery stenosis or aldosterone excess may be suggested by these data, but require additional confirmation.

Results from prospective clinical trials indicate that many essential hypertensives require two or more medications to meet blood pressure (BP) goals.[2–5] Achieving goal BP remains difficult, particularly in older patients with systolic hypertension.[6] Failure to achieve goal levels despite intensified use of antihypertensive agents is among the most common reasons to consider further diagnostic studies looking for secondary hypertension. Historical, physical or biochemical clues to secondary hypertension may indicate a superimposed condition that has developed in a patient with pre-existing essential hypertension.

The objective of this chapter is to outline a rational plan for evaluation for secondary

Table 4.1 Initial diagnostic laboratory testing for hypertensive patients

Recommended tests	*Relevance to a secondary cause*
Complete blood count	Polycythemia
Blood chemistry	
Potassium	Hyperaldosteronism (primary or secondary)
Sodium	Hyperaldosteronism (primary or secondary)
Creatinine	Renal parenchymal disease, renovascular hypertension
Fasting glucose	
Total cholesterol	
HDL cholesterol	
Electrocardiogram	
Urinalysis	Renal parenchymal disease

Objective 1 is to identify known causes of high blood pressure. The other laboratory tests are directed to objective 2 (to assess the presence or absence of target-organ damage and cardiovascular disease, the extent of the disease and the response to therapy), and objective 3 (to identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment). HDL, high-density lipoprotein.

causes that may be contributing to hypertension in a given patient. Many of these considerations hinge upon elements of the history or clinical presentation during management of patients initially considered to have 'essential hypertension'. Decisions on extent of testing and indications for intervention are often complex and may justify referral to a clinical hypertension specialist. It is important to recognize that the outcome of additional diagnostic testing is seldom to cure hypertension. In truth, the detection and treatment of a secondary cause to achieve a complete cure is rare. Rather, testing is indicated to detect contributing causes that if corrected, will lead to improved responsiveness to prescribed antihypertensive medications. The overriding goal is to address the causative mechanisms as a means to achieve optimal treatment of hypertension and lower the morbidity and mortality of associated hypertensive disease.

2. DEFINITION OF SECONDARY CAUSES OF HYPERTENSION

Secondary hypertension is the presence of a specific condition in the patient that is known to cause hypertension. Major secondary causes of hypertension are listed in Table 4.2. A secondary factor may be the primary mechanism for an individual patient to develop hypertension. More often, it is a contributor to failure to achieve blood pressure control. Implicit in the investigation of such causes is the assumption that specific intervention will allow more effective antihypertensive therapy. Before starting an extensive set of studies, the clinician must consider the extent to which intervention applies to his/her patient. If an individual is not a candidate for renal revascularization or can be treated simply with antihypertensive medications, is identification of renovascular disease as a secondary cause necessary? If the answer is negative, one should consider foregoing complex diagnostic procedures.

This caveat applies especially to elderly or high-risk patients for whom one must weigh the risks of evaluation and intervention against the potential for benefit. Intensive evaluation may be more appropriate in the younger individual and for those with more severe BP elevation or atypical features, where there is greater likelihood of a secondary cause and greater potential to prevent long-term cardiovascular

Table 4.2 Major causes of secondary or treatment resistant hypertension

Abnormal renal function	Renal parenchymal disease[a] Ureteral or bladder outlet obstruction[a]
Abnormal renal perfusion	Renovascular hypertension[a] Aortic coarctation[a]
Hormonal disturbance	Primary aldosteronism[a] Hypo- or hyperthyroidism[a] Pheochromocytoma[a] Cushing's disease[a]
Drug interactions or drug effects	NSAIDs Sympathomimetic agents Exogenous corticosteroids Immunosuppressive agents Erythropoietin Antidepressants Oral contraceptives Licorice Illicit drugs (cocaine, amphetamines) Herbal preparations (ephedra)
Lifestyle factors	Obesity or weight gain Ethanol abuse Smoking High sodium intake
Other causes	Obstructive sleep apnea[a]

[a] Potentially reversible causes that if treated may lead to a cure of hypertension. NSAIDs, nonsteroidal antiinflammatory drugs.

complications regardless of age. For those with multiple medical problems or shortened expected survival, conservative management with medical therapy may be the optimal choice.

2.1 Historical features

Selected features of the medical history offer clues to the presence of a secondary cause (Box 4.1). Rarely are these factors diagnostic alone. Suggestive historical elements are reviewed below.

Population studies in Western countries indicate that systolic and diastolic BPs rise steadily from childhood to approximately age 50.

Box 4.1 Historical features suggesting secondary hypertension

- Young age at presentation
- Severity
- Treatment resistance
- Absent family history of hypertension
- Specific drug intolerance
- Exposure to NSAIDs or other agents
- Obstructive sleep apnea
- Spells of hypertension
- Surgical history or features of outflow obstruction

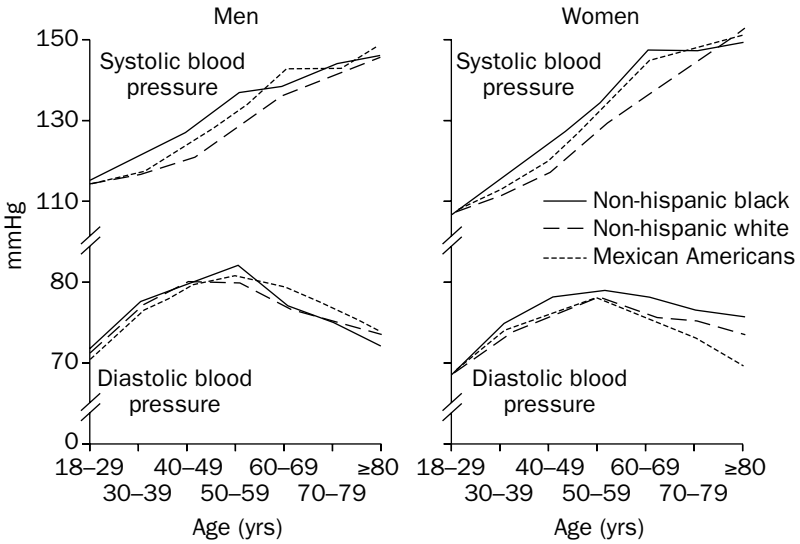

Fig. 4.1 Natural history of blood pressure with age. Population studies in Western cultures demonstrate that systolic blood pressure rises steadily with age. Diastolic blood pressure rises to approximately age 50 years then falls, resulting in a widened pulse pressure. Data from NHANES III.[7]

Thereafter, systolic pressures rise, but diastolic levels fall producing a widened 'pulse pressure' (Figure 4.1).[7] Since a BP of 140/90 mmHg or above has been chosen commonly to identify 'hypertension' in adults, the prevalence of this condition rises steadily with age. Hence, patients destined to develop essential hypertension typically present in the third and fourth decades. As systolic blood pressure continues to rise with age into the sixth decade and beyond, individuals may present with isolated systolic hypertension later in life. Deviation from this progression as when sustained hypertension is detected below age 30, should raise suspicion of a secondary factor. A *diagnosis of hypertension in a young person* merits more complete investigation for additional reasons. The long-term effects and costs of lifelong therapy are substantial even if BP is controlled. Moreover, early diagnosis of a secondary cause provides an opportunity for curative treatment that may be lost with maintenance of hypertension over a longer time.

The *severity* of hypertension and the need for multiple agents may suggest a secondary cause.[8–10] While the most common cause for malignant or accelerated hypertension is untreated essential hypertension, acceleration of previously well-controlled hypertension similarly suggests a superimposed secondary mechanism. Malignant hypertension is now uncommon, yet the associated morbidity and mortality of this condition argue for complete diagnostic evaluation to exclude secondary etiologies. Severe hypertension in pregnancy, particularly if associated with fetal loss, merits aggressive evaluation for secondary causes before further attempts at conception.

Resistant hypertension is defined as the failure to control BP to normal levels ($< 140/90$ mmHg) using three or more antihypertensive medications, including a diuretic at an effective dosage. Reported prevalence rates vary from $< 1\%$ at a hypertension job site clinic to 11–13% in hypertension referral clinics.[11,12] While resistant hypertension affects a minority of treated hypertensive patients, the resulting target organ damage causes a disproportionately high risk of cardiovascular events.[13] In a series of 104 carefully studied resistant hypertensives enrolled in an intensive drug titration trial, one or more secondary causes were identified in 35% (Table 4.3). While 13% had received treatment directed specifically at the secondary cause, they remained resistant to therapy. This underscores the challenge of distinguishing between the presence of an exacerbating condition and defining its contribution to resistance. Remarkably, success rates for intensive medication titration were similar for those in whom a secondary cause was identified yet not corrected and those without a

Table 4.3 Frequency of secondary causes in a referred population of resistant hypertensives

Cause	*Percentage*
Renal artery stenosis	13.5%
Primary aldosteronism	8%
Obstructive sleep apnea[a]	17%
One or more secondary causes	35%

[a] An additional 6% were suspected to have obstructive sleep apnea by symptoms but did not undergo testing.

secondary cause. Rates of secondary hypertension reported in other series range from 6% to 11%.[14,15] Suboptimal drug titration is identified as the most common cause for resistance in 57–61%.

Essential hypertension commonly occurs in family members, within and across generations. Genetic studies support a polygenic inheritance. Identification of hypertension in an individual *without a family history of hypertension* should raise suspicion that the individual may not have essential hypertension and a secondary cause may be present. The converse does not hold true, as patients with a family history of essential hypertension may have secondary hypertension or may develop a superimposed secondary cause.

Multiple drug intolerance is not related directly to the presence of secondary hypertension. It does, however, justify a more detailed evaluation and accentuates the potential benefit of detecting a treatable cause. With increased recognition that many hypertensives will require two or more antihypertensive agents to achieve control and the adoption of lower BP targets, the risk for side effects related to prescribed medications has increased. Some individuals label themselves intolerant to agents that were ineffective in past trials, perhaps as monotherapy. Use of these agents in combination or at different dosage may be effective and well tolerated. *Specific drug intolerance* may be a clue to a secondary cause. Examples include development of hypokalemia that is unexpected or more extreme than anticipated with regard to the prescribed regimen or the need for large amounts of potassium replacement to maintain normokalemia suggesting excessive aldosterone production. Other examples are included in Table 4.4.

Noncompliance whether related to drug intolerance, financial constraints or other causes, may result in untreated or inadequately treated hypertension and significant long-term morbidity including target organ damage and acceleration to more severe levels.[8] Noncompliance with prescribed medications can at times be addressed by simplifying the regimen or changing to agents better tolerated

Table 4.4 Drug responses as clues to secondary hypertension

Presentation	*Potential secondary cause*
Hypokalemia with use of low dose or potassium sparing diuretic	Mineralocorticoid excess – Primary hyperaldosteronism – Secondary hyperaldosteronism Corticosteroid excess
Worsening hypertension with introduction of beta blockade	Pheochromocytoma
Acute renal failure with introduction of ACEI or ARB	Renovascular hypertension

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

by the individual patient. When this approach is unsuccessful, more detailed evaluation may be justified, to exclude all potentially treatable contributing conditions.

Nonsteroidal antiinflammatory drugs (NSAIDs) and COX II inhibitors are among the most common causes for resistant hypertension. These agents reduce vasodilatory prostaglandins, particularly within the kidney and produce a rise in systemic resistance and impaired sodium excretion. Epidemiologic studies indicate that NSAID exposures cause enough BP elevation to trigger the initial diagnosis of hypertension in some individuals.[16] Use of NSAIDs during antihypertensive therapy can blunt the effectiveness of several classes of drugs and allow BP to rise substantially.[17,18]

A variety of vasoconstrictive sympathomimetic agents may cause hypertension. Among the most common of these are cold remedies containing agents, such as phenylephrine, pseudoephedrine and until recently, phenylpropanolamine. Numerous herbal preparations containing ephedra, Ma Hwong, St. John's wort or ginseng have been associated with worsened hypertension.[19] Confectioners' black licorice and chewing tobacco contain glycyrrhizic acid causing a clinical picture suggestive of primary aldosteronism. Other prescription medications may also aggravate hypertension. Specific offending agents include the immunosuppressive calcineurin inhibitors cyclosporine and tacrolimus, and erythropoietin. Some of the medications used for treatment of mood disorders or depression (e.g. methylphenidate, venlafaxine) can produce labile and sometimes severe rises in BP. Sibutramine, an anorexiant/stimulant used for weight reduction, may cause or exacerbate hypertension by inhibiting catecholamine reuptake.

Several recent series report an association between *obstructive sleep apnea* and hypertension.[20,21] One series of referred resistant hypertensive patients reported a prevalence of obstructive sleep apnea of 83%.[22] Obstructive sleep apnea at night was associated with daytime hypertension, even after adjusting for body mass index or measures of body fat distribution. While treatment of sleep apnea is indicated for several reasons, the long-term effect on BP levels is less clear. Central obesity, shirt collar size of 17 or higher, snoring, witnessed apnea, and daytime hypersomnolence are strong clinical features and support the need for additional testing.

While pheochromocytoma is rare, a history of *hypertensive spells* and lability should prompt screening to exclude this condition. Patients harboring catecholamine-secreting tumors may be asymptomatic but usually produce symptoms and sustained or paroxysmal hypertension. Spells can be variable in presentation but are often stereotypical in the individual.[23] For women presenting with hypertension during pregnancy, screening for pheochromocytoma should be done at the time of discovery of the hypertension since maternal and fetal morbidity and mortality are high if it is not diagnosed antepartum.

The combination of hypertension and urinary obstructive symptoms suggests *renal obstruction* as a possible cause. Renal insufficiency is likely to be evident. Obstructive uropathy may occur from pelvic malignancy, as a complication of pelvic surgery or more commonly due to benign prostatic hypertrophy.

2.2 Physical findings

The physical examination of a hypertensive individual should focus on the cardiovascular system, looking for evidence of target organ damage. Target organ effects disproportionate to the documented time of onset and severity are suggestive of secondary hypertension, potentially related to loss of normal circadian rhythm. A variety of other physical findings may help guide the search for secondary causes (Table 4.5). Detection of *café-au-lait* spots or neurofibromas supports investigation for pheochromocytoma even if symptoms are absent. Redundant pharyngeal soft tissues and large neck size support evaluation for obstructive sleep apnea, if coupled with appropriate clinical symptoms. Presence of a posterior cervical fat pad, moon facies, and pigmented striae suggest Cushing's disease. Thigh measurement of BP should be obtained and compared to

Table 4.5 Physical findings in secondary hypertension

Physical finding	*Potential secondary cause*
Café-au-lait spots or neurofibromas	Pheochromocytoma
Posterior cervical fat pad, moon facies, pigmented striae	Cushing's disease
Thigh BP lower than brachial BP	Coarctation, generalized atherosclerosis including renal artery stenosis
Goiter or thyroid nodule	Hyperthyroidism, hypothyroidism
Large neck size with narrow hypopharynx	Obstructive sleep apnea
Continuous murmur over posterior thorax	Coarctation
Abdominal systolic-diastolic bruit	Renal artery stenosis
Arterial bruits in multiple locations	Renal artery stenosis
Palpable enlarged kidneys	Polycystic kidney disease

brachial measurement in hypertensive individuals under age 30 years. Lower BP in the leg suggests coarctation and merits further imaging studies. Carotid or femoral bruits support renovascular disease, due to either fibromuscular dysplasia or atherosclerotic disease. A continuous abdominal systolic-diastolic bruit is highly suggestive of renovascular disease and imaging studies are indicated. While abdominal systolic bruits are not specific for renovascular disease, detection of an abdominal bruit increases the possibility of renal artery disease 5-fold.[24] Palpable enlarged kidneys suggest polycystic kidney disease. Systemic manifestations of diseases, such as systemic lupus erythematosus or scleroderma, may support secondary hypertension due to renal involvement.

These findings serve as clinical clues to suggest specific secondary causes for hypertension in an individual patient. In most instances, physical findings require confirmatory testing for firm diagnosis.

2.3 Laboratory abnormalities

Electrolyte abnormalities may provide helpful clues to secondary hypertension. Hypokalemia suggests hyperaldosteronism, either primary if the sodium level is higher than 140 mEq/L,[25] or secondary if less than 140 mEq/L. A normal serum potassium level in a situation where hyperkalemia is expected may also suggest aldosterone excess. Elevated serum creatinine or an abnormal urinalysis indicates renal parenchymal disease. Elevated hemoglobin suggests polycythemia, due to a primary disease process or excessive exogenous treatment using erythropoietin.

Disturbed circadian BP rhythm may be a clue to secondary hypertension. BP normally falls 10–20% at night, for both systolic and diastolic measurements. Loss of the normal nocturnal pressure fall poses additional cardiovascular risk and can occur with aging. An actual rise in nocturnal readings demonstrated by overnight ambulatory BP monitoring may occur in the setting of parenchymal renal disease, renovascular hypertension, hyperaldosteronism, or settings of corticosteroid excess (Figure 4.2). Sustained nocturnal elevations correlate with left ventricular hypertrophy, lacunar infarcts, and microalbuminuria.[26–28] Thus, identifying target organ injury out of proportion to office BPs can provide a

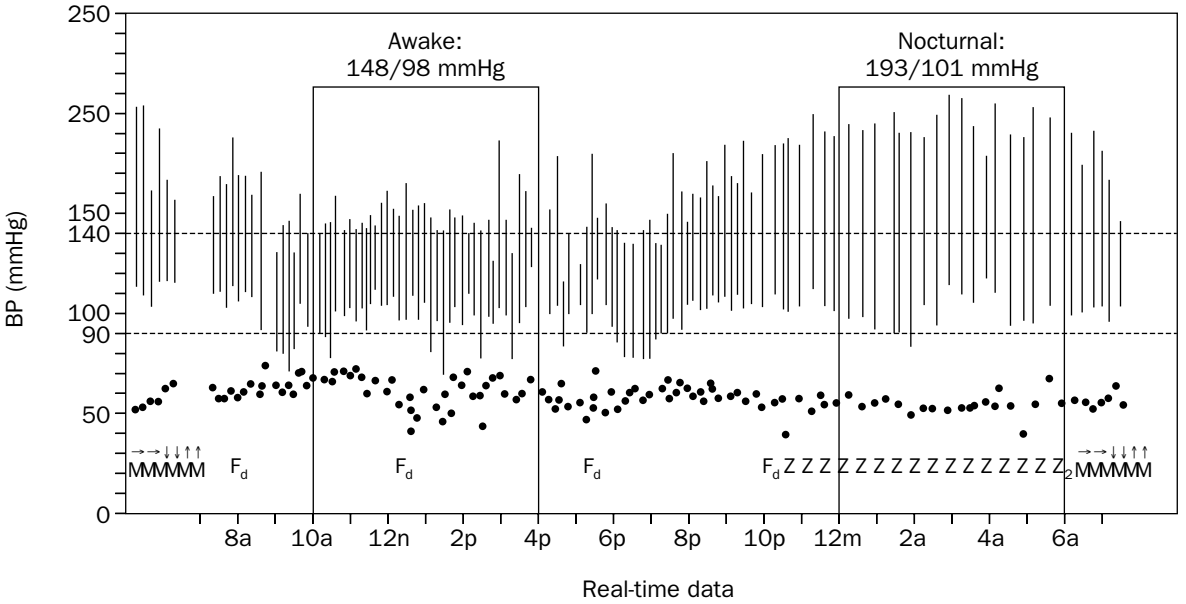

Fig. 4.2 Abnormal circadian blood pressure rhythm. 24-hour ambulatory blood pressure (BP) monitoring in a liver transplant recipient treated with cyclosporine-based immunosuppression. Although daytime pressures were elevated, the highest BPs occurred during the nocturnal period (marked by zzz). Nocturnal hypertension has been associated with rapid development of target-organ damage.

clue to nocturnal hypertension and may reflect a secondary cause.

Incidental findings discovered during investigation of other medical problems, may suggest secondary hypertension. Adrenal masses discovered on abdominal imaging studies are most likely nonfunctional incidentalomas, but biochemical testing is appropriate to exclude endocrine excess states. Detection of bilateral large cyst-filled kidneys suggests autosomal dominant polycystic kidney disease.

2.4 Clinical syndromes

Particular constellations of symptoms and findings suggest specific forms of secondary hypertension. As these conditions can be serious, even life-threatening, expanded diagnostic testing should be considered.

The onset of acute renal failure in the first 14–21 days after introduction or dose escalation of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) should raise immediate concern that occult renal artery stenosis, usually bilateral, is present. Classically, the urine sediment is bland, but may mimic acute tubular necrosis in some settings. A similar presentation may occur in the setting of a single functioning kidney with renal artery stenosis, either a native kidney or renal allograft. Small vessel disease may mimic this picture but is a diagnosis of exclusion. Rapid onset of pulmonary edema (termed 'flash pulmonary edema') also suggests tight bilateral renal artery stenosis.

Improvement of hypertension during pregnancy with exacerbation after delivery suggests primary aldosteronism, masked by progesterone blockade of aldosterone receptors during pregnancy.[29] Alternatively, primary aldosteronism may present as severe hypertension with hypokalemia during pregnancy requiring definitive treatment by laparoscopic adrenalectomy to preserve fetal survival.[30,31] The onset of new or severe hypertension during pregnancy should be fully evaluated postpartum, to prevent recurrence in a subsequent pregnancy.

Episodic hypertension with spells may suggest secondary hypertension and frequently prompts specialist referral. While pheochromo-

cytoma must be considered and excluded, it is uncommon. Here, clinical clues may help direct the investigation. BP lability may result from the use of short-acting agents, rapid drug metabolism, or the use of sympathomimetic agents. The addition of a NSAID or ingestion of large amounts of sodium may contribute to BP lability by volume expansion thereby interfering with the efficacy of prescribed antihypertensive agents. Unexpected or extreme hypokalemia may indicate primary or secondary aldosterone excess, renal potassium wasting or the surreptitious use of diuretic or laxative agents. The combination of hypertension, tachycardia, and anxiety symptoms suggests panic attacks or other psychiatric etiology.

2.5 How to evaluate for secondary hypertension

The primary goal of secondary evaluation is to tailor treatment to the specific underlying cause. The risks and expense of evaluation, particularly when considering invasive procedures must be weighed against the risks of overlooking a treatable cause. In general, the younger the patient and the more severe the hypertension, the more intensive should be the efforts to detect and treat a secondary cause. Even for an older individual, failure to achieve BP goals after attempts at medication titration, progressive decline in renal function or the progression of target organ damage during treatment merit reconsideration of a secondary cause.

An extensive discussion of the evaluation and treatment of renovascular hypertension is beyond the scope of this chapter and the reader is referred to more in-depth reviews.[32] It is important to distinguish renal parenchymal disease from renovascular hypertension. A general scheme for separating the two is shown in Figure 4.3. Parenchymal renal disease is characterized by an elevated serum creatinine and an active urinary sediment. Renal biopsy may be indicated to reach a definitive diagnosis. Renal outflow tract obstruction whether due to prostatic obstruction, a mass lesion or prior surgery should be considered and excluded before moving to invasive vascular testing or treatment. Normal renal imaging and a bland urinary sediment suggest renal vascular disease and coupled with drug-resistant hypertension merit further renal imaging as shown. Duplex ultrasonography (US) can provide images of the renal arteries and evaluate blood flow velocity and pressure waveforms, but there is a 10–20% failure rate due to operator inexperience, obese body habitus or intestinal gas.[33] Gadolinium-enhanced magnetic resonance (MR) angiography and computed tomographic (CT) angiography provide excellent views of the renal circulation and aorta, but are less reliable for visualizing distal segments and small accessory arteries.[34,35] Gadolinium is not

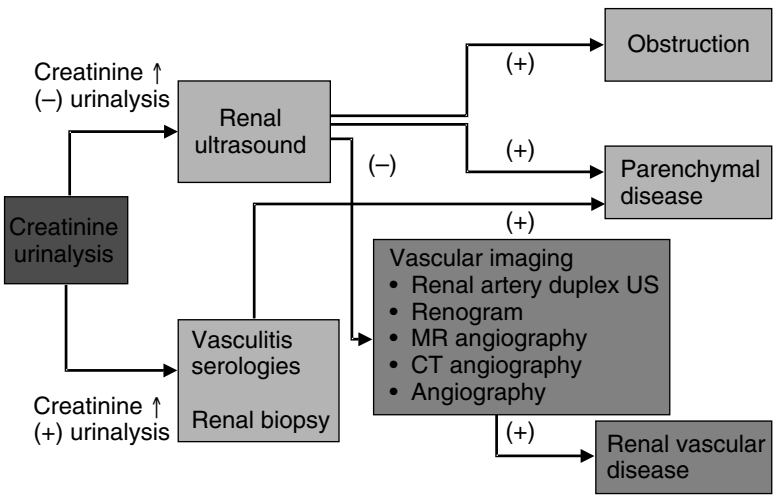

Fig. 4.3 Evaluation algorithm for renal and renovascular hypertension. Parenchymal renal disease is characterized by an elevated serum creatinine and abnormal urinalysis. Normal renal parenchymal imaging and a bland urinalysis suggest renal vascular disease and further vascular imaging is indicated.

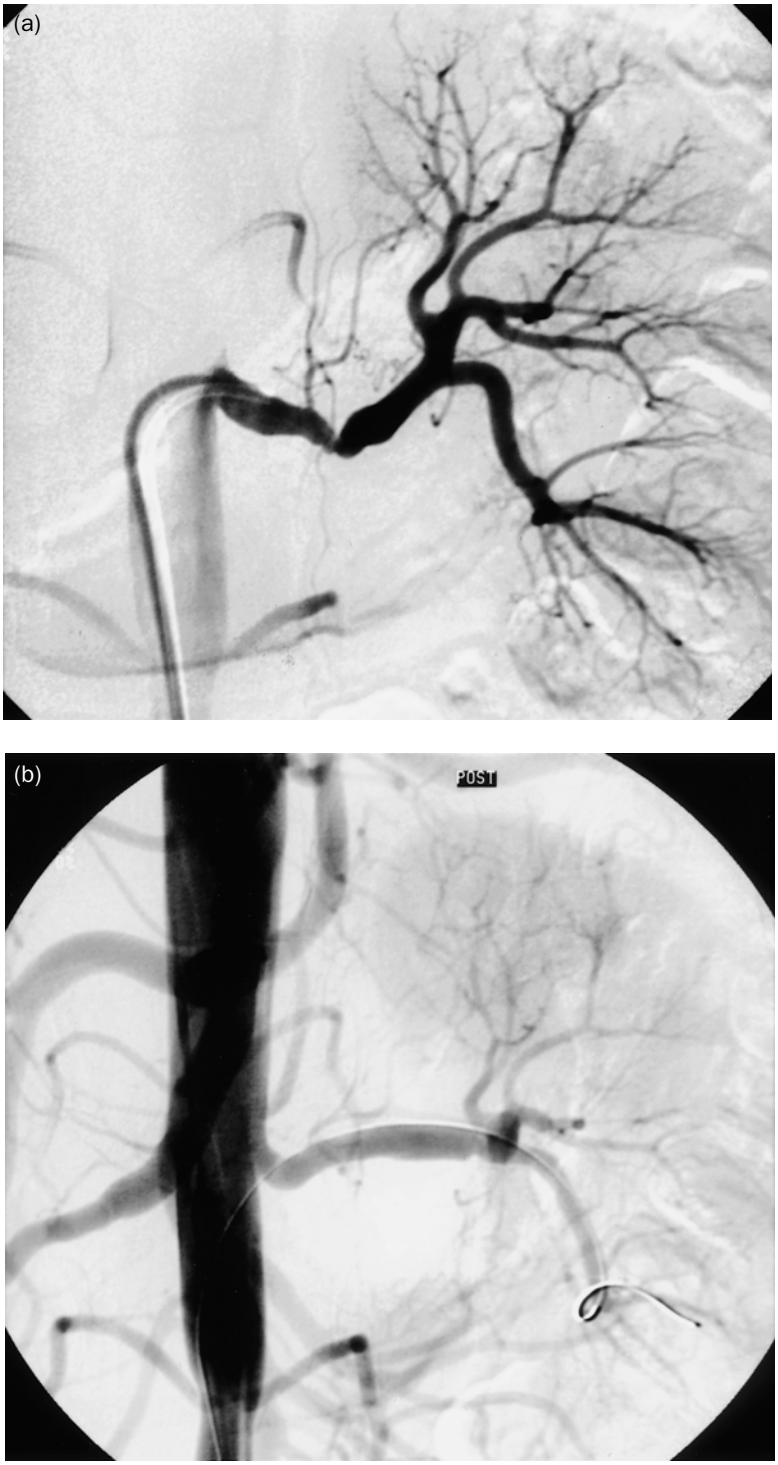

Fig. 4.4 Renovascular hypertension due to atherosclerotic renal artery disease. (a) shows a mid-left renal artery stenosis causing renovascular hypertension. After angioplasty and stent placement (b), there was improvement in the angiographic appearance and lessened severity although persistence of hypertension.

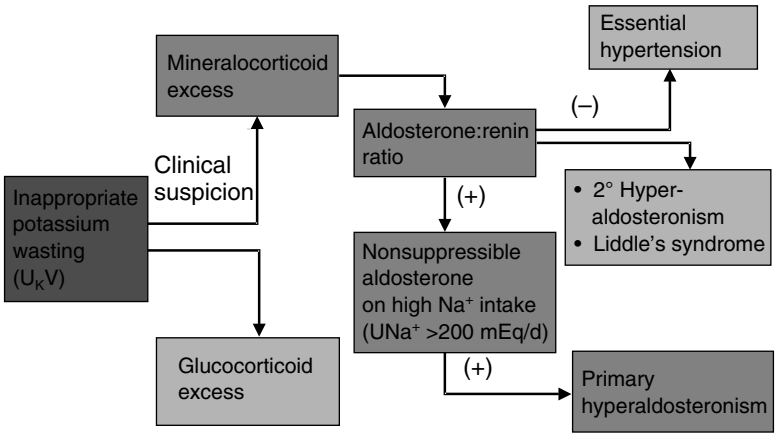

Fig. 4.5 Evaluation algorithm for inappropriate potassium wasting. Once glucocorticoid excess is excluded, the aldosterone: renin ratio can be used to screen for primary aldosteronism. Diagnosis is based on failure to suppress aldosterone in a high sodium state.

nephrotoxic and is useful for patients with renal insufficiency. Significant renal vascular disease causing resistant hypertension or progressive renal dysfunction can respond well to renal revascularization and for selected individuals, percutaneous or surgical intervention may salvage critical renal function (Figure 4.4).

Clinical features should guide the investigation of hormonal secondary causes (Figures 4.5 and 4.6). Classification of hypokalemia by mineralocorticoid or glucocorticoid excess will focus the diagnostic pathways and limit the complexity of additional testing (Figure 4.5). Hyperaldosteronism is increasingly recognized as a correctable cause for resistant hypertension, thus screening should be considered early in the evaluation. The initial evaluation is directed to demonstration of inappropriate aldosterone production, using the aldosterone to renin ratio or salt loading. Once the diagnosis of primary hyperaldosteronism is confirmed, imaging studies are indicated to discriminate adenomatous disease from adrenal hyperplasia (Figure 4.6). Invasive adrenal vein sampling may be necessary to predict the success of adrenalectomy in individual cases.[36]

Table 4.6 outlines preliminary testing to evaluate for less common secondary causes. The early presentation for many of these conditions may be subtle and screening is appropriate even without florid clinical manifestations. The pursuit of secondary causes is intended to ensure treatment of all potential contributing mechanisms so that BP control is achieved. At each step in the pathway, the clinician must decide whether the condition has been sufficiently excluded in the individual patient or whether more definitive testing is indicated.

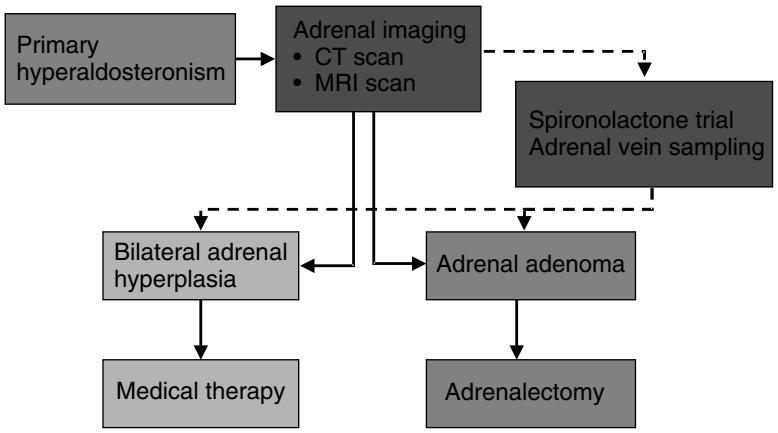

Fig. 4.6 Evaluation algorithm for primary hyperaldosteronism. Once the diagnosis of primary aldosteronism is confirmed, adrenal imaging is utilized to detect an adenomatous lesion. Many aldosterone-producing adenomas are quite small and adrenal vein sampling may be necessary to confirm autonomous unilateral aldosterone production before adrenalectomy.

Table 4.6 Laboratory evaluation for other secondary causes

Secondary cause	*Tests*
Pheochromocytoma	Plasma metanephrines 24 h urine metanephrines and fractionated catecholamines Adrenal computed tomography MIBG scanning
Cushing's disease	24 h urine cortisol 1 mg overnight dexamethasone suppression test Adrenal computed tomography
Hyper- or hypothyroidism	Thyroid-stimulating hormone Total and free thyroxine, triiodothyronine Thyroid ultrasound
Hyperparathyroidism	Serum calcium, phosphorus, parathyroid hormone
Obstructive sleep apnea	Overnight oximetry Polysomnography with CPAP trial
Coarctation	Simultaneous arm and thigh BP measurement Aortogram/Magnetic resonance angiography/ Ultrasound

MIBG, Iodine 123 meta-iodobenzylguanidine scintigraphy; CPAP, continuous positive airway pressure.

Such decisions should consider patient age, long-term prognosis, risks of leaving the condition undetected, risks of intervention, and adequacy of medical therapy.

SUMMARY

Blood pressure levels in Western countries rise with advancing age, thus the prevalence of hypertension increases. Typically, there is a gradual pressure rise which responds to treatment with one or a combination of two or three antihypertensive medications to achieve normal BP levels. When the clinical picture departs from this pattern, there is greater likelihood that a secondary cause may be present.

In this chapter we have attempted to highlight those clinical clues and settings that suggest a higher likelihood of secondary hypertension and the rationale and goals of further diagnostic evaluation. The majority of those with resistant hypertension have underlying essential hypertension and most can be controlled with an appropriate multi-agent regimen. Failure to achieve BP targets on escalating doses and numbers of medications signals the need to pursue secondary causes. Indeed, many individuals with secondary hypertension can also be treated to goal BP levels using medical therapy. Identification of secondary hypertension may result in improved blood pressure responsiveness to fewer medications and achievement of goal pressure levels.

While it is important to remember that the identification and treatment of a secondary cause rarely results in a cure of the hypertension, these situations can be most rewarding to the clinician and the patient when they occur. For those settings where intervention is indicated, we have outlined general strategies for evaluation. Such interventions even when indicated do carry some risk, especially in elderly individuals with multiple comorbidities. Due to

the complexity of individual circumstances, it may be appropriate to consult a clinical hypertension specialist to weigh the risks and benefits, and direct further intervention.

REFERENCES

1. JNC Committee (JNC VI). The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. Arch Intern Med 1997; **157**:2413–2446.
2. Staessen JA, Fagard R, Thijs L et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; **350**:757–764.
3. Hansson L, Lindholm LH, Ekborn T et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999; **354**: 1751–1756.
4. ALLHAT. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. JAMA 2000; **283**:1967–1975.
5. Estacio R, Jeffers BW, Hiatt WR et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. N Engl J Med 1998; **338**:645–652.
6. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2001; **345**:479–486.
7. Burt VL, Whelton P, Rocella EJ et al. Prevalence of hypertension in the US adult population: Results from the third National Health and Nutrition Examination Survey (NHANES), 1988–1991. Hypertension 1995; **25**:305–313.
8. Shea S, Misra D, Ehrlich MH, Field L, Francis CK. Predisposing factors for severe, uncontrolled hypertension in an inner-city minority population. N Eng J Med 1992; **327**:776–781.
9. Davis BA, Crook JE, Vestal RE, Oates JA. Prevalence of renovascular hypertension in patients with grade III or IV hypertensive retinopathy. N Engl J Med 1979; **301**:1273–1276.
10. Vaughan CJ, Delanty N. Hypertensive emergencies. Lancet 2000; **356**:411–417.
11. Alderman MH, Budner N, Cohen H, Lamport B, Ooi WL. Prevalence of drug resistant hypertension. Hypertension 1988; **11**(3, Suppl II):II71–II75.
12. Swales JD, Bing RF, Heagerty AM et al. Treatment of refractory hypertension. Lancet 1982; **1**:894–896.
13. McAlister FA, Lewanczuk RZ, Teo KK. Resistant hypertension: an overview. Can J Cardiol 1996; **12**:822–828.
14. Garg JP, Folker AC, Munavvar I, Elliott WJ, Black H. Resistant hypertension revisited. Am J Hypertens 2002; **15**(4, Part 2 of 2);25A (Abstract).
15. Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. Arch Intern Med 1991; **151**:1786–1792.
16. Gurwitz JH, Avorn J, Bohn RL et al. Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. JAMA 1994; **272**:781–786.
17. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal and anti-inflammatory drugs on blood pressure. Arch Intern Med 1993; **153**:477–484.
18. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994; **121**:289–300.
19. Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. Ann Intern Med 2002; **136**:42–53.
20. Nieto FJ, Young TB, Lind BK et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA 2000; **283**:1829–1836.
21. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Eng J Med 2000; **342**:1378–1384.
22. Logan AG, Perlikowski SM, Mente A et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 2001; **19**:2271–2277.
23. Young WF. Pheochromocytoma and primary aldosteronism: Diagnostic approaches. Endocrinol Metab Clin North Am 1997; **26**:801–827.
24. Krijnen P, van Jaarsveld BC, Steyerberg EW et al. A Clinical Prediction Rule for renal artery stenosis. Ann Intern Med 1998; **129**:705–711.
25. Gregoire JR. Adjustment of the osmostat in primary aldosteronism. Mayo Clin Proc 1994; **69**:1108–1110.
26. Verdecchia P, Schillaci G, Guerrieri M et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990; **81**:528–536.

27. Shimada K, Kawamoto A, Matsubayashi K et al. Diurnal blood pressure variations and silent cerebrovascular damage in elderly patients with hypertension. J Hypertens 1992; **10**:875–878.
28. Bianchi S, Bigazzi R, Baldari G, Sgherri G, Campese V. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. Am J Hypertens 1994; **7**:23–29.
29. Murakami T, Ogura EW, Tanaka Y, Yamamoto M. High blood pressure lowered by pregnancy. Lancet 2000; **356**:1980.
30. Solomon CG, Thiet M, Moore F Jr, Seely EW. Primary hyperaldosteronism in pregnancy. A case report. J Reprod Med 1996; **41**:255–258.
31. Aboud E, de Swiet M, Gordon H. Primary aldosteronism in pregnancy—should it be treated surgically? Ir J Med Sci 1995; **164**:279–280.
32. Safian RD, Textor SC. Medical Progress: Renal Artery Stenosis. N Engl J Med 2001; **344**:431–442.
33. Hansen KJ, Tribble RW, Reavis SW et al. Renal duplex sonography: evaluation of clinical utility. J Vasc Surg 1990; **12**:227–236.
34. Gedroyc WMW, Neerhut P, Negus R et al. Magnetic resonance angiography of renal artery stenosis. Clin Radiol 1995; **50**:436–439.
35. Elkohen M, Beregi JP, Deklunder G. A prospective study of helical computed tomography angiography versus angiography for the detection of renal artery stenoses in hypertensive patients. J Hypertens 1996; **14**:525–528.
36. Young WF. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev 1999; **7**:207–214.

Section II

Treatment – General

5

Approaches to maximize cardiovascular risk reduction in kidney disease

Sheldon Tobe

Definition of kidney disease • Epidemiology of cardiovascular disease in those with renal disease • What are the risk factors for cardiovascular events in patients with renal disease? • Hypertension • Diabetes • Dyslipidemia • Smoking • Anemia • Left ventricular Hypertrophy (LVH) • Thrombotic and inflammatory markers including TGF-Beta • Proteinuria and albuminuria • Homocysteine (hcy) • References

1. DEFINITION OF KIDNEY DISEASE

The National Kidney Foundation (NKF) has recently set specific definitions for different stages of kidney disease based on the GFR as estimated from the serum creatinine level (see Table 5.1).[1] The use of stages rather than descriptive terms, such as mild/moderate and severe, is consistent with the Joint National Committee on Hypertension's (JNC VI) sixth report where blood pressure levels were also divided into stages. Renal function like blood pressure is a continuum but dividing it into specific stages helps to split people with chronic kidney disease (CKD) into identifiable groups. These groups are useful as they are associated with increasing symptomatology, increasing risk for end-stage renal disease (ESRD) and also for cardiovascular disease. The size of the

Table 5.1 Definition and stages of chronic kidney disease

Stage	*Desciption*	*GFR (mL/min/1.73 m^2)*
1	Kidney damage with normal or higher GFR	≥90
2	Kidney damage with mildly lower GFR	60–89
3	Moderately lower GFR	30–59
4	Severely lower GFR	15–29
5	Kidney failure	<15 (or dialysis)

GFR, glomerular filtration rate. Adapted from Am J Kidney Dis.[1]

Table 5.2 Prevalence of stages of end-stage renal disease in the US population

Stage	*Category*	*Total %*
1	GFR ≥ 90	64
2	GFR 60–89	31.2
3	GFR 30–59	4.2
4	GFR 15–29	0.2
5	ESRD < 15	0.2

GFR, glomerular filtration rate. Adapted from National Health and Nutrition Examination Surveys (NHANES) and United States Renal Data Service (USRDS).

population of those with severe renal disease, (GFR 15–29 ml/min stage 4 CKD) is approximately the same size as those with ESRD (stage 5 CKD) and is much smaller than the population that has stage 3 CKD (GFR 30–59 ml/min) (see Table 5.2).

2. EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN THOSE WITH RENAL DISEASE

There is increasing evidence that the risk for cardiovascular disease CVD and mortality rises with the stage of chronic kidney disease (CKD). In the HOT study (Hypertension Optimum Treatment) the relative risk of mortality for hypertensive participants with a glomerular filtration rate (GFR) less than 60 mL/min (stage 3 or greater) was 1.6 times that of those with more normal GFR.[2] The same was found in the Heart Outcomes Prevention Evaluation (HOPE) study in a subanalysis in subjects with CKD at higher risk for CVD.[3] The risk of CVD in the dialysis population is 5–8 times that of the general adult population,[4] and the annual mortality rate for dialysis patients is also greater than in the general population. For example, the mortality rate of dialysis patients aged 25 years is 500 times that of the general population at the same age.[4] Thus, the risk of cardiovascular disease and death rises with CKD and continues to rise markedly as patients develop ESRD. The CKD population is therefore a large reservoir of cardiovascular risk and thus a prime target for risk factor reduction.

The Hypertension Detection and Follow-up Program (HDFP) followed 10 940 people aged 30–69 years throughout the United States, for at least five years in a community-based, randomized controlled trial of treatment for hypertension. This study tracked serum creatinine concentration from baseline and included a significant proportion of people with CKD. It was therefore able to measure the effect of CKD on outcomes as well as compare the effect of risk reduction (blood pressure lowering) on those with and without CKD and on renal function as an end-point itself. Lower blood pressure resulted in fewer cardiovascular events. For persons with a serum creatinine concentration greater than or equal to 1.7 mg/dL, mortality was more than three times that of all other participants.[5] Five year mortality from all causes was lower in the intensively treated blood pressure group compared to usual care (64 vs 77/1000 patient-years),[5,6] and blood pressure reduction was also found to be renal-sparing as discussed below.

Blood pressure, diabetes, and CKD were shown to impact on cardiovascular mortality and morbidity in the Multiple Risk Factor Intervention Trial (MRFIT) study where 332 544 men were screened. There was a strong graded relationship between blood pressure, particularly for isolated systolic hypertension and cardiovascular mortality (see Figure 5.1).[7] There was also a graded relationship between both systolic and diastolic blood pressure and progression to ESRD (see Figure 5.2).[8] The risk of CVD, as well as progression of renal disease and cardiovascular mortality, rises in the presence of diabetes, particularly with more severe renal disease. Over an average follow-up of 16 years the age-adjusted incidence of ESRD in the MRFIT study cohort with diabetes was 199.8/100 000 person-years compared with 13.7/100 000 person years for those without diabetes.[9]

Further evidence for the graded risk in mortality occurring with more severe renal disease, comes from the Wisconsin Epidemiologic Study of Diabetic Retinopathy. The mortality rate per 1000 patient-years was 57.7 for those with no renal disease, 116.5 with microalbuminuria, and

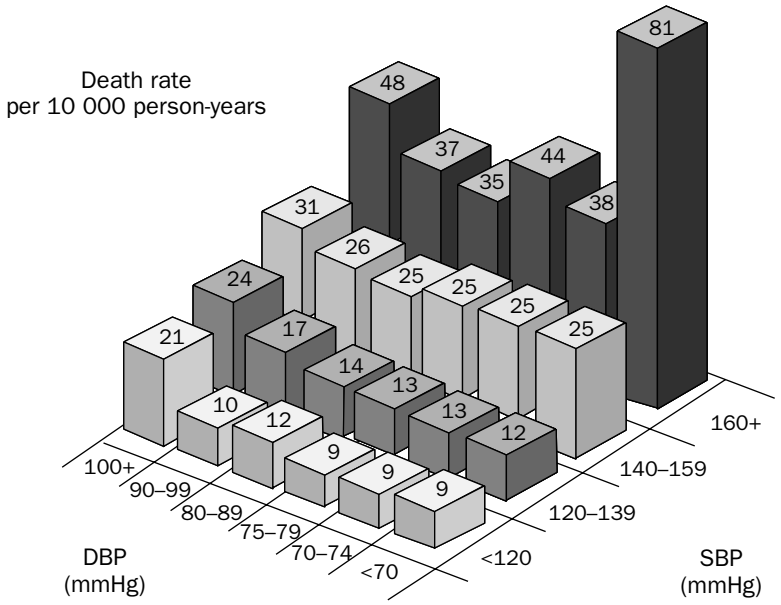

Fig. 5.1 Effect of blood pressure on mortality due to coronary heart disease: MRFIT. DBP, diastolic blood pressure; SBP, systolic blood pressure. Adapted from Neaton et al.[7]

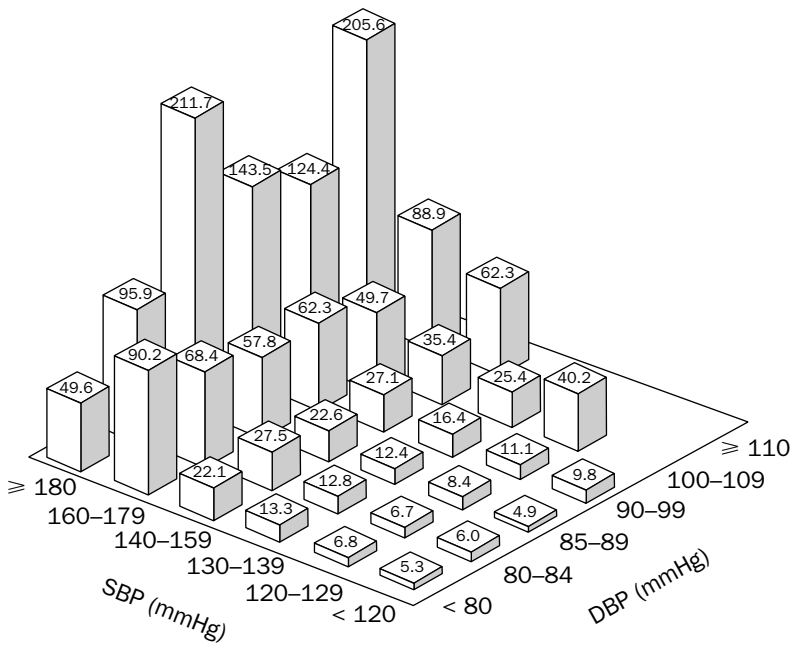

Fig. 5.2 End-Stage renal disease by baseline blood pressure in 332 544 men screened: MRFIT. Adapted from Klag.[8]

172.2 with diabetic nephropathy (Figure 5.3).[10] The mortality rate reported for diabeties on hemodialysis is 258 per 1000 patient-years.[11]

More recently reported mortality rates from clinical treatment trials of patients with type 2 diabetes are lower. For example, the total mortality rate for people with type 2 diabetes without renal disease ranged from (22.4/1000) patient-years to 27.2/1000 patient-years in the UK Prospective Diabetes Study (UKDPS) 38 study,[12] to 22.5–37.2/1000 patient-years in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.[13] In the Reduction of Endpoints in Non-insulin with the Angiotensin II

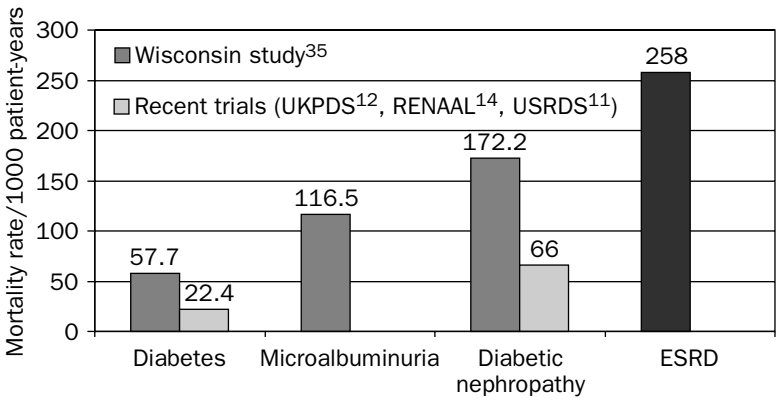

Fig. 5.3 Mortality rates in diabetes by severity of kidney disease in 12 year prospective observational study vs recently completed treatment trials in diabetes and USRDS, diabetes on hemodialysis.

Antagonist Losartan (RENAAL) study of people with type 2 diabetes and very severe nephropathy total mortality rates were 66–68/1000 patient-years.[14] This probably reflects the effect of more recent aggressive blood pressure lowering as well as attention to other risk factors as part of the newer study protocols. A graded increase in cardiovascular complications is therefore seen with the progression in severity of renal disease.

3. WHAT ARE THE RISK FACTORS FOR CARDIOVASCULAR EVENTS IN PATIENTS WITH RENAL DISEASE?

The traditional risk factors for cardiovascular disease (CVD) are the same for those with renal disease as for the general population (see Box 5.1). It is generally recognized that atherosclerotic vascular disease in one organ system (cerebrovascular, cardiovascular, peripheral vascular, renovascular) results in an approximately 30% risk of disease in another organ system (see Figure 5.4).[15] There is still an open question about whether the presence of renal disease in and of itself is a mediator or just a marker of CVD. Because the most prevalent risk factors for ESRD – diabetes, hypertension, and advancing age – are also risk factors for CVD it is difficult to establish whether the renal disease is itself a marker of or a mediator of higher cardiovascular risk. In an analysis of data from the National Health and Nutrition Examination Survey (NHANES) I epidemiologic follow-up study, after adjustment for traditional cardiovascular risk factors there was no independent association between moderate renal insufficiency and total mortality or cardiovascular mortality.[16] Clinical trials have demonstrated that those with more severe stages of renal disease had greatly increased risks of cardiovascular morbidity and mortality and total mortality.[2,3] The finding of microalbuminuria is now widely recognized as a marker for cardiovascular risk both in people with and without diabetes. With the dramatic mortality rates for people with diabetes and severe nephropathy and in those on dialysis it seems likely that factors resulting from the loss of renal function and damage to the kidneys will be found to

Box 5.1 Traditional risk factors for cardiovascular disease

- Diabetes
- Hypertension
- Dyslipidemia
- Smoking
- Age
- Male gender and postmenopausal status
- Family history of premature cardiovascular disease

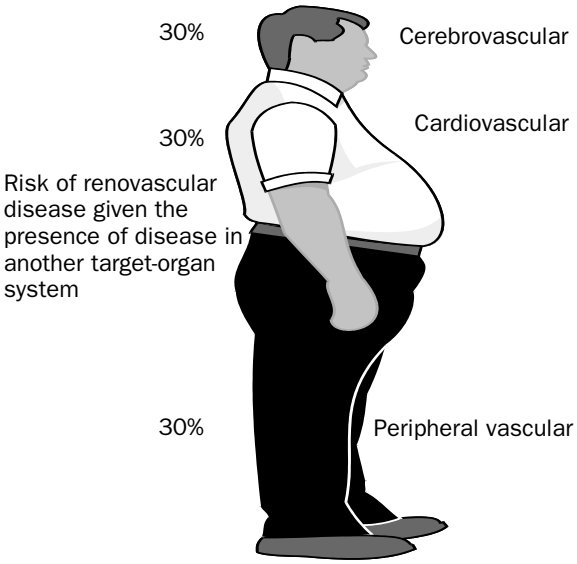

Fig. 5.4 Interrelationship between atherosclerotic vascular disease in different target organs

promote cardiovascular risk. Given the list in Box 5.2 it seems only a matter of time before the presence of renal disease is found to be a mediator as well as a marker of cardiovascular risk.

Box 5.2 Potential risk factors for cardiovascular disease in the setting of chronic kidney disease

- Albuminuria
- Dialysis procedure
- Homocysteine
- Lipoprotein (a)
- Fibrinogen levels
- Markers of inflammation (e.g. C-reactive protein)
- Extent of insulin resistance (metabolic syndrome)
- Presence of subclinical atherosclerosis
- TGF-beta

4. HYPERTENSION

Hypertension is a shared risk factor for progressive renal disease and for cardiovascular disease. Its prevalence increases with more severe renal disease particularly in the presence of proteinuria (Table 5.3).[17] Independent risk factors for the presence of hypertension in CKD are renal failure, greater age, the presence of diabetes, dyslipidemia, and proteinuria.[18]

In the Hypertension Detection and Follow-up Program, intensive stepped care protocol-driven blood pressure control was compared to usual referred care, renal function was followed as a secondary end-point.[5] Better blood pressure control was found to be renal-protective and the decline in glomerular filtration rate (GFR) over 5 years was significantly less in the more intensively treated group compared to the usual care group. In addition more people had an improvement in renal function in the intensively treated group than the control group. Renal protection through blood pressure lowering was more marked among those with renal insufficiency at baseline. In those with baseline creatinine between 1.5 mg/dL and 1.7 mg/dL, the incidence of decline in GFR over the 5 year study was 113.3/1000 in the intensive group and 226.6/1000 in the usual care group compared with 21.7/1000 and 24.6/1000, respectively, for the entire study cohort. This was the first study to link renal function and outcomes. It was also the first to demonstrate that lowering blood pressure could not only reduce cardiovascular end-points but could also slow and sometimes reverse the progression of CKD. As discussed later in this chapter, a reduction of progression of renal disease would also be expected to lessen the impact of renal insufficiency on cardiovascular disease.[5]

4.1 Hypertension and dialysis

While there is overwhelming evidence that lower blood pressure leads to better results in people with hypertension, diabetes, isolated systolic hypertension, and in renal disease, there is less clarity in the dialysis population.

Table 5.3 Prevalence of albuminuria and high blood pressure, or both, in US adults

Stage	*Normal*	*Albuminuria only*	*High BP only*	*Albuminuria and high BP*
1	78.7	5.9	12.2	3.3
2	61.2	5.2	26.0	7.7
3	20.2	5.9	41.2	32.8
4	22.8	0.7	13.4	63.5

Adapted from Coresh.[64]

Data from the United States Renal Data Service (USRDS) have demonstrated that mortality rates were most clearly linked to post-dialysis blood pressures and that post-dialysis systolic blood pressure was associated with an elevated mortality risk both for low and high levels as compared with levels in between. There was a striking increase in mortality associated with the lowest blood pressures.[19] This was also demonstrated by Klassen et al. who found that higher post-hemodialysis systolic blood pressure was correlated with lower 1 year mortality rates.[20] For every 10 mmHg increase in systolic blood pressure there was a 13% lower risk of death.[20] In addition, for every 10 mmHg increase in pulse pressure there was a 12% higher hazard of death (see Figure 5.5). From this figure it becomes evident that the highest mortality in these dialysis patients was associated with the lowest systolic blood pressure combined with the widest pulse pressure (lowest diastolic blood pressure). The lowest mortality was associated with a systolic blood pressure of 130–150 mmHg, with diastolics 80 – 90 mmHg. It is not until the systolic blood pressure rises above 170 mmHg that higher blood pressure was associated with higher risk. A simple way to assess patients' risk based on this finding is that those whose systolic blood pressures were double or more than the diastolic blood pressure were at greater risk.

While the finding of higher mortality with lower blood pressure in hemodialysis patients seems to be a paradox, when taken in context with the principles for progression of cardiac disease in the dialysis population, it begins to make sense.[21] The prevalence of left ventricular hypertrophy (LVH) rises in the CKD population to 75% of those starting dialysis. This is driven at least in part by hypertension, anemia, volume overload, and also possibly the uremic milieu.[21,22] As the heart hypertrophies there is a rising myocardial oxygen demand. During periods of more rapid heart rate with reduced diastolic time for perfusion, ischemia due to atherosclerosis, periods of hypotension or spikes of hypertension, will be followed by injury leading to a profibrotic state. The eventual result is pump failure with a fibrosed dilated cardiomyopathy and an inability to generate higher blood pressures. Patients so involved will clearly have the highest mortality. It has not yet been demonstrated whether this process can be prevented or reversed, but studies are now underway. Prevention strategies could include: prevention of the development of anemia at any time, maintenance of normal blood pressures throughout the period of CKD and initiation of dialysis, monitoring for progressive ventricular hypertrophy, and use of antihypertensives known to lead to LVH regression as well as risk factor reduction to lessen atherosclerosis.

4.2 Hypertension and nephropathy

The rate of deterioration of renal function in patients with CKD appears to correlate directly with higher blood pressure levels. The presence of more severe proteinuria and hypertension are both risk factors for renal progression. The Modification of Diet in Renal

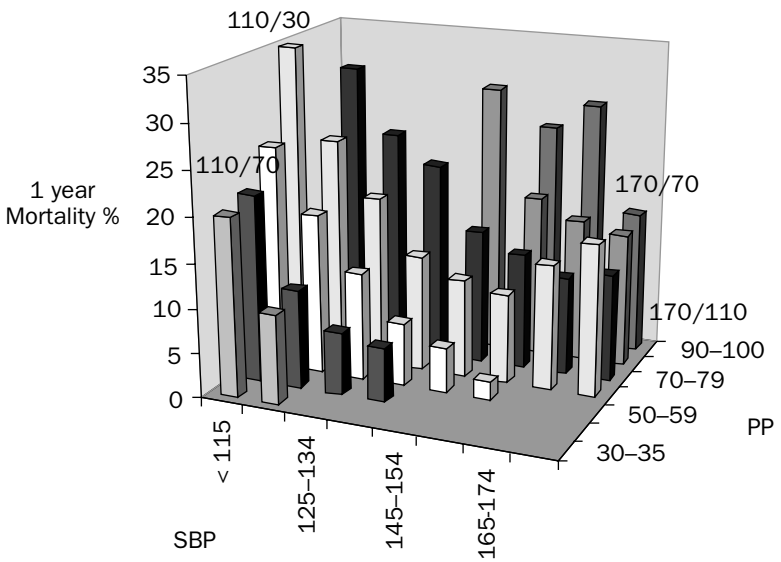

Fig. 5.5 1 year mortality in hemodialysis patients by systolic blood pressure and pulse pressure. Adapted from Klassen et al.[20]

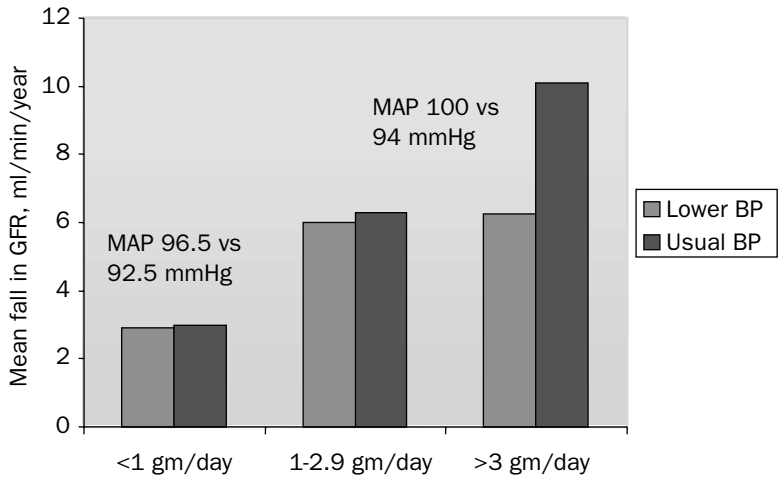

Fig. 5.6 MDRD (Medical Diet in Renal Disease Study) showed that aggressive BP control preserves renal function in proteinuric patients. MAP; mean arterial pressure. Adapted from Klahr et al.[23]

Disease (MDRD) trial evaluated the impact of two target blood pressures in patients with nondiabetic renal disease and baseline GFR <60 mL/min.[23] Lower blood pressure was associated with slower progression of renal disease and less hospitalization. This was more pronounced for those with higher baseline urinary protein levels. For those with urinary protein at baseline of 3 gm/day or more, blood pressure control to 125/75 mmHg was the most effective for slowing deterioration of renal function (see Figure 5.6). Angiotensin-converting enzyme inhibitors (ACEIs) slow the deterioration of renal function compared to conventional therapy in nephropathic patients.[24] In the long-term extension of the Ramipril Efficacy In Nephropathy (REIN) study, for example, long-term treatment with ramipril virtually eliminated the development of end-stage renal failure in those who were free from ESRD over the first three years of the study.[25]

5. DIABETES

The risk of ESRD is nine times higher in people with diabetes, even when other risk factors, such as blood pressure and lipid levels, are controlled.[9] Diabetes is a well-established risk state for cardiovascular disease and diabetics have a probability for experiencing adverse cardiovascular events equal to that of patients without diabetes who have had a myocardial infarction.[26] Population-based epidemiologic studies have established that the association between blood pressure level (systolic or diastolic) and cardiovascular risk is continuous and graded in people with diabetes. Hypertension incidence increases by 3% for each year of diabetes, and is three times more likely in patients with proteinuria and 23% more likely in those with higher HbA_{1C} levels.[27] Abnormal levels of albuminuria in people with diabetes is one of the strongest predictors for long-term mortality rates.[28]

Lowering blood pressure appears to be the most potent risk-reduction strategy for diabetics with hypertension when compared with tighter blood sugar control reflected by improved HbA_{1c} levels.[29] Treatment of hypertension may confer greater, if not equal, benefit to persons with diabetes compared with age-matched hypertensive persons without diabetes.[30–32] The following paragraphs review evidence for risk reduction in people with diabetes without and with renal disease.

Clinical trials in people with diabetes with normal renal function include the HOT study, the UKPDS, and ABCD (Appropriate Blood Pressure Control Study of Diabetes) Study of Normotensives among others. In the HOT study, 18 790 people with hypertension (DBP >100–115 mmHg) were treated to three different diastolic blood pressure goals (90, 85, 80 mmHg). Among the 1501 with diabetes, the rate of major cardiovascular events was 51% lower in those patients randomized to target blood pressures less than or equal to 80 mmHg compared to those with target pressures of 85–90 mmHg (see Figure 5.7).[2] In the UKPDS 38, the effect of tighter compared to usual blood pressure control was investigated in 1148 hypertensive people with type 2 diabetes. Blood pressure was lowered from 160/94 mmHg at baseline to 144/82 mmHg in the tight control group and 154/87 mmHg in the usual care group. Lower blood pressure resulted in a reduction of a composite of cardiovascular end-points as well as a 44% reduction of stroke, a reduction of retinopathy, and a trend to lower progression of nephropathy.[12] In the normotensive arm of the ABCD trial 485 people with type 2 diabetes were randomized to two different levels of blood pressure and two drug treatment groups in a 2 × 2 factorial design. This trial found that while there was no benefit to the main outcome measure GFR, in either the intensive (128/75 mmHg) or moderate (137/81 mmHg) blood pressure arms or between drug classes (ACEI vs dihydropyridine calcium antagonist), the lower blood pressure arm did have a significantly reduced progression of renal disease. There was a reduction in progression to micro and to macroalbuminuria (see Figure 5.8).[33] There was also a lower risk of stroke and lower progression of diabetic retinopathy in the lower BP group.[33]

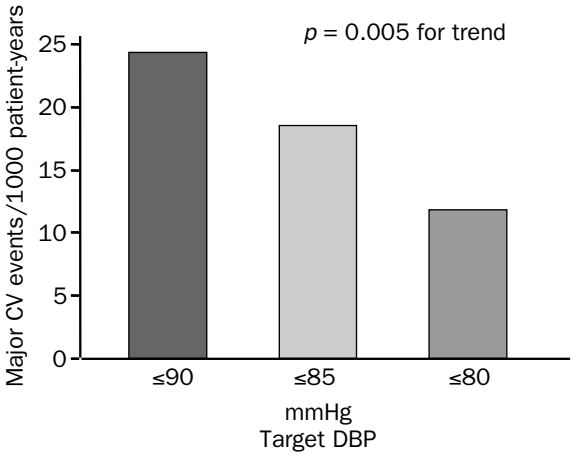

Fig. 5.7 Significant benefits from intensive blood pressure reduction in diabetics. Adapted from Hansson et al 1998[65]

The finding of microalbuminuria indicates a higher risk of cardiovascular events as well as an increased risk of developing diabetic nephropathy. In a review by Eastman and Keen, microalbuminuria was associated with a 10-fold increased risk of cardiovascular events, making it a more powerful marker than hyper-

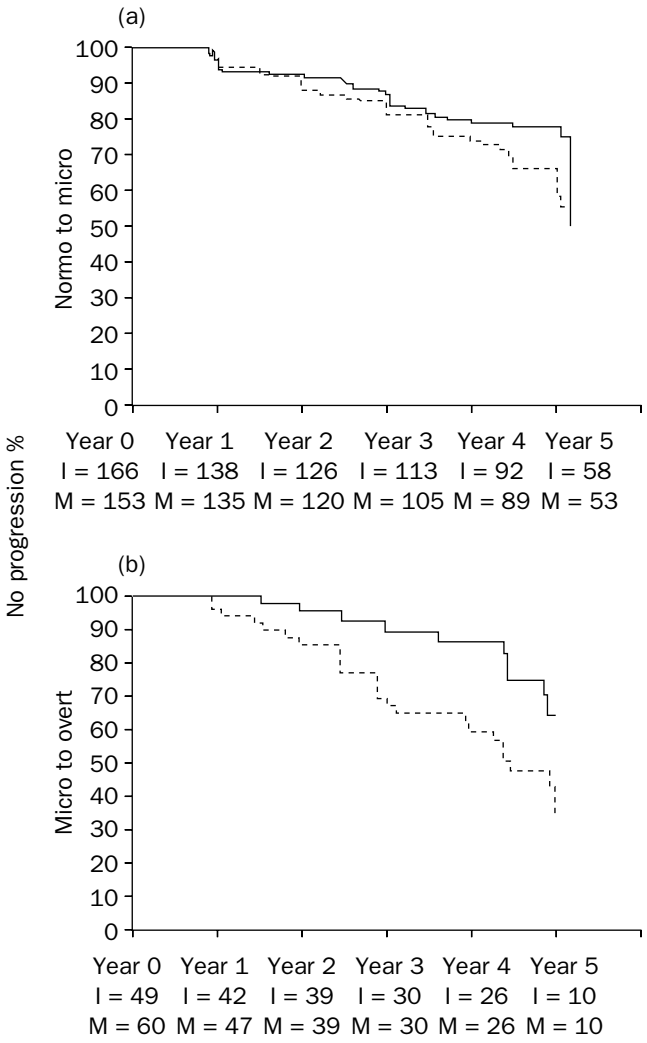

Fig. 5.8 ABCD Normotensive Study results: intensive vs moderate BP control. Kaplan Meier plot of renal disease progression. (a) Progression from normoalbuminuria to microalbuminuria. (b) Progression from microalbuminuria to macroalbuminuria. Adapted from Schrier et al.[33]

tension, elevated cholesterol or smoking.[34] In the Wisconsin study, 840 people with type 2 diabetes were followed for up to 12 years after a screening visit including a urine albumin level. The cardiovascular disease mortality rate for those with normoalbuminuria at baseline was 36.9 per 1000 person-years, and the mortality rates for those with microalbuminuria and gross proteinuria were 85.5 and 123.0 per 1000 person-years, respectively.[35] Because of confounders associated with microalbuminuria, such as age, duration of diabetes, blood pressure, lipids, etc, microalbuminuria should not be considered a mediator, but rather a marker of cardiovascular risk. Interestingly, higher cardiovascular risk has also been shown in nondiabetics with microalbuminuria.[36]

The degree of proteinuria reflects the severity of renal disease and the risk of renal disease progression. For example, in the IRMA II study (Irbesartan in Patients with Type 2 Diabetes and microalbuminuria Study Group) there was a 15% conversion to diabetic nephropathy in the 201 patients assigned to the placebo group over 24 months.[37] In the Irbesartan Diabetic Nephropathy Trial (IDNT) of people with type 2 diabetes and advanced diabetic nephropathy with urine albumin excretion averaging 4 g per day and creatinine levels averaging 1.67 mg/dl (150 μmol/L) there was an overall 16.7% rate of

progression to ESRD and an overall mortality rate of 15.3% over 31 months.[38] The RENAAL study in a similar patient population as the IDNT, demonstrated a progression to ESRD in 20–25% and an overall mortality rate of 21% over 41 months' average follow-up.[39] Urine albumin excretion therefore reflects an increasing continuum of risk of both kidney and cardiovascular disease. Mortality rates in patients with diabetic nephropathy are significantly higher than in patients with microalbuminuria.

Based on the data reviewed above there is a debate about how best to protect people with type 2 diabetes and hypertension. One can propose an argument for starting angiotensin II receptor blocker (ARB) therapy for renal protection in those with microalbuminuria or diabetic nephropathy.[37–39] In the Micro-HOPE study the use of anti-angiotensin II therapy with an ACEI was demonstrated to significantly reduce the risk of myocardial infarction, stroke, cardiovascular death, and total mortality. Therefore, although the use of an ARB in people with type 2 diabetes and nephropathy has been shown to be renal-protective, only an ACEI as demonstrated in the HOPE study provided cardiac protection.[40] ACEIs should, therefore, be part of the treatment plan for every person with diabetes who has at least one other risk factor present, such as microalbuminuria, hypertension, smoking, dyslipidemia, etc. ARBs should be used for all ACEI intolerant patients. The threshold level for initiating anti-angiotensin treatment for the finding of microalbuminuria in people with diabetes is a urine albumin level of 30 mg/day or 20 mg/L, independent of blood pressure. The blood pressure treatment targets for those with diabetes are systolic blood pressure $<$130 mmHg and diastolic blood pressure $<$80 mmHg.[41] The treatment threshold for initiating antihypertensive therapy is the same as the target 130/80 mmHg. Non-pharmacologic therapies should not be forgotten, including diet, exercise, and smoking cessation. Also, all patients at risk should be on cardiac dose aspirin, which was also found to lower cardiovascular events in those with renal insufficiency.[42]

It is now clear that patients with diabetic nephropathy require multiple medications to control their blood pressure.[43] Assuming that an ACEI has been started as initial therapy or added if not already present, what is the next step? Given the synergy of ACEIs and ARBs with diuretics, addition of a low-dose thiazide is reasonable (i.e. hydrochlorothiazide 12.5 mg/d or 25 mg/d) as add on therapy. Low-dose diuretics have been proven to be safe and effective for treating patients with isolated systolic hypertension and diabetes.[44,45] The next drug to be added should be a long-acting calcium antagonist. There is data demonstrating that the non-dihydropyridines provide more renal protection and act synergistically with ACEIs in people with diabetes and nephropathy.[46] There is also compelling evidence that in nephropathic patients both with and without diabetes that dihydropyridine calcium antagonists should not be used without concommittent anti-angiotensin II therapy (ACEI or ARB).[38,47] Many studies, however, have demonstrated the cardiovascular safety of dihydropyridine calcium antagonists when used with other agents to control blood pressure in diabetics.[14,38] As an average of three or more medications will be necessary to bring blood pressure towards the target in people with diabetes and hypertension, most patients with diabetes will require aggressive management of their blood pressure. It is therefore important that clinicians are confident in the use of all antihypertensives as discussed below. The algorithm shown in Figure 5.9 is a simplification of the one proposed in a recent consensus conference.[43] Trials are currently underway and are being planned to examine the question about which order and which drugs should be used for maximum blood pressure efficacy as well as cardiovascular and renal safety.

Clinicians must be comfortable with using anti-angiotensin II therapy in all people with renal disease. When an ACEI or ARB is prescribed it is helpful to measure serum creatinine and potassium levels at baseline. In patients felt to be at high risk for bilateral renal artery stenosis, it may be helpful to re-measure these parameters 1–2 weeks after initiation and after substantial increases in dose. If the creatinine

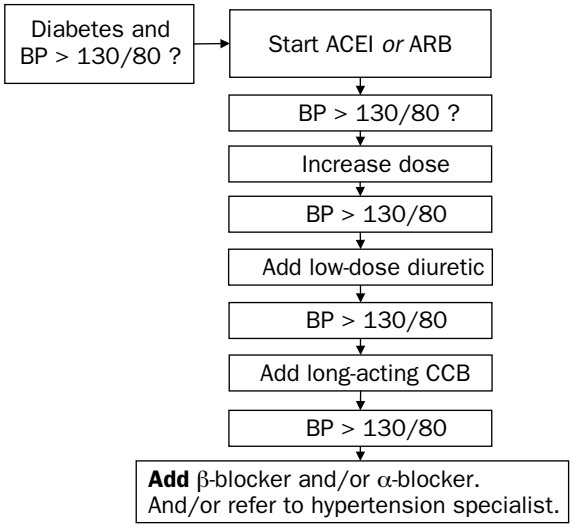

Fig. 5.9 Blood pressure treatment algorithm for diabetes. CCB, calcium channel blocker. Adapted from Tobe et al.[63]

level increases by more than 30% or the potassium level exceeds the upper limit of the local laboratory's normal range, the ACEI should be reassessed and a consideration of referral to a renal expert considered. A rise in creatinine of up to 30% after the initiation of ACEIs or ARBs results from the change in intraglomerular hemodynamics caused by the anti-angiotensin II effect. This hemodynamic effect is considered to be in large part responsible for the renal-protective effect and is reversible if therapy is discontinued.[48] A small rise in creatinine is therefore likely a good prognostic marker. If the creatinine level rises to a much greater degree, therapy with ACEIs or ARBs should be discontinued and the patient investigated for severe renovascular disease. If hyperkalemia develops on anti-angiotensin II therapy, and this was a rare finding in the IDNT and RENAAL studies, ACEI or ARB therapy can usually be continued and the potassium managed with diet modification and the use of loop diuretics.

Clinicians must also be confident in using other add on therapies, such as the calcium antagonists. Because of the finding in nephropathic patients of poorer renal outcomes with the use of dihydropyridine calcium antagonists when used alone without anti-angiotensin II therapy, these agents should not be used alone in patients with proteinuria. Although the recently completed ABCD study in normotensive people with diabetes demonstrated no differences in outcomes between an ACEI and a dihydropyridine calcium antagonist, it stands to reason that these patients have a certain probability of developing nephropathy over their lifetimes and should be on anti-angiotensin II therapy if they have hypertension. The calcium antagonists are appro-priate and efficacious for add-on therapy.[14,38] Larger trials with convincing outcomes are required to confirm earlier reports that non-dihydropyridine calcium antagonists are more nephroprotective than the dihydropyridine calcium antagonists.

6. DYSLIPIDEMIA

Dyslipidemia is highly prevalent in the general population in people with CKD and in those on dialysis. However, patients with the nephrotic syndrome are quite unique with dyslipidemia defining part of their syndrome. Hyperlipidemia is essentially universal in patients with the nephrotic syndrome, including diabetic nephropathy, with 90% having elevated low-density lipoprotein (LDL) (>130 mg/dL) and over half with low high-density lipoprotein (HDL) (<35 mg/dL) and high triglycerides (TGs) >200 mg/dL.[1] Also, almost half have increased lipoprotein (a).[1] In dialysis patients, the most common lipid abnormality found is low HDL and higher triglycerides with almost half of peritoneal dialysis and one quarter of hemodialysis patients found to have small LDL particles. Many also have high levels of lipoprotein (a). There is more and more attention being paid to the intermediate-density lipoprotein. This may be estimated from the difference between the total cholesterol and the HDL plus the LDL. There are only associations at this time with cardiovascular outcomes. Oxidized LDL has also been associated with a higher risk. One analogy has the LDL delivering lipid to macrophages in the vasculature and HDL taking it away. In this scenario, oxidized LDL would be the most potent at creating lipid-laden macrophages. In peritoneal dialysis LDL

levels tend to be higher than on HD and there are fewer with low HDL but more with elevated TGs.[62]

There are few clinical trials for treatment of dyslipidemia in CKD and none in the dialysis population, and most of our practice is extrapolated from the large trials in the non-kidney disease population. We therefore assume that reduction of LDL with statins or fibric acid derivatives will lead to cardiovascular risk reduction in those with CKD or on dialysis. Whether lipid reduction in this population will be renal sparing is still an open question. The National Kidney Foundation KDOQI summarized 15 trials looking for an association of dyslipidemia with CVD and progression of renal disease. Half the studies showed a relationship, but half did not.[1] They concluded that a relationship with renal progression could not be made. In patients with nephrotic syndrome, both with and without diabetes, high levels of LDL would be expected to predispose to vascular disease. Currently, no intervention trials have investigated whether treatment reduces CVD, but the expected protection against CVD from lipid reduction would seem to be greater given the degree of dyslipidemia in this group. The evidence linking dyslipidemia with renal disease progression in nephrotic patients is suggestive but inconclusive at this time.

In hemodialysis patients there are no intervention trials to guide therapy. There is some question about risk and benefit of dyslipidemia treatment as there is a higher risk of myositis and rhabdomyolysis from antilipid agents in the dialysis population. One large clinical trial that would have answered this question was stopped, when the drug studied was taken off the market. Attempts are currently underway to try to restart a similar trial with another agent. Studies looking at the effect of different dialysis membranes and dialysis solutions on the lipid profile were inconclusive. There are no data for peritoneal dialysis patients. As these patients often have high LDL and triglyceride levels, possibly as a result of high glucose exposure, there is a question about whether to start statins or fibric acid derivatives first.

The best treatment option for patients with nephrotic syndrome is to induce a remission if possible. Conservative management including the use of ACEIs, dietary salt restriction, and avoidance of high protein diets may help. Lipid-lowering diets have not resulted in the same magnitude of lipid changes that drug therapy can bring about. It seems wise at this time to use available clinical guidelines, such as the NCEP (National Cholesterol Education Program), for treatment thresholds and target levels of all patients. HMG-CoA reductase inhibitors should be the first line therapy for LDL control. One must be concerned about and the patient must monitor for myositis particularly if higher doses are used or if lipid-reducing agents are used in combination. In people with CKD it is wise to use lower doses of fibric acid derivatives.

For patients on dialysis the use of HMG-CoA reductase inhibitors is recommended for those with elevated LDL and fibric acid derivatives for those with high LDL and triglycerides. One must always be alert for myositis and rhabdomyolysis. In all dialysis patients it is recommended to reduce the dose of fibric acid derivates by 50% of the usual recommended starting dose and to monitor very carefully preferably in consultation with a lipid specialist if combinations of antilipid drugs are required. It seems reasonable in this high risk population to aim for LDL levels under 100 mg/dL as has recently been advocated for people with diabetes.[49]

7. SMOKING

Smoking is the most potent of the reversible risk factors for cardiovascular disease. Patients may focus on trying to make changes in glucose lipid and blood pressure levels while they continue to smoke because of its addictiveness. Smoking is associated with worsening of renal function and higher cardiovascular risk. The NKF-K/DOQI summarized that overall, smoking presented an increased risk for renal progression and cardiac disease in patients with CKD.[1] Currently, there are no trials of smoking cessation in CKD or in patients on dialysis.

However, it is entirely reasonable to extrapolate from the massive literature available on smoking that smoking cessation will reduce cardiovascular, cerebrovascular, peripheral vascular, and renovascular risk in people with CKD. As well as counseling, patients may find buproprion with or without the nicotine patch helpful in quitting. Because of the complexity of most CKD or dialysis patient's drug regimens and comorbidities, use of these agents must be individualized and consultation with a pharmacist with expertise in chronic kidney disease, if available, is always of benefit.

8. ANEMIA

Anemia has long been associated with CKD. The etiology is primarily due to a reduction of erythropoietin production as well as to deficiencies of iron and carnitine, vitamin B_{12}, and folate, as well as blood loss. Hemoglobin levels fall as the GFR falls such that at the time of dialysis 85% of patients are anemic. However, there is great inter-individual variation between patients. There is a strong association between the level of hemoglobin and left ventricular hypertrophy (LVH) and heart failure in CKD and in patients on dialysis.[50,51] Low hemoglobin levels have been associated with greater LVH, heart failure, and hospitalization for heart disease (see Table 5.4). Anemia is believed to lead to cardiac disease through an inability to deliver sufficient oxygen to the tissues. Compensating for the loss of oxygen-carrying capacity, cardiac output is increased through increased heart rate and contractility, ultimately leading to LVH as discussed above.

In mild to moderate kidney disease seen in half of patients with severe congestive heart failure the use of erythropoietin and iron to restore hemoglobin level resulted in a dramatic improvement in heart failure physiologic parameters, including a much lower need for loop diuretics and hospitalization. The correction of hemoglobin to 12.5 g/dL from 11.0 g/dL in the control group also led to an improvement of ejection fraction of 5% versus a fall in the control group of an equal amount.[52] No large trials have been completed looking at the cardiac benefits of hemoglobin normalization in patients with CKD without heart failure. Smaller trials have demonstrated a regression in LVH with restoration of hemoglobin levels above 12 g/dL. A number of larger trials are ongoing internationally to investigate this.

In the dialysis population, there are important clinical trials of hemoglobin normalization that found different results when patients with different degrees of cardiac disease were studied. Besarab et al. in the Normalization of Hemoglobin study conducted in hemodialysis patients with severe cardiac disease (symptomatic heart failure, ischemic heart disease, or severe left ventricular dilatation) found that normalization of hemoglobin, (hemocrit of 42% vs 30%) was associated with a reduction in survival and greater dialysis access thrombosis.[53] The Canadian Normalization of Hemoglobin trial conducted in hemodialysis patients with concentric LVH or left ventricular dilatation but no severe cardiac disease found that normaliza-

Table 5.4 Relationship of left ventricular hypertrophy (LVH) and anemia in chronic kidney disease

	GFR mL/min/1.73 m²	*Severity of LVH*	*Degree of anemia*
Stages 1 and 2 General population	≥ 60		
Stage 3 Moderate	30–59	↑	↑
Stage 4	15–29	↑↑	↑↑
Stage 5 On dialysis	< 15	↑↑↑	↑↑↑

GFR, glomerular filtration rate.

tion of hemoglobin from 10.0 g/dL to 13.5 g/dL did not cause regression of cardiac changes but may prevent further left ventricular dilation.[54]

The current threshold for starting treatment with erythropoietin therapy is 10.0 g/dL with the target to be 11.0–12.0 g/dL. Studies are ongoing in the dialysis and pre-dialysis populations to determine whether prevention of the fall in hemoglobin will help to prevent the development of LVH altogether. It is important to maintain a patient's iron, vitamin B_{12}, and red blood cell (RBC) folate levels in the normal range to maximize the effectiveness of erythropoietin therapy. Because ferritin is an acute phase reactant, the transferrin saturation is also used to monitor iron stores and availability. One might also consider annually monitoring patients on dialysis and those with CKD for changes in left ventricular mass, to help in adjusting therapy. It also is self-evident that in the setting of CKD one should assess new or worsening anemia and diagnose its cause before assuming that it is due simply to erythropoietin deficiency caused by CKD.

9. LEFT VENTRICULAR HYPERTROPHY (LVH)

LVH is a known independent risk factor for sudden death in people without kidney disease. It has been used as a surrogate marker of cardiovascular disease because it is a simple noninvasive measure. LVH has been found to be highly prevalent among patients with CKD, risking to very high rates in those starting dialysis. Parfrey et al. found that only 16% of Canadian patients starting on dialysis had normal echocardiographs with the majority having concentric LVH.[55] Because of the negative health implications of LVH it makes sense to reduce factors that exacerbate it, such as reducing blood pressure to less than 130/80 mmHg.

In dialysis patients, there is little known about the effect of blood pressure lowering. As blood pressure lowering toward normal has been demonstrated to be efficacious in every other group it stands to reason that the maintenance of a more normal blood pressure in the dialysis population also makes sense. The post-hemodialysis blood pressure should be used to assess the need and response to antihypertensive medication. The pre-hemodialysis blood pressure is more related to interdialytic volume changes. At this time, without clinical trials to guide us, it makes sense to aim for a post-hemodialysis blood pressure of 140/80–90 mmHg. It also makes sense to try to avoid volume overload as much as possible in both the hemodialysis and peritoneal dialysis population. If minoxidil, which is an excellent and potent antihypertensive for the dialysis population, is used, it should be combined with other agents known to reduce left ventricular mass including beta-blockers to block reflex sympathetic activation.

10. THROMBOTIC AND INFLAMMATORY MARKERS INCLUDING TGF-BETA

There are many factors that are currently being investigated as risk factors for cardiovascular disease in patients with CKD. Many of these are linked to higher levels of angiotensin II which is known to cause vascular and cardiac remodeling and hypertrophy through hemodynamic and cellular changes. These include inflammatory markers, such as C-reactive protein (CRP); thrombogenic factors, such as fibrinogen; and oxidative stress. One cytokine that has generated great interest is transforming growth factor-beta (TGF-beta). Because angiotensin II is known to stimulate this prosclerotic cytokine in the kidney it has been extensively studied in models of kidney disease in diabetes and has been associated with falling renal function. There is no evidence yet that TFG-beta from the damaged kidney is a prosclerotic force in the heart but this may turn out to be an important hypothesis that may lead to changes in how we combine medications. A small trial has shown a positive correlation between this cytokine and urinary protein excretion in people with and without diabetes.[56] It also demonstrated a fall in TGF-beta with the addition of an ACEI with an additional independent reduction after the combination with an ARB.[56]

11. PROTEINURIA AND ALBUMINURIA

Abnormal amounts of albumin in the urine are relatively common particularly in people at higher risk for cardiovascular disease. Proteinuria has long been recognized to be a risk factor in people with diabetes,[34] and in people without diabetes for cardiovascular and total mortality.[57] For example, in the HOPE trial, which studied people aged 55 and over with previous cardiovascular disease or diabetes and one additional risk factor, microalbuminuria, was found in 32.6% of those with diabetes and 14.8% of those without, at baseline.[58] The presence of microalbuminuria doubled the relative risk of adverse cardiovascular events and total mortality in people with and without diabetes.[58] In the HOPE study, treatment with an ACEI reduced the risk of cardiovascular events particularly in people with diabetes and those with proteinuria.

The albuminuria by itself clearly cannot affect the endothelium directly. However, albuminuria is associated with other risk factors linked to vascular disease, including hyperglycemia from diabetes, hypertension, dyslipidemia, hyperhomocysteinemia, smoking, and markers of inflammation, such as C-reactive protein. Albuminuria may lead to progression of renal tubular damage through increased protein trafficking, a process that would likely be exacerbated by high protein diets. Renal disease in itself may be a mediator of cardiovascular disease. Therefore, albuminuria is an easily measured marker of other cardiovascular risk factors. It also provides an easy to measure response to therapy, and reduction in albuminuria has been linked to reductions in cardiovascular disease and reductions in progression of renal disease in both people with and without diabetes.

Currently, clinical practice guidelines recommend screening for albuminuria in people with type 2 diabetes at the time of diagnosis and then annually.[59] There are no recommendations for screening people without diabetes for microalbuminuria at this time. However, it makes sense that if microalbuminuria or nephropathy was found in someone without diabetes, he/she should be investigated for cause and treated as someone with double the cardiovascular risk. In recent hypertension trials the finding of proteinuria was also associated with more rapid declines in GFR.[23] This was also seen in the recently completed AASK trial (African American Study of Kidney disease) where the decline in GFR over the course of the trial was more rapid in those those with greater proteinuria.[47] In the AASK trial where an ACEI was compared to a beta-blocker and to a dihydropyridine calcium antagonist, it was clear that a calcium antagonist should not be used singly in a patient with proteinuria and hypertension. From this study and others in complicated hypertension it is clear that multiple medications are required to control blood pressure in this high-risk group. These patients should be on an ACEI or ARB, as well as other medications required to lower blood pressure to target. One well done study has demonstrated efficacy in combining ACEI and ARB together in non-diabetic nephropathy.[66]

12. HOMOCYSTEINE (HCY)

HCY levels have been found to be elevated in patients with kidney disease. There have been associations made with higher risk for vascular occlusive disease with lower folic acid and vitamin B_{12} levels and higher HCY levels.[60] It has been recognized that HCY levels can be reduced by treatment with folic acid. Treatment with folic acid reduced levels by 25% (Figure 5.10 and Table 5.5).[60] The addition of vitamin B_{12} reduced levels a further 7% and vitamin B_6 did not add any benefit.[60] Proportional and absolute reductions in HCY were seen with higher HCY levels and lower folate levels at baseline. While levels can be brought to normal in patients with CKD they can not be brought to normal in dialysis patients. Schnyder et al. found that treatment with folic acid 1 mg, vitamin B_{12}, 400 μg, and pyridoxine 10 mg for 6 months reduced the re-stenosis rate following coronary angioplasty in central Europe (see Figure 5.11).[60,61] This study was criticized as being irrelevant to the United States population due to the fortification of US grains with folic acid. To date, there are no randomized trials of HCY lowering in patients with CKD or in dialy-

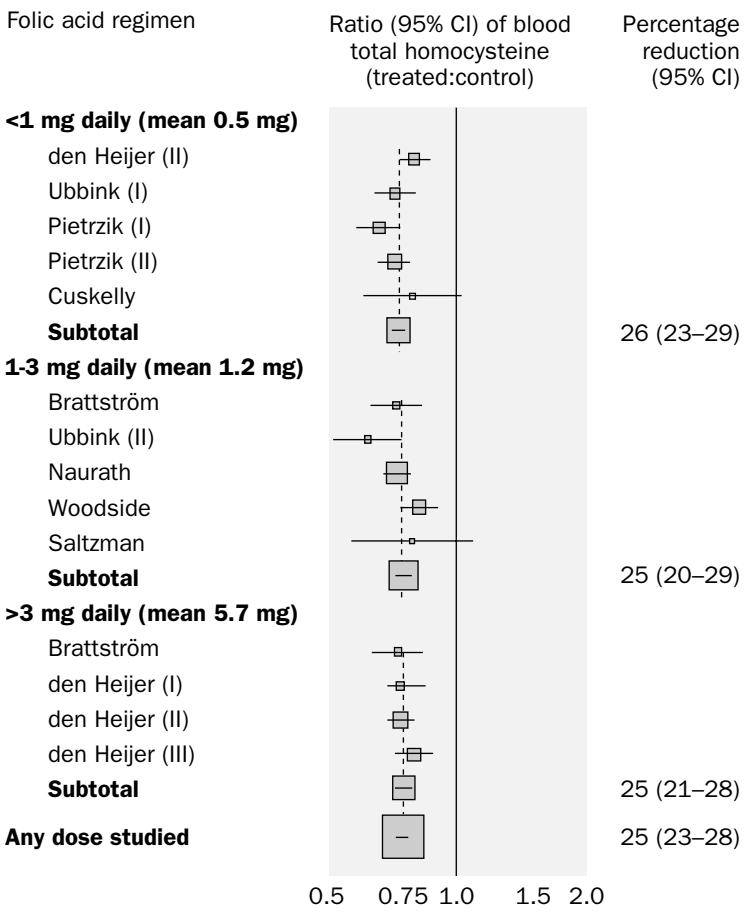

Fig. 5.10 Reductions in blood homocysteine concentrations with folic acid supplements according to pre-treatment blood concentrations of homocysteine, folate, and vitamin B_{12}. Squares indicate the ratios of post-treatment blood homocysteine among subjects allocated folic acid supplements to those of controls; size of square is proportional to number of subjects, and horizontal line indicates 95% confidence interval. Adapted from Homocysteine Lowering Trialists' Collaboration.[60]

Table 5.5 Predicted proportional reduction in blood homocysteine concentrations with folic acid supplementation (0.5–5 mg/day). Adapted from Homocysteine Lowering Trialists' Collaboration.[60]

	Folate concentrations before randomization (nmol/L)				
	20	*15*	*12*	*10*	*5*
Homocysteine concentrations before randomization (μmol/L)					
5	10%	13%	15%	16%	23%
10	19%	21%	23%	25%	30%
12	21%	23%	25%	27%	32%
15	23%	26%	28%	29%	34%
20	27%	29%	31%	32%	37%

sis patients. Large randomized clinical trials are underway. Presently, it seems wise to add folic acid supplementation 0.5–5 mg daily for people with CKD. These people are known to have elevated levels of homocysteine and are at higher risk of cardiovascular disease. Folic acid is inexpensive and well tolerated so that it presents a very good risk:benefit for the patient. However,

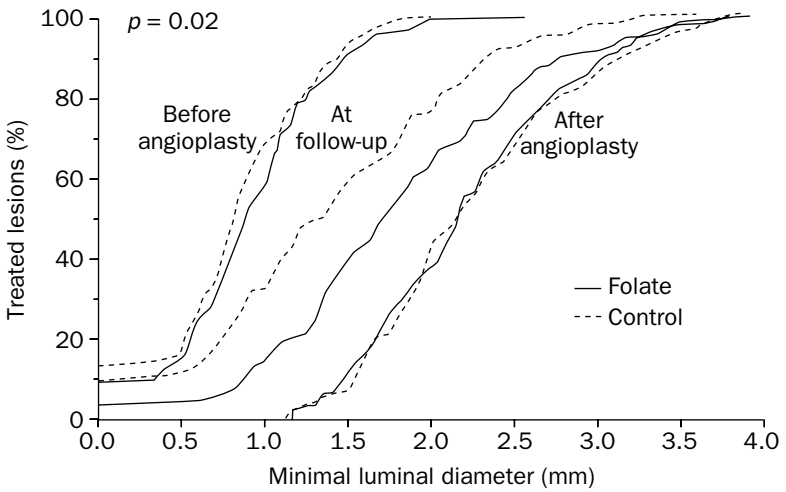

Fig. 5.11 Decreased rate of coronary re-stenosis after lowering of plasma homocysteine levels. Adapted from Schnyder.[61]

it must be remembered that the data this recommendation is based on are extrapolations from observational studies and their use cannot be claimed to be evidence-based at this time.

REFERENCES

1. NKF-K/DOQI Clinical practice guidelines; chronic kidney disease. Am J Kidney Dis 2002; **39**:S170–S212.
2. Ruilope LM, Salvetti A, Jamerson K et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the Hypertension Optimal Treatment (HOT) study. J Am Soc Nephrol 2001; **12**:218–225.
3. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med 2001; **134**:629–636 [See comments].
4. Levey AS, Beto JA, Coronado BE et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kid Dis 1998; **32**:853–906.
5. Shulman NB, Ford CE, Hall WD et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. Hypertension 1989; **13**:180–193.
6. Five-year findings of the hypertension detection and follow-up program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. JAMA 1979; **242**:2562–2571.
7. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med 1992; **152**:56–64.
8. Klag MJ, Whelton PK, Randall BL et al. Blood pressure and end-stage renal disease in men. N Engl J Med 1996; **334**:13–18.
9. Brancati FL, Whelton PK, Randall BL et al. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. JAMA 1997; **278**:2069–2074.
10. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med 2000; **160**:1093–1100.
11. Causes of death. USRDS. United States Renal Data System. Am J Kid Dis 1997; **30**:S107–S117.
12. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998; **317**:703–713 [See comments, published erratum appears in BMJ 1999 Jan 2; **318**:29].
13. Dahlof B, Devereux RB, Kjeldsen SE et al. Cardiovascular morbidity and mortality in the

Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; **359**:995–1003.
14. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345**:861–869 [See comments].
15. Wachtell K, Ibsen H, Olsen MH et al. Prevalence of renal artery stenosis in patients with peripheral vascular disease and hypertension. J Hum Hypertens 1996; **10**:83–85.
16. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. Kidney Int 2002; **61**:1486–1494 [Comment].
17. Jones CA, McQuillan GM, Kusek JW et al. Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis 1998; **32**:992–999 [Published erratum appears in Am J Kidney Dis 2000 Jan; **35**:178].
18. Ridao N, Luno J, Garcia de Vinuesa S et al. Prevalence of hypertension in renal disease. Nephrol Dial Transplant 2001; **16**(Suppl 1):70–73.
19. Port FK, Hulbert-Shearon TE, Wolfe RA et al. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kid Dis 1999; **33**:507–517 [See comments].
20. Klassen PS, Lowrie EG, Reddan DN et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. JAMA 2002; **288**:695–696.
21. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. J Am Soc Nephrol 2001; **12**:1079–1084 [Review 48 refs].
22. Foley RN, Parfrey PS, Harnett JD et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995; **47**:186–192.
23. Klahr S, Levey AS, Beck GJ et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994; **330**:877–884 [See comments].
24. Agodoa LY, Appel L, Bakris GL et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2001; **285**:2719–2728 [See comments].
25. Ruggenenti P, Perna A, Gherardi G et al. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy In Nephropathy. Lancet 1998; **352**:1252–1256 [See comments].
26. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; **339**:229–234.
27. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Moss SE. The incidence of hypertension in insulin-dependent diabetes. Arch Intern Med 1996; **156**:622–627.
28. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Eight to nine year mortality in known non-insulin dependent diabetics and controls. Kidney Int 1992; **41**:731–735.
29. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; **352**:837–853 [See comments, erratum appears in Lancet 1999 Aug 14; **354**:602].
30. Curb JD, Pressel SL, Cutler JA et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA 1996; **276**:1886–1892 [Published erratum appears in JAMA 1997 May 7; **277**:1356, see comments].
31. Hansson L, Lindholm LH, Niskanen L et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999; **353**:611–616 [See comments].
32. Tuomilehto J, Rastenyte D, Birkenhager WH et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. N Engl J Med 1999; **340**:677–684 [See comments].
33. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kid Int 2002; **61**:1086–1097.
34. Eastman RC, Keen H. The impact of cardiovascular disease on people with diabetes: the

potential for prevention. Lancet 1997; **350**(Suppl 1):SI29–SI32 [Review, 29 refs].
35. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med 2000; **160**:1093–1100.
36. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. Hyperinsulinemic microalbuminuria. A new risk indicator for coronary heart disease. Circulation 1995; **91**:831–837.
37. Parving HH, Lehnert H, Brochner-Mortensen J et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001; **345**:870–878 [See comments].
38. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; **345**:851–860 [See comments].
39. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345**:861–869 [See comments].
40. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000; **355**:253–299 [See comments].
41. McAlister FA, Levine M, Zarnke KB et al. The 2000 Canadian recommendations for the management of hypertension: Part one – therapy. Can J Cardiol 2001; **17**:543–559.
42. Ruilope LM, Salvetti A, Jamerson K et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. J Am Soc Nephrol 2001; **12**:218–252.
43. Bakris GL, Williams M, Dworkin L et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000; **36**:646–661.
44. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension final results of the systolic hypertension in the elderly program (shep). shep cooperative research group. JAMA 1991; **265**:3255–3264 [See comments].
45. Cooper ME. Renal protection and angiotensin converting enzyme inhibition in microalbuminuric type I and type II diabetic patients. J Hypertens Suppl 1996; **14**:S11–S14 [Review, 47 refs].
46. Bakris GL, Weir MR, DeQuattro V, McMahon FG. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. Kidney Int 1998; **54**:1283–1289.
47. Agodoa LY, Appel L, Bakris GL et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2002; **285**:2719–2728.
48. Mathiesen ER, Hommel E, Hansen HP, Smidt UM, Parving HH. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. BMJ 1999; **319**:24–25.
49. Grundy SM, Howard B, Smith S Jr et al. Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association. Circulation 2002; **105**:2231–2239.
50. NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis Online 2001; **37**:S182–S238 [Erratum appears in Am J Kidney Dis 2001 Aug; **38**:442].
51. Levin A, Thompson CR, Ethier J et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis Online 1999; **34**:125–134.
52. Silverberg DS, Wexler D, Sheps D et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001; **37**:1775–1780.
53. Besarab A, Bolton WK, Browne JK et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and erythropoietin. N Engl J Med 1998; **339**:584–590 [See comments].
54. Foley RN, Parfrey PS, Morgan J et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int 2000; **58**:1325–1335.
55. Parfrey PS, Foley RN, Harnett JD et al. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant 1996; **11**:1277–1285.

56. Agarwal R, Siva S, Dunn SR, Sharma K. Add-on angiotensin II receptor blockade lowers urinary transforming growth factor-beta levels. Am J Kidney Dis Computer file 2002; **39**:486–492.
57. Grimm RH Jr, Svendsen KH, Kasiske B, Keane WF, Wahi MM. Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Kidney Int Suppl 1997; **63**:S10–S14.
58. Gerstein HC, Mann JF, Yi Q et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001; **286**:421–426.
59. Meltzer S, Leiter L, Daneman D et al. 1998 clinical practice guidelines for the management of diabetes in Canada. Canadian Diabetes Association. CMAJ 1998; **159**(Suppl 8):S1–S29 [See comments, Review, 302 refs].
60. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. BMJ 1998; **316**:894–898.
61. Schnyder G, Roffi M, Pin R et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. N Engl J Med 2001; **345**:1593–1600.
62. Neal D, Lee P, Murphy B, Best J. Low-density lipoprotein particle size distribution in end-stage renal disease treated with hemodialysis or peritoneal dialysis. Am J Kidney Dis 1996; **27**:84–91.
63. Tobe SW, Pylypchuk G, Wentworth J et al. Improving car and quality of life for people with chronic illness. Abstract from Canadian Society of Nephrology, May 2003, Kidney International 2003.
64. Coresh J, Wei GL, McQuillan G et al. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the Third National Health and Nutrition Examination Survey (1988–1994) Arch Intern Med 2001; **161**:1207–1216.
65. Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; **1755**:1755–1762.
66. Nakao N, Yoshimura A, Morita H et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 2003; **361**:117–124.

6

Approaches to achieve blood pressure goals

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Introduction • Blood pressure goals • Barriers to achieving blood pressure goals • Treatment approaches • Summary • References

1. INTRODUCTION

There is little doubt that patients with even mild elevations in blood pressure should be managed pharmacologically. Clinical trial evidence demonstrating the benefit of drug therapy in hypertension continues to grow while meaningful differences between drug classes are becoming less apparent. One of the most important challenges in hypertension management today is to achieve the favorable results observed in clinical trials in the broader population of hypertensive patents seen in clinical practice. It appears that what is being accomplished in terms of achieving goal blood pressure (BP) in the general population of hypertensive patients has fallen well short of what should be expected based on trial evidence.[1] This chapter reviews and analyses the available evidence regarding various treatment approaches to hypertension management and their impact on achievement of goal blood pressure.

2. BLOOD PRESSURE GOALS

The ultimate goal of antihypertensive therapy is to reduce the risk of microvascular and macrovascular complications that occur secondary to elevated blood pressure (BP). There is disagreement as to what is the most appropriate BP goal for patients with hypertension.[2] It is generally accepted that patients with hypertension complicated by the presence of end-organ damage or risk factors for coronary heart disease (such as diabetes) require greater reductions in BP to prevent adverse clinical events.

The most recent BP targets recommended by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) as well as all other organizations focused preservation of kidney function are summarized in Table 6.1.[1] The JNC VI recommends a target BP of $<140/90$ mmHg for uncomplicated hypertension. The Hypertension Optimal Treatment (HOT) trial found that the fewest major adverse clinical events occurred at a mean treated BP of 138/83 mmHg and that the lowest risk of cardiovascular mortality occurred at a BP of 139/86 mmHg.[3] Lower BPs did not further reduce or increase adverse clinical events and mortality, except for an apparent increase in risk in a subgroup of patients whose diastolic BP were reduced to less than 70 mmHg. The World

Table 6.1 Summary of blood pressure targets in hypertensive patients with either diabetes or renal insufficiency

Group	*Year*	*Goal BP (mmHg)*	*Initial therapy*
Canadian HTN Society	2002	<130/80	ACEI/ARB
American Diabetes Association	2002	<130/80	ACEI/ARB
National Kidney Foundation (CKD)	2002	≤130/80	ACEI/ARB
National Kidney Foundation	2000	≤130/80	ACEI
British HTN Society	1999	<140/80	ACEI
WHO/ISH	1999	<130/85	ACEI
JNC VI	1997	<130/85	ACEI

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II blocker; CKD, chronic kidney disease.

Health Organization (WHO) and International Society of Hypertension (ISH) recommend a target BP <130/85 mmHg for uncomplicated hypertension.

In patients with isolated systolic hypertension (ISH), the JNC VI recommends a target systolic BP of <140 mmHg if possible.[1] Considering that some patients may have markedly elevated untreated systolic pressures, the JNC VI suggests that 160 mmHg can be used as an interim goal. Caution must be taken when treating patients with ISH as there is evidence that when diastolic pressures are reduced to less than 65 mmHg, the risk of stroke is actually increased.[2]

In patients with renal parenchymal disease from any cause, the current JNC VI BP target is <130/85 mmHg for patients without proteinuria and <125/75 mmHg in patients with proteinuria (>1 g/24 h).[1] The Canadian Hypertension Society recommends a BP goal in patients with nephropathy which is slightly lower (130/80 mmHg) than that recommended by JNC VI.[4] This more aggressive goal is supported by the findings of the HOT trial, the Modification of Diet in Renal Disease (MDRD) trial, and the United Kingdom Prospective Diabetes Study (UKPDS).[3,5,6]

The JNC VI recommended the BP target in patients with diabetes is <130/85 mmHg. In the UKPDS, however, the lower the systolic BP (at least down to 110 mmHg), the lower the risk of microvascular and macrovascular complications.[6] The impact of changes in diastolic BP and resultant rates of complications was not evaluated in the UKPDS.

3. BARRIERS TO ACHIEVING BLOOD PRESSURE GOALS

It is clear that the number of patients achieving even the modest BP goal of < 140/90 mmHg is unacceptable with only 27% of hypertensive patients being controlled (Table 6.2).[1] A major reason that BP is not being controlled is that nearly 32% of patients are not aware they are hypertensive (Table 6.3). Of patients who are aware, 15% are not treated. Of the 54% being treated, almost half are not being treated to goal. Efforts to enhance screening and identification of undiagnosed hypertensives and more aggressive treatment of patients already on antihypertensive therapy should increase the percentage at goal. Potential causes of an inadequate response to anithypertensive therapy are summarized in Box 6.1.

3.1 Technical barriers

An accurate BP measurement should not be difficult to obtain. Attention to the use of an appropriately sized cuff, having the patient seated for at least 5 minutes prior to BP measurement, having patients refrain from smoking

Table 6.2 Trends in the awareness, treatment, and control of high blood pressure in adults: United States, 1976–1994

	NHANES II (1976–80)	*NHANES III (Phase 1) (1988–91)*	*NHANES III (Phase 2) (1991–94)*
Awareness	51%	73%	68%
Treatment	31%	55%	53%
Control	10%	29%	27%

NHANES, National Health and Nutrition Examination Survey.

Table 6.3 Why goal blood pressures are not being achieved

NHANES III (Phase 2)	*Data*	*Difference*
Aware	68.4%	
		14.8% aware but not treated
Treated	53.6%	
		26.2% treated but not controlled
Controlled	27.4%	

NHANES, National Health and Nutrition Examination Survey.

or ingesting caffeine for at least 30 minutes prior to BP measurement, using an appropriately calibrated BP recording device, and taking a minimum of two BP readings two minutes apart, are important considerations in obtaining accurate BP measurements. 'White coat' hypertension and pseudohypertension typically seen in the elderly are common causes of falsely elevated BPs.[1]

3.2 Patient barriers

The most common patient-related causes of treatment failure typically occur secondary to compliance problems.[7] Patient noncompliance may result from a lack of understanding about the disease process, the development of side effects leading to a reduction in quality of life, cost of medication, or limited access to medical care. It should be pointed out, that even when cost of drugs and access to medical care are considered adequate, treatment of BP often remains substandard.[8] The JNC VI has made a number of recommendations for improving patient compliance to antihypertensive therapy (Box 6.2).[1]

Another patient-related reason for a failure to achieve BP goals is the inability of patients to initiate and/or maintain therapeutic lifestyle changes.[9] Excess sodium intake leading to volume overload, excessive alcohol consumption, marked obesity, and ingestion of substances known to raise the BP or interfere with the action of antihypertensive therapy, are all potential reasons for failure to achieve BP goals.

Box 6.1 Potential causes of inadequate response to antihypertensive therapy

Technical Barriers
- 'White coat' hypertension
- Pseudohypertension
- Improper BP assessment technique

Patient-related causes
- Noncompliance
- Access to medical care
- Costs of drugs
- Side effects to drugs
- Lack of understanding of disease process
- Failure to initiate/maintain lifestyle changes
- Ingestion of aggravating substances

Physician-related causes
- Failure to intensify therapy (especially with elevated systolic BP)
- Time/practice limitations
- Knowledge base
- Fear of side effects to drugs

Box 6.2 JNC VI Recommendations to improve patient adherence to antihypertensive therapy

- Be aware of signs of patient nonadherence to antihypertensive therapy.
- Establish the goal of therapy: to reduce blood pressure to nonhypertensive levels with minimal or no adverse effects.
- Educate patients about the disease, and involve them and their families in its treatment. Have them measure blood pressure at home.
- Maintain contact with patients; consider telecommunication.
- Keep care inexpensive and simple.
- Encourage lifestyle modifications.
- Integrate pill-taking into routine activities of daily living.
- Prescribe medications according to pharmacologic principles, favoring long-acting formulations.
- Be willing to stop unsuccessful therapy and try a different approach.
- Anticipate adverse effects, and adjust therapy to prevent, minimize, or ameliorate side effects.
- Continue to add effective and tolerated drugs, stepwise, in sufficient doses to achieve the goal of therapy.
- Encourage a positive attitude about achieving therapeutic goals.
- Consider using nurse case management.

3.3 Physician and health care system barriers

A number of studies have confirmed that physicians are not aggressive enough in treating hypertension to goal. In a survey of 11 000 cardiac patients in Europe, 84% who had BPs above their target did not have their medication regimens altered.[10] The physicians of these same patients indicated that they would be willing to change medication regimens by increasing doses, adding a new drug, or by switching drugs. A physician survey conducted by the National Heart, Lung, and Blood Institute of 3740 physicians from a variety of disciplines in the United States indicated that the most common reasons for failure to control BP were failure to change lifestyle (67%), failure to take medications as instructed (42%), patient lack of understanding (39%), costs of drugs (39%), adverse drug effects (34%), and physician fees (23%).[11]

Berlowitz et al. examined the care of 800 hypertensive patients treated at five New England Veterans Affairs clinics over a two year period.[8] Of the patients, 40% had BP readings $> 160/90$ mmHg despite an average of six hypertension-related visits per year. Only 25% of patients had BP readings $< 140/90$ mmHg. Over the two year follow-up, there were a total of 6391 hypertension visits. In patients with systolic BP > 155 mmHg and diastolic BP > 90 mmHg, medications were changed at 25.6% of visits. When the systolic BP was > 165 mmHg and the diastolic BP was < 90 mmHg, medication changes occurred at 21.6% of visits. Increases in therapy were most common (35% of the time) at visits where the diastolic BP was > 90 mmHg and a change in therapy occurred at the preceding visit.

Oliveria, et al. conducted a similar study in the Henry Ford Health System in the Detroit metropolitan area.[12] Survey data on 270 patient visits where BP was uncontrolled was collected. Medication changes occurred at only 38% of these visits. The most common reason cited for the failure to make medication adjustments was that physicians were satisfied with the existing BP value (56%). Other reasons cited for not changing medication regimens were that additional monitoring was needed before changing the drug regimen (35%), the focus of the visit was not for hypertension (29%), poor patient acceptance (9%), the priority was to improve compliance (9%), and intensifying therapy would cause side effects (5%). The majority of the physicians surveyed indicated that they were aware of and followed the JNC VI guidelines. The BP at which these physicians recommended initiation of drug therapy was between

87 mmHg and 91 mmHg diastolic and between 142 mmHg and 150 mmHg systolic. These physicians also indicated that they thought that 57–61% of their patients had their BP controlled.

The studies by Berlowitz and Oliveria clearly indicate that there is a division between the theory and practice of hypertension management when physicians, faced with patients with elevated BP and a history of hypertension, change medications in only 22–38% of these patients.[8,12] This division occurs despite evidence that physicians are aware of guidelines recommending more aggressive treatment and that physicians indicate a willingness to change therapy when faced with an uncontrolled BP. It appears that a major component of the failure to treat uncontrolled BP is a lack of appreciation that the systolic BP is the best predictor of morbidity and mortality. These studies also indicate that access to health care and the costs of drugs are less important in achieving BP goals as compared to the aggressiveness of physician management.

A recommendation to minimize the number of inadequately treated hypertensive patients has recently been proposed.[13] This recommendation focuses on five key questions: (1) Is the blood pressure being measured accurately and have confounders such as 'white coat' hypertension, been evaluated? (2) Is the patient taking medications or other substances that adversely affect BP? (3) Does the patient have an aggravating condition, such as sleep apnea secondary to obesity? (4) Is the patient compliant with their medication regimen? (5) Is the patient receiving an unbalanced medication regimen using multiple medications from the same therapeutic class? Once these questions have been adequately addressed and the BP remains elevated, secondary causes would then need to be considered.

4. TREATMENT APPROACHES

4.1 Selection of drug therapy

The most important action to slow progressive renal failure in hypertensive patients is to lower the BP to goal.[14] All classes of antihypertensives are effective in lowering BP in renal insufficiency, but the use of multiple drugs is usually necessary to achieve the BP goal. All national and international recommendations, including the JNC VI, the WHO/ISH, and the American Diabetes Association, indicate that angiotensin-converting enzyme inhibitors (ACEIs) are the preferred initial agent for patients with hypertension and renal parenchymal disease or renovascular disease and for patients with hypertension and diabetes.[1,4,15] This recommendation is based on the finding that ACEIs have been shown to be renoprotective independent of their BP-lowering effect. The dose of ACEI should be titrated into the moderate or high dose range as tolerated.[1] After an ACEI is started, an initial transient rise in serum creatinine may occur over the first 2–3 months of therapy.[16] If the serum creatinine increases more than 1 mg/dL above baseline, the serum potassium and creatinine should be remeasured. If they remain persistently elevated, a diagnosis of renal artery stenosis should be considered. If renal artery stenosis is confirmed, ACEI and angiotensin II receptor blockers (ARBs) should be discontinued as these drugs can cause renal failure in this setting.[17] In patients with renal artery stenosis, percutaneous transluminal renal angioplasty (PTRA) with or without stenting should be considered.[18] For patients where PTRA is not technically feasible, surgical revascularization should be considered.

The use of ACEI as first-line therapy in patients at risk of nephropathy is supported by a number of randomized trials, the most recent of which were the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO-HOPE) substudy of the Heart Outcomes Prevention and Evaluation (HOPE) trial and the African American Study of Kidney Disease and Hypertension (AASK) trial.[19,20] The development of nephropathy was reduced by 24% (95% CI, 3–40%; $p = 0.027$) with ramipril treatment in the MICRO-HOPE trial over a 4.5 year follow-up. The reduction in nephropathy was independent of BP reduction.

The change in slope of glomerular filtration rate (GFR) decline was not significantly different

across drug treatment groups or BP target groups in the AASK.[20] Ramipril did reduce the composite risk of reduced GFR, end-stage renal disease, and death by 22% compared to metoprolol ($p = 0.042$) and 38% compared to amlodipine ($p = 0.005$). Metoprolol reduced the risk of the combined secondary end-points by 19% compared to amlodipine, but this was not significant ($p = 0.19$). The BP targets did not have an effect on the development of the combined secondary endpoints. The AASK investigators concluded that achievement of even the modest BP target of 140/90 mmHg was sufficient to reduce the progression of renal disease. The results of the MICRO-HOPE and AASK have reconfirmed the importance of ACEI therapy as the cornerstone of antihypertensive therapy in patients with or at risk of nephropathy.

For patients who cannot take ACEI, the angiotensin II receptor blockers (ARBs) have been shown to have a favorable impact on cardiovascular mortality and the progression of nephropathy. Moreover, for people with nephropathy from type 2 diabetes, ARBs are the only class of antihypertensive agents proven to reduce the rise of end-stage renal disease (ESRD). Therefore, the most recent recommendations by the American Diabetes Association and the Canadian Hypertension Society support the use of ARBs as first-line agents in people with nephropathy and proteinuria resulting from diabetes (See Table 6.1). The trials on which these recommendations are based are discussed later in this chapter. Moreover, The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study found that the primary outcomes (myocardial infarction, cardiac mortality, and stroke) occurred in 11% of losartan patients compared with 13% of atenolol patients ($p = 0.009$).[21] The primary reason for the reduction in the composite outcome was a significantly lower risk of stroke with losartan (5%) versus atenolol (7%) ($p = 0.0006$). In a subgroup analysis of 1195 diabetic patients enrolled in the LIFE trial, the primary composite outcome, cardiovascular mortality, total mortality, and admission for heart failure were significantly reduced with losartan compared to atenolol.

Three recent randomized controlled trials have confirmed the beneficial effects of ARBs in reducing the progression of nephropathy.[22–24] In the Irbesartan Microalbuminuria in Type 2 Diabetic Subjects (IRMA-2) study, patients with hypertension and type 2 diabetes and with microalbuminuria were randomized to irbesartan 150 mg/d, irbesartan 300 mg/d and placebo.[22] The primary end-point of this trial was the development of proteinuria at $>$ 300 mg/d or a 30% increase in proteinuria over baseline. The 300 mg dose of irbesartan reduced the achievement of the primary end-point by 70% compared to placebo ($p > 0.0004$). The 150 mg irbesartan dose reduced the primary end-point by 39%, but this was not statistically significant ($p = 0.085$). In the Irbesartan Diabetes Nephropathy Trial (IDNT), irbesartan 300 mg/d was compared to amlodipine 10 mg/d and placebo in 1715 hypertensive patients with type 2 diabetes with proteinuria $>$900 mg/d.[23] The primary end-point was the first occurrence of the doubling of the serum creatinine, the development of ESRD, or death. Irbesartan reduced the primary end-point by 26% versus placebo ($p = 0.02$) and 34% versus amlodipine ($p = 0.006$). In the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) trial, 1513 patients with type 2 diabetes and proteinuria $>$ 900 mg/d, losartan 50–100 mg/d was compared to placebo.[24] The primary end-point in this study was the first occurrence of a doubling of serum creatinine, the development of ESRD, or death. Losartan reduced the occurrence of the primary end-point by 16% compared to placebo ($p = 0.024$).

In patients not achieving their BP goal with ACEI or ARB monotherapy, additional drugs should be added to achieve the BP target. All of the major trials evaluating the intensity of BP reduction with event reduction in patients with diabetes and/or nephropathy have demonstrated that to achieve aggressive BP reductions requires an average of 3.2 different medications per day.[14] Diuretics are a reasonable addition to an ACEI or ARB as they produce additive BP-lowering effects and are inexpensive. Thiazides

may be used if renal insufficiency is not advanced (serum creatinine < 2.5 mg/dL).[1] If patients have advanced renal insufficiency, a loop diuretic with or without metolazone will be required.[1]

Alternative therapies to diuretics may be considered given the presence of other disease states. Beta-blockers lower BP effectively especially when the resting heart rate is greater than 84 beats per minute.[25] If the heart rate is lower than this, beta-blockers have little additional effect on BP when combined with ACEI. Combinations of beta-blockers with ACEIs or ARBs have not been shown to have additive effects on renal disease progression.[14] Beta-blockers do reduce cardiovascular risk in patients with ischemic heart disease, especially in those with diabetes.[26]

The renal protective effects of calcium channel blockers (CCBs) is less consistent than that of ACEIs or ARBs.[14] Non-dihydropyridine CCBs (diltiazem, verapamil) have been shown to reduce proteinuria and nephropathy progression independent of ACEI therapy.[27,28] Dihydropyridine CCBs have not been shown to slow renal disease progression in patients with established nephropathy in the absence of an ACEI.[14,29–31] Table 6.4 summarizes the differences between dihydropyridine and non-dihydropyridine CCBs which explain the differential effects of CCBs on renal morphology and function.

In patients with early forms of diabetic nephropathy and preserved renal function (GRF > 80 mL/min), however, dihydropyridine CCBs have been shown to slow renal disease (ABCD trial).[31] This is most likely the result of aggressive BP lowering ($<130/80$ mmHg) rather than a specific effect of the CCB. Once renal disease is established, dihydropyridine CCBs should not be used in the absence of an ACEI to preserve renal function.

The benefits of CCBs on cardiovascular risk in patients with nephropathy and/or diabetes are also not uniform. The non-dihydropyridine CCBs (diltiazem, verapamil) have been shown to reduce cardiovascular morbidity and mortality (MDPIT, DAVIT II, NORDIL).[32–34] The non-dihydropyridine CCBs should be avoided in patients with heart failure and used cautiously in patients receiving beta-blockers because of their additive adverse effects on conduction and contractility. Studies with dihydropyridine CCBs have produced conflicting results. The results of the ABCD and FACET studies indicate that cardiovascular events were more likely to occur with dihydropyridine CCBs than with ACEI.[35,36] In contrast, the HOT, Syst-Eur, and INSIGHT studies found a favorable effect of dihydropyridines on cardiovascular morbidity and mortality.[3,37,38]

Other classes of drugs (alpha-blockers, centrally acting adrenergic inhibitors, direct-acting vasodilators) may be added to the drug regimens

Table 6.4 Factors that help explain the differential effects of CCBs on renal morphology and function

Parameter	*CCB effect*	
	DHP, CCBs	*Non-DHP CCBs*
Albuminuria/proteinuria	–	↓[a]
Mesangial volume expansion (diabetes)[b]	–	↓
Glomerular scarring[b]	–	↓
Renal autoregulation[c]	Abolished	Partially abolished

[a] Decreased only if BP reduced and on low salt diet.[b] Data from animal models.[c] Data from both animal and human experiments. CCB, calcium channel blocker; DHP, dihydropyridine; –, no effect; ↓, decrease. Adapted from Bakris et al, 1997.[28]

of patients with renal disease or diabetes to achieve BP goals. However, none of these agents have been shown to specifically preserve renal function independent of their use with ACEIs or their effect on BP.[14] These drugs should be considered only as second- or third-line therapy following the use of ACEIs ARBs, or non-dihydropyridine CCBs.

4.2 Management of proteinuria

Excess excretion of urinary albumin is a marker for endothelial cell injury in both the kidney and peripheral vasculature. Any degree of albuminuria portends a poor renal and cardiovascular outcome in diabetic patients.[39] In non-diabetic patients, albuminuria is associated with a higher incidence of adverse cardiovascular events. Microalbuminuria (>30 mg/day to <300 mg/day) is indicative of increased vascular permeability, while frank proteinuria indicates the presence of either glomerular or tubulointerstitial disease. Patients with frank proteinuria invariably progress to end-stage renal disease.

Data from several trials have demonstrated that the severity of albuminuria at baseline correlates with the speed and severity of deterioration in renal function.[40,41] The greater the degree of baseline proteinuria, the greater the reduction in BP required to slow renal disease progression. Clinical trials in patients who have lost more than 35% of their renal function, with or without diabetes have shown that reductions in proteinuria of more than 30% below baseline produce marked reductions in renal disease progression.[39–42] Correlation between reductions in proteinuria and preservation of renal function in patients with near-normal renal function (GFR > 80 mL/min) at baseline have been inconsistent.[14] Reductions in BP in hypertensive patients without reductions in proteinuria do not provide maximal protection against renal disease progression.[14,39]

ACEIs have been shown to delay progression of renal disease in patients with type 1 diabetes, renal insufficiency, and proteinuria.[14] ARBs have been shown to provide renal protection in patients with type 2 diabetes, renal insufficiency, and proteinuria.[22–24] Although it should be expected that both ACEI and ARBs would have favorable effects in patients with either type 1 or 2 diabetes, there is little evidence with ARBs in type 1 diabetes and ACEI in type 2 diabetes. The addition of CCBs to ACEIs have been shown to reduce proteinuria as well as cardiovascular events in patients with diabetes.[14,36] Other classes of antihypertensive agents, although effective in reducing BP, have not been shown to reduce proteinuria or delay renal disease progression.[14]

4.3 Treatment approaches

The traditional approaches to the initiation of drug therapy for hypertension have typically been referred to as 'stepped-care' or 'substituted monotherapy'.[1] Although the efficacy of these treatment approaches have not been directly compared, achievement of a target BP of <130/80 mmHg is unlikely using the substituted monotherapy approach unless the elevation in baseline BP is very mild.[3] In substituted monotherapy approach, patients are started on an initial low dose of a drug. If the BP goal is not achieved, the patient is switched to an agent from another class. Dosage titration can occur prior to the switch. The net result is that patients are switched from agent to agent until a single drug is found which controls the BP. The theoretical advantage of such an approach is the use of fewer drugs, fewer side effects, better compliance, and lower drug cost. The disadvantages are the potential delay in finding a single drug that works and the reality that only a minority of patients will ultimately be controlled with a single drug. It is estimated that only 20% of patients will respond to initial dose substituted monotherapy and only 30–55% of patients will respond to titrated-dose monotherapy (each drug titrated to maximal doses prior to any switch).[43] Even when drug class selections are based on race and age in mild hypertension (baseline BP 155/100 mmHg), titrated monotherapy will only control 55–68% of patients.[44] Claims of very high monotherapy success rates (approaching 80%), are based on treatment of patient populations without comorbidities and very mild hypertension. In

the Treatment of Mild Hypertension Study (TOMHS), for instance, amlodipine achieved a 78% success rate.[45] However, the mean baseline BP in his study was only 140/91 mmHg.

In the stepped-care approach, patients are started on an initial drug and monitored for an appropriate interval. If the BP goal is not reached and there are no significant side effects, a second drug from another therapeutic class is added. If BP targets are not reached, a third or even a fourth agent is then added sequentially. Depending on the drug class and the patient population, dose titration prior to the addition of other drugs may be appropriate. Some drug classes, however, have relatively flat-dose response curves with little additional BP gain following dose titration.[46] Obviously, if significant side effects occur, drug discontinuance and substitution of another agent will be required. The primary disadvantage of this approach is that a greater number of drugs has to be taken leading to a more complex regimen, lower compliance, and greater cost. To achieve BP targets in the majority of high-risk patients, however, combination therapy is the norm and not the exception.

Regardless of the treatment approach, it is important to remember that patient response to individual drugs may vary widely. Despite this variance, the magnitude of the BP reduction with the most commonly used classes of antihypertensive drugs is typically no more than 10–14 mmHg systolic and 6–8 mmHg diastolic.[47] In a meta-analysis of the four major drug classes (ACEIs, beta-blockers, CCBs, and diuretics), there were no significant differences in the magnitude of the BP-lowering effect among these classes.[47] This may occur in part because of the phenomenon known as 'the regression to the mean'. Regardless, if a patient requires a reduction in systolic BP of 15 mmHg or more and/or a reduction in diastolic BP of 10 mmHg or more, the likelihood that goal BP can be achieved with monotherapy is not good. Hence, patients requiring this magnitude of BP reduction will generally require the use of two or more antihypertensive agents.

There are a number of drug combinations (two drugs taken separately) that have shown additive effects on BP reduction and/or cardiovascular event reduction.[46] A diuretic added as a second-line agent to an ACEI, an ARB or a beta-blocker is an excellent choice as this combination produces additive BP reductions at little additional cost. In addition, combinations of an ACEI, an ARB or a beta-blocker plus a diuretic are available as fixed-dose combinations (both drugs in a single pill) which reduces the number of pills that patients are required to take (Table 6.5). The combination of a CCB with a diuretic have produced mixed BP lowering results. This combination often produces only minimal additional BP-lowering over the use of either agent alone. This may result in part from the finding that CCBs, especially the dihydropyridines, are naturetic.[46]

The combination of an ACEI with a beta-blocker produces additive BP lowering only if

Table 6.5 Examples of fixed-dosed combination products for hypertension

BB + Diuretic	*ACEI + Diuretic*	*ARB + Diuretic*	*CCB + ACEI*
Corzide	Capozide[a]	Hyzaar	Lexxell
Inderide LA	Lotensin HCT	Diovan HCT	Lotrel
Lopressor HCT	Prinzide	Micardis-Plus	Tarka
Tenoretic	Vaseretic		Teczem
Ziac[a]	Zesteretic		

[a] Approved for initial therapy. BB, beta-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker. Adapted from Bakris et al, 1997.[2]

the resting heart rate is 84 beats per minute or higher.[25] Unlike the data supporting their combined use patients with heart failure, there is no evidence that a combination of an ACEI and a beta-blocker produces additive benefit on cardiovascular events or renal disease progression in patients with diabetes or renal disease.[14] The primary benefit of adding beta-blockers to ACEI is one of BP reduction and management of documented ischemic heart disease or heart failure. The combined use of an ACEI and CCB produces both an additive reduction in BP and cardiovascular events.

One of the principles of selecting agents for use in antihypertensive combination is to choose agents with different mechanisms of action.[48] It is important to note that when ACEIs and ARBs are combined, they produce additive BP reductions with little or no increase in side effects. The combined use of a dihydropyridine and a non-dihydropyridine CCB has been shown to produce substantial additive BP reductions.[49] However, the combined use of two CCBs has been associated with a substantial increase in side effects, primarily peripheral edema. At the present time, the use of combinations of drugs with similar mechanisms of actions should be limited to patients failing BP control with drug combinations of agents with different mechanisms of action.

Given the fact that patients with hypertension and diabetes or renal disease are typically receiv-

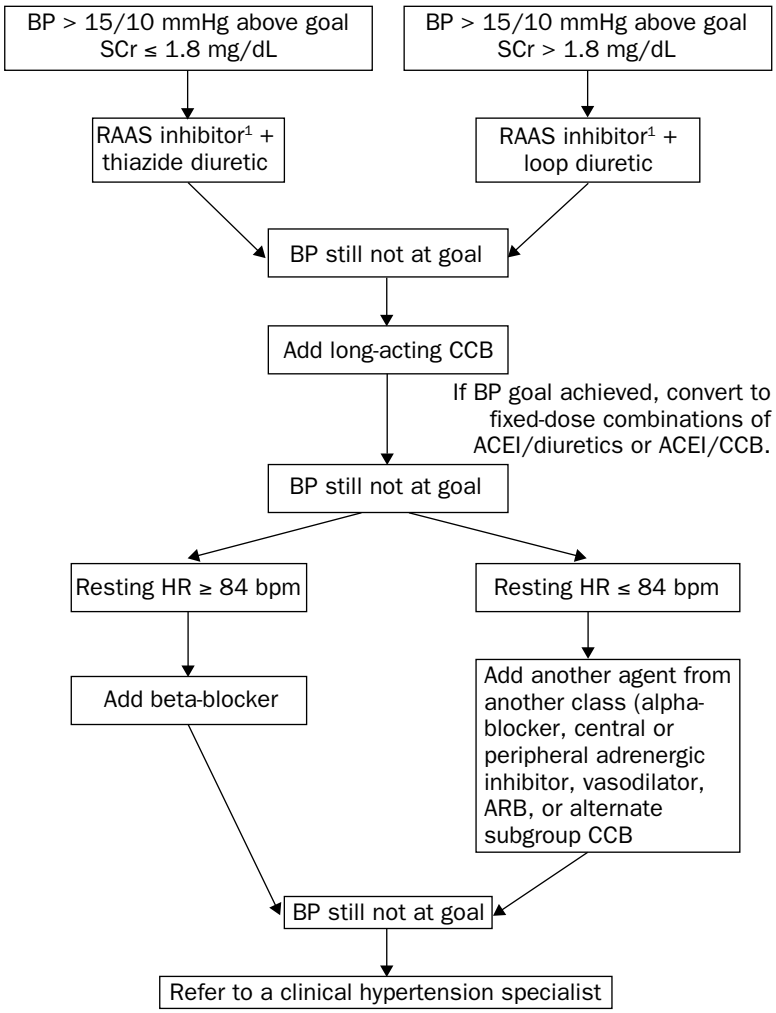

Fig. 6.1 Proposed algorithm for patients with hypertension and either diabetes or renal insufficiency with baseline BP > 15/10 mmHg above treatment BP goal. This algorithm is suggested for patients without other documented clinical conditions (angina, myocardial infarction, heart failure) for which many of the medications recommended here would already be used. SCr, serum creatinine; RAAS, renin-angiotensin-aldosterone system; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker. ACEI preferred for type 1 diabetes; ARBs preferred for type 2 diabetes. ACEI should be titrated to high doses if tolerated; ARB may be substituted for ACEI if side effects occur. Adapted from Bakris et al, 1997.[28]

ing a large number of medications, the use of a fixed-dose combination product appears to make both practical and economic sense.[43,47] Figure 6.1 outlines a treatment approach recommended for patients with hypertension and renal insufficiency or diabetes with a baseline BP >15/10 mmHg above their target BP. Unless BP is <140/90 mmHg at the time of initiation of therapy, the initial choice of drug therapy should be a combination of an ACEI plus a thiazide or loop diuretic (depending on renal function). If the patient cannot take an ACEI because of hypersensitivity or if they develop a dose-limiting side effect, an ARB can be substituted for the ACEI. If the BP goal is not achieved on an ACEI/ARB plus diuretic combination, a long-acting CCB should be added. If BP is still not controlled after the addition of a CCB, a number of other treatment options are available including the addition of a beta-blocker, an alpha-blocker, a centrally or peripherally acting adrenergic inhibitor, or even another CCB or an ARB.

SUMMARY

Current evidence-based recommendations indicate that the goal BP for patients with hypertension and renal disease or diabetes should be 130/80 mmHg or lower. In patients with proteinuria greater than 1 gm/d and renal insufficiency, the goal BP should be 125/75 mmHg or lower. Caution is advised not to lower the diastolic below 65 mmHg in elderly patients with isolated systolic hypertension. ACEIs (or ARBs in patients unable to take ACEIs) are the initial drugs of choice in patients with diabetes or renal insufficiency because of the ability to slow progression of renal disease and to reduce cardiovascular morbidity and mortality. It is also clear, however, that to achieve the aggressive BP targets needed to slow the progression of renal disease, that combinations of antihypertensive therapy are required. The addition of diuretics, CCBs, and beta-blockers to ACEIs would seem appropriate. The use of fixed-dose combinations of ACEIs and a diuretic, ACEIs and CCBs, and ARBs and a diuretic may improve patient compliance and lower costs. Achieving BP targets requires attention to technical issues as well as patient and physician-related factors. Perhaps the most important of these barriers is the failure of physicians to intensify treatment in hypertensive patients presenting with a BP not at target. Clinical trial evidence has clearly demonstrated the value of achieving target BP in reducing the progression of renal disease and reduce cardiovascular morbidity and mortality. The challenge today is to accomplish in the general population of hypertensive patients what has been demonstrated to be possible in randomized clinical trials.

REFERENCES

1. JNC Committee (JNC VI). The sixth report of the Joint National Committee on the prevention, detection, evaluation, and treatment of high blood Pressure. Arch Intern Med 1997; **157**: 2413–2446.
2. Kaplan NM. What is goal blood pressure for the treatment of hypertension? Arch Intern Med 2001; **161**:1480–1482.
3. Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet 1998; **351**:1755–1762
4. Feldman RD. The 1999 Canadian recommendations for the management of hypertension. On behalf of the Task Force for the Development of the 1999 Canadian Recommendations for the Mangaement of Hypertension. Can J Cardiol 1999; **15**(Suppl G):S57G–S64G.
5. Lazarus JM, Bourgoignie JJ, Buckalew VM et al. Achievement and safety of a low BP goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. Hypertension 1997; **29**:641–650.
6. Adler AI, Stratton HA, Neil HAW et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; **321**:412–419.
7. Miller NH, Hill M, Kottke T, et al. The multilevel compliance challenge: recommendations for a call to action; a statement for healthcare professionals. Circulation 1997; **95**:1085–1090.
8. Berlowitz DR, Ash AS, Hickey EC et al. Inadequate management of blood pressure in a

hypertensive population. N Engl J Med 1998; **339**:1957–1963.
9. Puddey IB, Parker M, Beilen LJ et al. Effects of alcohol and caloric restrictions on blood pressure and serum lipids in overweight men. Hypertension 1992; **20**:533–541.
10. Taylor Nelson Healthcare (market research survey). Epsom, UK: Copyright Cardiomonitor 1992.
11. Diagnosis and management of hypertension–1987: A nationwide survey of physicians' knowledge and reported behavior. Bethesda, MD: National Heart, Lung and Blood Institute, National Institutes of Health, US Department of Health and Human Services 1989.
12. Oliveria SA, Lapuerta P, McCarthy BD et al. Physician-related barriers to the effective management of uncontrolled hypertension. Arch Intern Med 2002; **162**:413–420.
13. O'Rorke JF, Richardson WS. What to do when blood pressure is difficult to control. BMJ 2001; **322**:1229–1232.
14. Bakris GL, Williams M, Dworkin L et al. Preserving renal function in adults with hypertension and diabetes: A consensus approach. Am J Kidney Dis 2000; **36**:646–661.
15. American Diabetes Association. Clinical practice recommendations 1999. Diabetes Care 1999; **22**(Suppl. 1):S1–S114.
16. Klahr S, Levey AS, Beck GJ et al. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. N Engl J Med 1994; **330**:877–884.
17. Textor SC. Renal failure related to angiotensin-converting enzyme inhibitors. Semin Nephrol 1997; **17**:67–76.
18. Bonelli FS, McKusick MA, Textor SC et al. Renal artery angioplasty: technical results and clinical outcome in 320 patients. Mayo Clin Proc 1995; **70**:1041–1052.
19. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; **355**:253–259.
20. Agodoa LY, Appel L, Bakris GL et al. African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomized controlled trial. JAMA 2001; **285**:2719–2728.
21. Lindholm LH, Ibsen H, Dahlof B et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002; **359**:1004–1010.
22. Parving HH, Lehnert H, Brochner-Mortensen J et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001; **345**:870–878.
23. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345**: 861–869.
24. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; **345**:851–860.
25. Belz GG, Breithaupt K Erb K et al. Influence of the angiotensin converting enzyme inhibitor cilazapril, the beta-blocker propranolol and their combination on haemodynamics in hypertension. J Hypertens 1989; **7**:817–824.
26. Giugliano D, Acampora R, Morfella R et al. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial. Ann Intern Med 1997; **126**:955–959.
27. Bakris GL, Copley JB, Vicknair N et al. Calcium channel blockers versus other antihypertensive therapies on progression of non-insulin-dependent diabetes mellitus associated nephropathy. Kidney Int 1996; **56**:1641–1650.
28. Bakris GL, Mangrum A, Copley JB et al. Effect of calcium channel or beta-blockade on the progression of diabetic nephropathy in African Americans. Hypertension 1997; **29**:744–750.
29. Ruggenenti P, Perna A, Benini R et al. Effects of dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibition, and blood pressure control on chronic non-diabetic nephropathies. J Am Soc Nephrol 1998; **9**:2096–2110.
30. Locatellli F, DelVecchio L, Marai P et al. The renoprotective effect of antihypertensive drugs. J Nephrol 1998; **11**:330–336.
31. Estacio RO, Gifford N, Jeffers BW et al. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 2000; **23**(Suppl 2):B54–B64.
32. Danish Verapamil Infarctions Trial II. Effect of verapamil on mortality and major events after acute myocardial infarction (the DAnish

Verapamil Infarction Trial II–DAVIT II). Am J Cardiol 1990; **66**:779–785.
33. Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med 1988; **319**:385–392.
34. Hansson L, Hedner T, Lund-Johansen P et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: The Nordic Diltiazem (Nordil) study. Lancet 2000; **356**:359–365.
35. Estacio RO, Barrett JW, Hiatt WR et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin- dependent diabetes and hypertension. N Engl J Med 1998; **338**:645–652.
36. Tatti P, Pahor M, Byington RP et al. Outcomes results of the Fosinopril versus Amlodipine Cardiovascular Events randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998; **21**:597–610.
37. Tuomilehto J, Rustenyte D, Birkenhager WH et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. N Engl J Med 1999; **340**:677–684.
38. Brown MJ, Palmer CR, Castaigne A et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium channel blocker or diuretic in the International Nifedipine-GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000; **356**:366–372.
39. Keane WF, Eknoyan, G. Proteinuria, albuminuria, Risk assessment, detection, elimination (PARADE): A position paper of the National Kidney Foundation. Am J Kidney Dis 1999; **33**:1004–1010.
40. Peterson JC, Adler S, Burkart JM et al. Blood pressure control, proteinuria, and the progression of renal disease: the Modification of diet in renal disease study. Ann Intern Med 1995; **123**:754–762.
41. Remuzzi G, Ruggenenti P, Benigni A. Understanding the nature of renal disease progression. Kidney Int 1997; **51**:2–15.
42. The GISEN group (Gruppo Italiano di Saudi Epidemiological in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal failure in proteinuric, non-diabetic nephropathy. Lancet 1997; **349**:1857–1863.
43. Hilleman DE. Cost-effectiveness of combination therapy. Am J Managed Care 1999; **5**(Suppl.): 5449–5455.
44. Materson BJ, Reda DJ, Cushman WC et al. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. N Engl J Med 1993; **328**:914–921.
45. Neaton JD, Grimm RH Jr, Prineas RJ et al. Treatment of Mild Hypertension Study: final results. JAMA 1993; **270**:713–724.
46. Giles TD, Sander GE. Beyond the usual strategies for blood pressure reduction: therapeutic considerations and combination therapies. J Clin Hypertens 2001; **3**:346–353.
47. Hilleman DE, Ryschon KL, Mohuiddin SM et al. Fixed-dose combination therapy vs monotherapy in hypertension: A meta-analysis evaluation. J Hum Hypertension 1999; **13**:477–483.
48. Epstein M, Bakris G. Newer approaches to antihypertensive therapy: use of fixed-dose combination therapy. Arch Intern Med 1996; **156**:1969–1978.
49. Sica DA. Combination calcium channel blocker therapy in the treatment of hypertension. J Clin Hypertens 2001; **3**:322–327.

7

ACE inhibitors and angiotensin II receptor blockers in kidney disease: are we denying protection to patients?

Matthew R Weir

Introduction • Renal autoregulation • Optimal blood pressure control • Clinical significance of microalbuminuria • ACE inhibitors and angiotensin ii receptor blockers: mechanism of action • RAAS blockade and the kidney • Expected changes in renal function: functional vs anatomical • Safety • is there a serum creatinine too high for a drug that blocks the RAAS? • Conclusions • Summary • References

1. INTRODUCTION

Drugs that block the renin-angiotensin-aldosterone system (RAAS) have demonstrated important utility as part of multidrug regimens in slowing the progression of renal disease as evidenced by statistical reduction in the risk for doubling of serum creatinine or preventing the need for dialysis or transplantation.[1,2] The predominant clinical trial evidence supporting the angiotensin-converting enzyme inhibitor (ACEI) is in patients with type 1 diabetes,[1] and nondiabetic renal disease.[2] The clinical trial evidence supporting the benefit of angiotensin II receptor blockers (ARBs) is derived from clinical trials in patients with type 2 diabetes and incipient nephropathy.[3,4] In these large clinical trial experiences with drugs that block the RAAS, there was a very low incidence (<2%) of cessation of drug therapy due to increases in serum creatinine or potassium, particularly when these drugs were utilized in patients with a serum creatinine of 3 mg/dL or less.[5,6] Moreover, there is also evidence that drugs that block the RAAS provide a greater relative risk reduction for progression of renal disease, the higher the serum creatinine at baseline prior to study entry.[1] Despite these observations, health care providers are notoriously overcautious about the use of drugs that block RAAS in system in patients with even mild degrees of renal insufficiency and frequently deny their patients the benefits of these drugs. This is particularly important when one considers the safety and clearly established benefits of these drugs for slowing the progression of renal disease, and the opportunity for preventing progression of cardiovascular disease.[7] Consequently, more careful consideration as to how to best use these drugs in patients with chronic renal disease is important, as the drugs provide much advantage as part of multidrug strategies in reducing both blood pressure,

proteinuria, and risk for progression of both renal and cardiovascular disease.

The subsequent review will focus on the mechanism of action of drugs that block the RAAS and how they can be best used as part of a good blood pressure-lowering strategy to reduce the likelihood of progression of renal disease. Although these drugs have different mechanisms of action, their primary function which is beneficial to the kidney, is likely related to their antihypertensive and antiproteinuric effects.

2. RENAL AUTOREGULATION

'Renal autoregulation' is a descriptive term that describes how the glomeruli within the kidney regulate intraglomerular pressure within a tight range so as to provide optimal pressure for glomerular ultrafiltration, yet avoid injurious pressures which could lead to glomerulosclerosis. The ideal operating pressure of the glomeruli and the peritubular capillary network is approximately one-half to two-thirds of systemic blood pressure.[8,9] The glomerular vasculature is arranged in such a way that an afferent glomerular arteriole is connected in series with the glomerular vascular bed and an efferent glomerular arteriole. Thus, there are arteriole resistors at the front and back end of the glomerulus. This system provides an active and capable means of maintaining tight control of glomerular capillary pressure (within 5 mmHg) despite a wide range of systemic pressures.[9] Systemic blood pressure, which is almost always higher than glomerular capillary pressure, induces a myogenic response of the afferent arteriole and consequent preglomerular vasoconstriction which helps step systemic pressure down to glomerular capillary pressure levels.[8] Thus, active preglomerular vasoconstriction is necessary as an important mechanism for regulating blood flow to the glomeruli. In addition, the efferent glomerular arteriole vasoconstricts during clinical situations of diminished effective arterial blood volume so as to restore glomerular capillary pressure levels necessary to maintain ultrafiltration.[10] The latter effect is largely under the influence of the peptide hormone, angiotensin II, which preferentially vasoconstricts the vascular bed of the efferent glomerular arteriole.[11] Thus, this system is well designed to deal with variations in systemic perfusion pressures to the kidney. However, when the glomerular vascular beds are injured, as may occur in either hypertension or diabetes, or both, the ability to properly vasoconstrict and vasodilate may become impaired, and with it the ability to properly autoregulate perfusion pressures within the glomeruli. Consequently, glomerular capillary pressure can increase, leading to hemodynamic injury, even with levels of blood pressure one traditionally considered as being 'normal' (systolic $<$140 mmHg).

In patients with inadequate renal autoregulation, careful treatment is required so as to reduce both systemic pressure and glomerular capillary pressure. The concept of renal autoregulation provides some insight as to how intensively we should attempt to control systemic blood pressure, and why drugs that selectively block the RAAS may have advantages over other commonly used antihypertensive drugs in protecting against glomerular capillary injury.

3. OPTIMAL BLOOD PRESSURE CONTROL

How low should the systemic blood pressure (BP) be to protect against glomerular capillary injury in a patient whose kidneys are not able to autoregulate properly? Conceivably, systemic BP should be reduced to glomerular capillary pressure levels that are optimal for maintaining filtration yet limit the appreciable risk for glomerular capillary hemodynamic injury. This level of systemic BP (perhaps less $<$ 80 mmHg mean arterial pressure) may result in syncopal symptoms and consequently may not be clinically appropriate. Thus, one needs to balance the need for upright posture and adequate systemic BP for central nervous system perfusion, yet at the same time control BP as best possible to reduce the likelihood of glomerular capillary pressure injury.

The incremental advantage of drugs that block the RAAS over commonly used antihypertensive drugs may lie in their ability to not only reduce systemic BP comparably with other

drugs, but also dilate the efferent arteriole as part of their selective ability to interfere with the activity of angiotensin II within the kidney. Thus, there is a greater consistency of effect for reducing both systemic and glomerular capillary pressure.

4. CLINICAL SIGNIFICANCE OF MICROALBUMINURIA

A clinical marker, which could provide early evidence of inadequate renal autoregulation as well as a systemic vasculopathy, is the presence of albumin in the urine. Microalbuminuria indicates not only evidence of damage of the glomerular capillary blood vessel, but also the possibility of elevated glomerular capillary pressure.[12] Thus, the simple measurement of albumin in the urine may be a useful screening tool for providing clinicians some insight as to how low one should control the BP and indicate a specific need for employing drugs that block the RAAS. Since the ability of drugs that block the RAAS to extinguish microalbuminuria and proteinuria correlates with protection against progressing from microalbuminuria to clinical proteinuria,[13–15] and from clinical proteinuria to doubling of creatinine or end-stage renal disease (ESRD),[1–4] it makes sense to employ these drugs as important clinical tools in protecting kidney function. Moreover, the results of clinical trials provide evidence that proteinuria is a modifiable risk factor for the progression of renal disease.[16]

5. ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS: MECHANISM OF ACTION

The development of angiotensin-converting enzyme inhibitors (ACEIs) as pharmacologic tools was largely an accident of snake venom toxicology. These chemicals were noted to selectively block the enzyme responsible for converting angiotensin I to angiotensin II.[17] In addition, ACEIs were also noted to inhibit the degradation of bradykinin, a vasodilatory peptide, which may be involved in the regulation of glomerular hemodynamics.[17] Although ACEIs possess other biologic effects not yet well appreciated, their mechanism of action was largely felt to be related to reduction in the plasma levels of angiotensin II and an increase in plasma bradykinin effect (Figure 7.1). However, clinical trials have not demonstrated this to be the case.[18] With chronic dosing, angiotensin converting enzyme levels remain suppressed, yet plasma angiotensin II levels return to normal.[18] There is only limited clinical evidence that ACEIs provide short-term inhibition of plasma bradykinin levels.[19] Although the ACEIs are effective in suppressing the activity of the

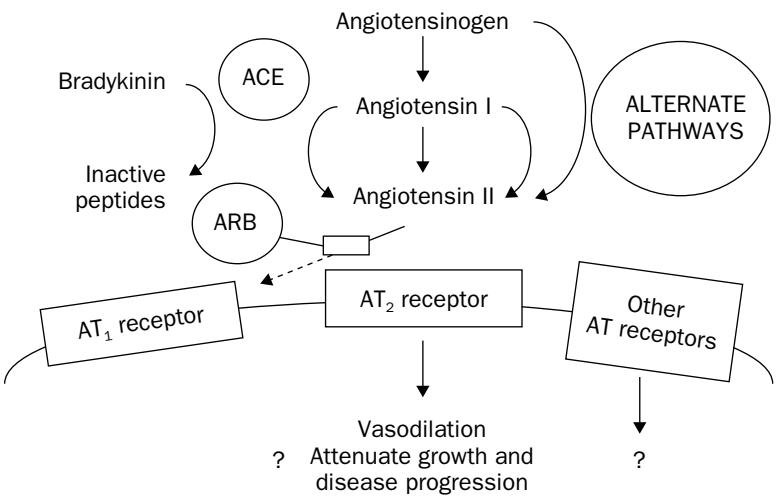

Fig. 7.1 The mechanism of action of angiotensin-converting enzyme inhibitors (ACEIs). Note the inhibition of angiotensin II synthesis and bradykinin degradation. Thus, there is a theoretical imbalance created favoring vasodilation over vasoconstriction. GFR, glomerular filtration rate. Adapted from Weir, Am J Hypertens 1999.[5]

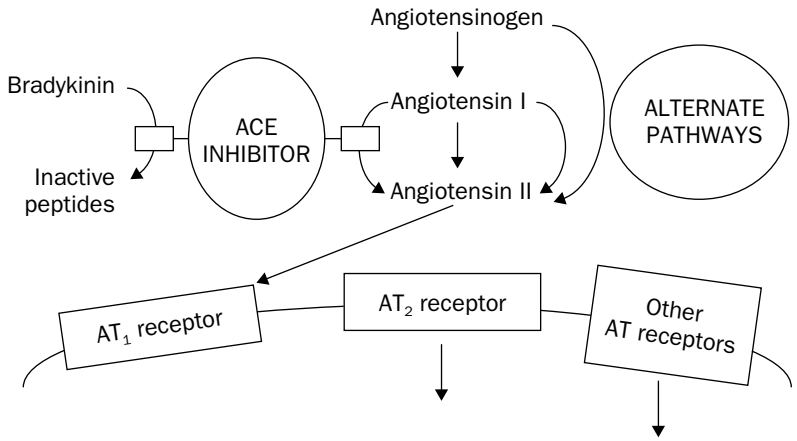

Fig. 7.2 The mechanism of action of angiotensin II type 1 receptor blocker (ARB). Note this drug interferes with the binding of angiotensin II (AngII) to its preferred high affinity receptor site, AT_1 receptor. There is no effect on AngII synthesis or on bradykinin degradation. In addition, Ang II is now available to bind to the AT_2 receptor and degradation products of AngII may bind to other AT receptors which may have biologic activity. Adapted from Weir, Am J Hypertens 1999.[5]

RAAS as evidenced by loss of feedback inhibition of renin production, the specifics of how this is accomplished remains to be elucidated. ACEIs as a group provide dose-dependent reduction in both systemic blood pressure and proteinuria.[20]

The angiotensin II receptor blocker is a chemically distinct moiety from the angiotensin-converting enzyme inhibitor. It is a chemical that specifically binds to the preferred binding site (type 1, AT_1) of angiotensin II (Figure 7.2).[21] These binding sites are constitutively expressed in vascular beds and tissues throughout the body and are thought to be most important receptor site for biologic activity of angiotensin II.[22] The type 1 site when stimulated leads to vasoconstriction, cell growth, and in the zona glomerulosa of the adrenal gland, to enhanced production of aldosterone. Other binding sites for angiotensin II have also been described. These include the type 2 (AT_2) site which, when stimulated, leads to vasodilation and inhibition of growth.[23] Moreover, circulating angiotensin II, unable to bind to its preferred type 1 site, when degraded, results in the accumulation of smaller peptides which also have binding sites and biologic activity which may contribute to the clinical effects of the angiotensin II receptor blocker.[24]

Despite dissimilar mechanisms of action in blocking the RAAS, angiotensin II receptor blockers (ARBs) provide similar degrees of blood pressure and antiproteinuric effects as the ACEIs.[25] Whereas titration of the ARB adds modestly to their antihypertensive effects, higher doses do increase the antiproteinuric effects.[26]

6. RAAS BLOCKADE AND THE KIDNEY

Despite their dissimilar mechanism of action, ACEIs and ARBs are consistently capable of reducing both systemic BP and glomerular capillary pressure. This results in less mechanical stretch and strain within the glomerular vascular beds and diminishes the transglomerular passage of albumin. Whether reducing glomerular capillary pressure or albuminuria is more important in delaying progression of renal injury is not known. What is clear from clinical trial evidence is that doing both provides an important clinical opportunity for retarding progression of renal disease.[27] The transglomerular passage of protein or albumin also puts more stress on the kidney as the renal tubular cells attempt to reabsorb the filtered proteins. Reabsorption of proteins creates an inflammatory response which can lead to chronic tubulointerstitial injury and scarring.[27]

Consequently, drugs that block the RAAS system are designed to reduce the workload of the kidney primarily through their effects on reducing glomerular capillary pressure and retarding the transglomerular passage of albumin. Thus, both glomerular and tubulointerstitial injury can be lessened with these drugs.

7. EXPECTED CHANGES IN RENAL FUNCTION: FUNCTIONAL VS ANATOMICAL

Given the fact that ACEIs and ARBs are chemicals designed to reduce renal work via the reduction of glomerular capillary pressure, one should realize that there should be an expected reduction in the glomerular filtration rate (GFR). They reduce both systemic BP and dilate the efferent glomerular arteriole. Therefore, the reduction in GFR may be as high as 25%. The degree of reduction of GFR depends in part on the patient's sodium balance and renal artery anatomy.[28] Greater volume expansion results in a lessened effect on reducing GFR, whereas sodium depletion may result in more substantial reductions in GFR (Figure 7.3). Patients with clinically significant renal artery disease will also demonstrate a more substantial reduction in GFR (Figure 7.4). Moreover, the greater the GFR in a given patient, the lesser the likelihood of an appreciable effect that would be noticeable from a clinical standpoint (i.e. an increase of serum creatinine from 0.8 mg/dL to 1.0 mg/dL) whereas, in patients with more advanced renal disease a 20–25% reduction in GFR can result in a more observable change (an increase in creatinine from 3.5 mg/dL to 4.2 mg/dL). Consequently, sodium balance (concomitant diuretic use, particularly loop diuretics), possible renal artery disease, and pre-existing renal function should be taken into consideration as one evaluates the functional change that occurs with the use of an ACEI or an ARB.

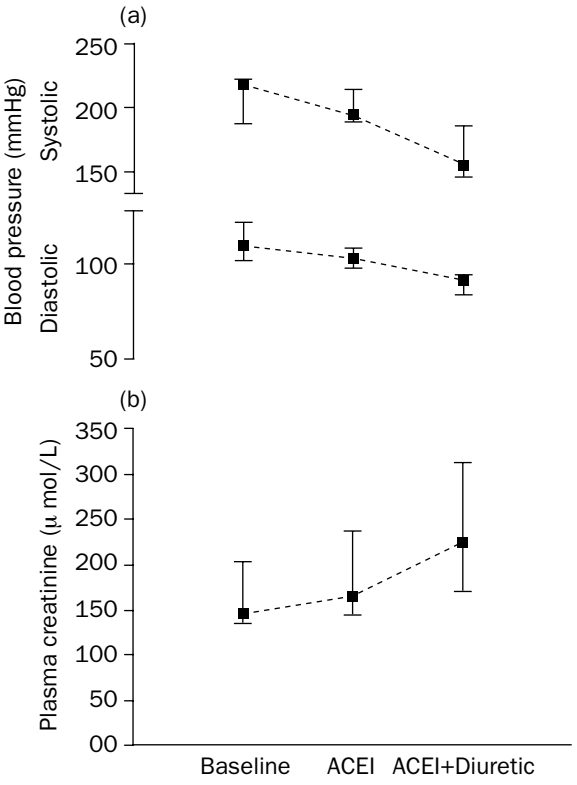

Fig. 7.3 (a) changes in systolic and diastolic blood pressure, and (b) plasma creatinine in 12 patients in which ACEI caused an increase in plasma creatinine of more than 20% only after the addition of a diuretic. Data are presented as median ± quartiles. Adapted from van de Ven et al, Kidney Int 1998.[28]

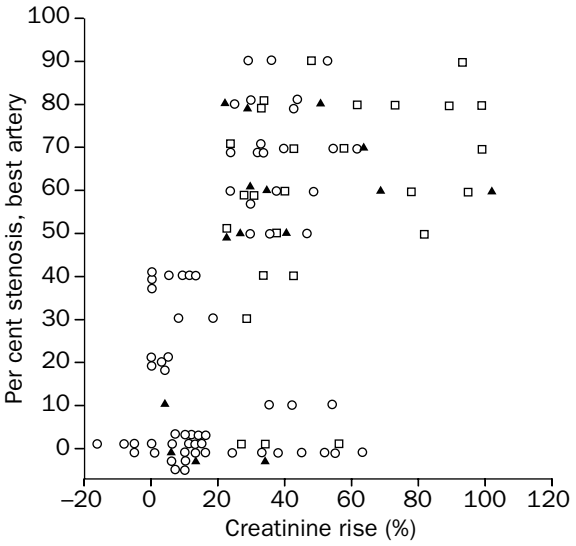

Fig. 7.4 Individual changes in plasma creatinine during ACE inhibition plotted against the per cent stenosis of the best artery in 108 patients. (□) patients in whom the ACEI was stopped after 4 days because the plasma creatinine increased by more 20% ($n = 26$); (▲) patients in whom plasma creatinine was measured after addition of diuretics to the ACEI for facilitation of blood pressure control ($n = 15$); (○) all other patients ($n = 67$). Adapted from van der Ven et al, Kidney Int 1998.[28]

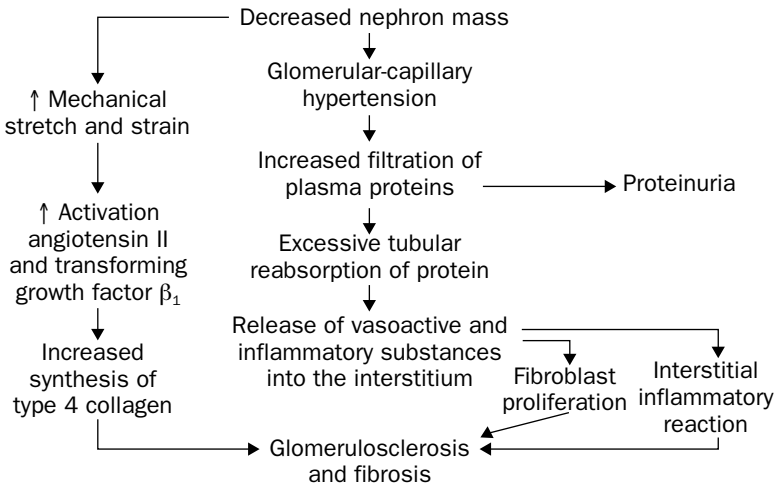

Fig. 7.5 The schematic events that lead to progressive loss of renal function in patients with proteinuria. Note that decreased nephron mass is associated with glomerular capillary hypertension and associated mechanical stretch and strain which leads to activation of the renin angiotensin/transforming growth factor beta-systems with associated enhanced production of type 4 collagen. In addition, glomerular capillary hypertension is also associated with increased proteinuria, which enhances the transglomerular passage of albumin and results in excessive renal tubular reabsorption of proteins. This is an effect that results in the release of vasoactive and inflammatory substances, which lead to enhanced fibroblast proliferation and an interstitial inflammatory reaction. As a net result, there is enhanced glomerulosclerosis. Adapted from Remuzzi and Bertani, N Engl J Med 1998.[27]

The functional change in GFR with an ACEI or an ARB results in an anatomical benefit with less glomerular capillary and tubulointerstitial injury (Figure 7.5).[6] The magnitude of the anatomical benefit can, in part,be predicted by the magnitude of acute reduction in GFR, when the drugs are first started (Figure 7.6).[29]

8. SAFETY

The results from clinical trials using either ACEIs or ARBs in patients with chronic renal failure demonstrate the safety of these drugs with serum creatinine in the 3–4 mg/dL range or less.[6] There is a low incidence (1–2%) of increase in serum potassium to 6.0 meq/L or clinically significant change of serum creatinine (>25%) in clinical trials of renal disease or congestive heart failure.[5,6,28] Acute reductions in GFR may also be related to concomitant use of nonsteroidal antiinflammatory drugs (NSAIDs), which impair renal prostaglandin synthesis and reduce renal blood flow and probably also glomerular ultrafiltration coefficient.[30] A careful volume examination of the patient and discussion about concomitant medications with the patient is usually sufficient to exclude these possibilities.

The presence of clinically significant renal artery disease is not uncommon, especially in older populations. The distinction between clinically significant and insignificant disease is of importance from a clinical standpoint because it will direct the need for appropriate therapy. Clinically significant renal artery disease manifests itself by an acute change in renal function beyond the expected 20–25% associated with the use of a drug that blocks the RAAS. This indicates the need for angioplasty, stenting or surgical repair. Correction of clinically significant renal artery disease may facilitate blood pressure control with fewer medications and lessen the likelihood for the development of ischemic nephropathy. Thus, drugs that block the RAAS can be both therapeutic and diagnostic via their effects on the kidney.

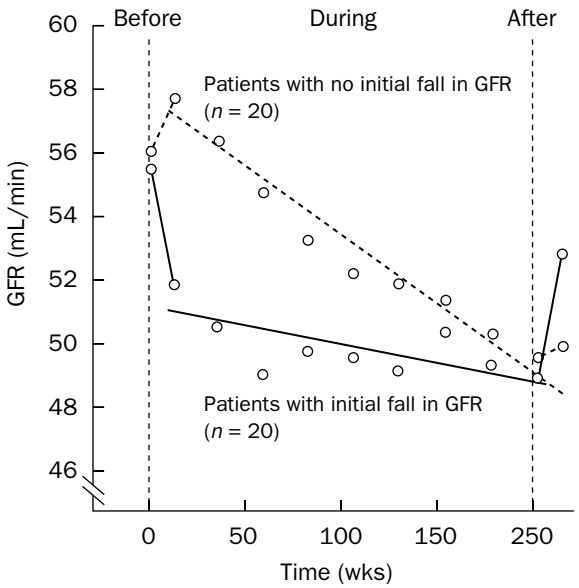

Fig. 7.6 Glomerular filtration rate (GFR) in patients with mild renal insufficiency before, during, and after withdrawal of different types of antihypertensive therapy. Note that patients experienced no initial decline in GFR with a calcium channel blocker (- - -), but there is a consistent slope of loss of renal function over time which does not abate when the drug is removed. In contrast, patients on an ACEI (—) experienced an immediate reduction in GFR due to reduction in glomerular capillary pressure. This is associated with much slower rate of loss of renal function over time. When the drug is removed after approximately 4 years of treatment, note an immediate restitution of GFR due to the removal of the hemodynamic effect of the ACEI. Adapted from Aperloo et al, Kidney Int 1997.[29]

Changes in serum potassium are also a predictable event with drugs that block the RAAS. Since these drugs interfere with aldosterone production, an increase in serum potassium of 0.3–0.5 meq/L should be planned on, and expected.[5] Increases of more than 0.3–0.5 meq/L are almost invariably associated with either concomitant use of salt substitutes (containing potassium chloride) or NSAIDs, or could indicate a patient with type IV renal tubular acidosis. Other predictive factors, such as elevated creatinine or heart failure, have been described (Table 7.1). Large-scale clinical trial experience has demonstrated the infrequent need for cessation of these drugs due to serum potassium levels of 6.0 meq/L or greater.[31] This is true whether one evaluates older subjects with age-related declines in GFR, or patients with functional reductions in GFR due to systolic heart failure, or patients with chronic renal insufficiency.[5,31] The infrequency of clinically significant increases in potassium (<2%) indicates the safety of using these drugs even in patients who are older or who have more complicated cardiorenal illness. Even hemodialysis patients can be safely treated with drugs that block the RAAS. Even though serum potassium does increase, the likelihood of having a serum potassium of 6.0 meq/L is no different statistically between patients on RAAS blockers or not.[32]

Overall, the described changes of glomerular hermodynamics with ACEIs and ARBs are quite similar. Some investigators have attempted to compare changes in serum potassium with an ACEI and an ARB. One clinical trial demonstrated modest effects with both classes of drugs on serum potassium in diabetic hypertensives with chronic renal insufficiency.[33] The serum potassium increased by 0.3 meq/L with lisinopril 20 mg compared to 0.2 meq/L with valsartan 160 mg. These described changes were small, rarely of clinical significance, and resulted in a minimal discontinuation rate. In the RENAAL trial which was a study in patients with chronic renal insufficiency due to type 2 diabetes and hypertension, there was less than 2% discontinuation rate due to increase creatinine or potassium with the ARB losartan, despite the fact that the starting creatinine was 1.9 mg/dL and a sizeable number of patients progressed to develop worsening renal function over the ensuing 3 years of treatment.[3] Likewise, in the IDNT trial, despite a serum creatinine of 1.7 mg/dL at the start of the trial, less than 2% of the patients developed electrolyte problems which required cessation of the ARB, irbesartan.[4] These data are nearly identical to the described experience in large clinical trials with ACEIs in patients with nondiabetic or diabetic renal disease, or congestive heart failure.[34–37] More recent clinical experience in using ACEIs or ARBs in patients with renal

Table 7.1 Independent risk factors predicting hyperkalemia

Factor	*Odds Ratio (95% CI)*
Serum urea nitrogen level ≥ 6.4 mmol/L (18 mg/dL)	2.5 (1.5–4.4)
Creatinine level	
–97–136 μmol/L (1.1–1.5 mg/dL)	1.5 (0.9–2.6)
– ≥137 μmol/L (≥1.6 mg/dL)	4.6 (1.8–12.0)
Use of long-acting ACEI	2.8 (1.3–6.0)
Congestive heart failure	2.6 (1.4–5.1)
Use of loop diuretic agent	0.4 (0.2–0.8)
Use of thiazide diuretic agent	0.4 (0.2–0.9)

Adapted from Reardon and Macpherson, Arch Intern Med 1998.[31]

transplants or those with ESRD receiving chronic dialysis indicate that although appreciable changes can occur in serum potassium, the drugs are in large part safe and well tolerated and associated with minimal likelihood of changes in serum potassium or creatinine.[32,38] Unfortunately, many nephrologists do not employ drugs that block the RAAS in patients with chronic kidney disease or with renal transplants for fear of electrolyte changes without fully appreciating the therapeutic cardiorenal benefits.[39]

Combined use of ACEIs and ARBs may be indicated in some patients as part of a strategy to reduce both BP and proteinuria. Recent clinical trials indicate that utilizing doses of these drugs are commonly employed in clinical practice, that using the two together can result in nearly additive reduction in proteinuria and BP.[40,41] Clinical trial experience using this combination in patients with varying levels of renal dysfunction indicate no greater likelihood of functional change in GFR or increase in serum potassium compared to the use of either drug alone, indicating that combination use is not a contraindication from a safety standpoint.[42]

9. IS THERE A SERUM CREATININE TOO HIGH FOR A DRUG THAT BLOCKS THE RAAS?

How high is too high? RAAS blockers clearly have demonstrated unique cardiovascular and renoprotective benefits. Is there a point where the 20–25% reduction in glomerular filtration rate (GFR) is too much?

The Collaborative Diabetic Nephropathy trial demonstrated that there was greater renoprotective benefit with captopril in patients with serum creatinine > 2.0 mg/dL (risk reduction 75%) compared to 1.0 mg/dL (risk reduction 4%).[1] However, not infrequently one can see patients with serum creatinine in the 3–4 mg/dL range. There is extensive clinical trial experience using ACEIs and ARBs in patients with serum creatinine up to 3.0 mg/dL. Above that, there is less information.

Once more advanced renal dysfunction is evident, say a GFR < 30 mL/min, there is less 'renal reserve', where GFR can increase via afferent glomerular arteriolar dilation. This would occur, for example, with an increase in protein in the diet. Thus, changes in GFR may be more problematic and could lead to clinically significant reductions in GFR, which could result in reduced metabolic function of the kidney with impaired vitamin D metabolism, erythropoietin synthesis, and maintenance of acid base balance. Consequently, lower doses of RAAS blockers should be employed, with more careful follow-up of fluid and electrolyte balance. This issue is particularly important in older patients who have an age-related decline in kidney function coupled with intrinsic kidney disease.

10. CONCLUSIONS

Given the irrefutable evidence from many clinical trials now indicating both renal and cardiovascular benefits of drugs that block the RAAS as part of an intensive strategy to control blood pressure, one cannot ignore the use of these drugs in every patient who needs blood pressure or proteinuria reduction unless there are obvious contraindications, such as pregnancy, angioedema or recurrent cough. ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) can be used alone, or in combination with one another, or with other classes. More investigation needs to establish the utility of supratherapeutic doses of there drugs for proteinuria reduction or cardiovascular event reduction.

SUMMARY

ACE inhibitors and angiotensin II receptor blockers are very similar in their activity to reduce glomerular capillary pressure, systemic blood pressure, and proteinuria, despite dissimilar mechanism of action. The functional and reversible changes in GFR associated with these drugs are in large part predictable and correlate with stabilization of renal function via their effects to lessen structural injury to the glomeruli and tubulointerstitium. Since patients

Table 7.2 Long-term outcome of renal function in clinical trials I: Impact of ACEI therapy

Study	*No.*[a]	*Duration of follow-up, (yrs)*	*Achieved MAP, mmHg*	*Renal function*[b]	
				< 8 mths	*Trial end*
Diabetic subjects					
Captopril Trial.[13]	207	3	105	?	−0.15 (Cr clear)
Bakris et al.[43]	18	5	98	−9.47 (GFR)[c]	−0.02 (Cr clear)
Lebovitz et al.[44]	28	3	104	?	−8.3 (GFR)
Nielsen et al.[45]	21	3	112	−3.97 (GFR)[c]	−7.1 (GFR)
Bjorck et al.[46]	40	2.2	102	−3.8 (GFR)	−2.0 (GFR)
Nondiabetic subjects					
AIPRI Trial[47]	300	3	100	+26 (Cr)	+31 (Cr)
REIN Trial	78	3.5	106	?	−6.3 (GFR)
Zucchelli et al.[48]	32	3	100	?	−0.04 (Cr Clear)
Hannedouche et al.[49]	52	3	105	?	−4.8 (GFR)
MDRD Trial[50]	255	3	105	−5.7 (GFR)	−3.8 (GFR)
			94	−14.4 (GFR)	−2.9 (GFR)
Ihle et al.[51]	36	2	101	−0.42 (GFR)	−0.7 (GFR)
Kamper et al.[52]	35	2.2	99	−3 (GFR)	−2.4 (GFR)

ACEI, angiotensin-converting enzyme inhibitor, MAP, mean arterial pressure; AIPRI, Angiotensin-converting enzyme inhibition in progressive renal insufficiency; REIN, Ramipril Efficacy in Nephropathy; MDRD, Modification of Dietary Protein in Renal Disease.

[a] Number of patients randomized to an ACEI in a given trial. Note that for the last 3 trials listed in the table, although many of these patients with a glomerular filtration rate (GFR) of 13 to 24 mL/min received an ACEI, they were not randomized to this class. They were randomized to a MAP level of either 102–107 mmHg or less than 92 mmHg.

[b] GFR is expressed as mL/min; creatinine clearance (Cr clear), mL/s; and serum creatinine (Cr), μmol/L. To convert creatinine clearance values to mL/min, divide by 0.01667; to convert serum creatinine to mg/dL, divide by 88.4.

[c] These values were converted to the annual decline rates by converting the GFRs obtained at or before 4 months. Note also that with the exception of 1 study, rates of GFR decline are slower at study end, especially in those with average BPs below 130/85 mmHg.

Adapted from Bakris and Weir, Arch Intern Med 2000.[6]

with renal disease have so much more morbidity and mortality risk from cardiovascular disease,[39] the important need for these classes of drugs in patients with renal insufficiency cannot go unrecognized. Efforts should be made to safely incorporate these drugs in every cardiovascular risk reduction regimen unless there are obvious contraindications. As evidenced in Table 7.2, the long-term outcome of renal function in renal disease progression trials is consistently positive, despite short-term reductions in creatinine clearance or GFR. Modifications in dietary potassium intake may be necessary. Avoidance of NSAIDs and salt substitutes should be encouraged, and careful manipulation of loop diuretic support to avoid diminished effective arterial blood volume is essential. When an increase in serum creatinine beyond 25% occurs, that is not ascribable to diminished volume or other drugs; an evaluation of renal artery anatomy should be performed. Occasional use of fludrocortisone and loop diuretics in combination, or kayexalate, to reduce serum potassium may be necessary.

Since the action of these drugs is understood, changes in serum creatinine and potassium are predictable, and should allay the fears of practitioners and provide the opportunity for more widespread use, particularly in patients with greater risk for both renal and cardiovascular disease progression.

REFERENCES

1. Lewis EJ, Hunsicker LG, Bain RP, Rhode RD. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. N Engl J Med 1993; **329**:1456–1462.
2. Jafar TH, Schmid CH, Landa M et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med 2001; **135**:73–87.
3. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345**:861–869.
4. Lewis EJ, Hunsicker LG, Rodby RA. Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Eng J Med 2001; **345**:851–860.
5. Weir MR. Are drugs that block the renin-angiotensin system effective and safe in patients with renal insufficiency? Am J Hypertens 1999; **12**:S195–S203.
6. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevation in serum creatinine: Is this a cause for concern? Arch Intern Med 2000; **160**:685–693.
7. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000; **342**:145–153.
8. Navar LG, Burke TJ, Robinson RR, Clapp JR. Distal tubular feedback in the autoregulation of single nephron glomerular filtration rate. J Clin Invest 1974; **53**:516–525.
9. Johnson RJ, Schreiner GF. Hypothesis: the role of acquired tubulointerstitial disease in the pathogenesis of salt-dependent hypertension. Kidney Int 1997; **52**:1169–1179.
10. Schor N, Ichikawa I, Brenner BM. Glomerular adaptation to chronic dietary sodium restriction or excel. Am J Physiol 1980; **238**:F428–F436.
11. Yuan BH, Robinette JB, Conger JD. Effect of angiotensin II and norepinephrine on isolated rat afferent and efferent arterioles. Am J Physiol 1990; **258**:F741–F750.
12. Mogensen CE. Hyperfiltration, hypertension, and diabetic nephropathy in IDDM patients. Diabetes Nutr Metab 1989; **2**:227–244.
13. Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. JAMA 1994; **271**:275–279.
14. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med 1996; **156**:286–289.
15. Parving HH, Lehnert H, Brochner-Mortensen J et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001; **345**:870–878.
16. Jafar TH, Stark PC, Schmid CH et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int 2001; **60**:1131–1140.

17. Zusman RM. Effects of converting-enzyme inhibitors on the renin-angiotensin-aldosterone, bradykinin, and arachidonic acid-prostaglandin systems: correlation of chemical structure and biologic activity. Am J Kidney Dis 1987; **10**:13–23.
18. Boomsma F, de Bruyn JH, Derkx FH et al. Long-term clinical experience with enalapril in essential hypertension. J Hypertens 1983; **1**(Suppl 1): 103–107.
19. Gainer JV, Morrow JD, Loveland A, King DJ, Brown NJ. Effect of bradykinin-receptor blockade on the response to angiotensin-converting enzyme inhibitor in normotensive and hypertensive subjects. N Engl J Med 1998; **339**:1285–1292.
20. Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Reduction of proteinuria by angiotensin converting enzyme inhibition. Kidney Int 1987; **32**:78–83.
21. Timmermans PB, Benfield P, Chiu AT et al. Angiotensin II receptors and functional correlates. Am J Hypertens 1992; **5**:S221–S235.
22. Dzau VJ, Sasamura H, Hein L. Heterogeneity of angiotensin synthetic pathways and receptor subtypes: physiological and pharmacological implications. J Hypertens 1993; **11**(Suppl): S13–S18.
23. Nakajima M, Hutchinson HG, Fujinaga M et al. The angiotensin II type 2 (AT_2) receptor antagonizes the growth effects of the AT_1 receptor: gain-of-function study using gene transfer. Proc Natl Acad Sci USA 1995; **92**:10663–10667.
24. Iyer SN, Ferrario CM, Chappell MC. Angiotensin-(1–7) contributes to the antihypertensive effects of blockade of the renin-angiotensin system. Hypertension 1998; **31**:356–361.
25. Gansevoort RT, de Zeeuw D, de Jong PE. Is the antiproteinuric effect of ACE inhibition mediated by interference in the renin-angiotensin system? Kidney Int 1994; **45**:861–867.
26. Weinberg MS, Weinberg AJ, Cord R, Zappe DH. The effect of high dose candesartan cilexetil beyond maximal recommended doses in reducing urinary protein excretion. J Am Soc Nephrol 2000; **11**:79A (Abstract).
27. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med 1998; **339**:1448–1456.
28. Van de Ven PJ, Beutler JJ, Kaatee R et al. Angiotensin converting enzyme inhibitor-induced renal dysfunction in atherosclerotic renovascular disease. Kidney Int 1998; **53**:986–993.
29. Apperloo AJ, de Zeeuw D, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney Int 1997; **51**:793–797.
30. Clive DM, Stoff JS. Renal syndromes associated with non-steroidal anti-inflammatory drugs. N Eng J Med 1984; **310**:563–572.
31. Reardon LC, Macpherson DS. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med 1998; **158**:26–32.
32. Knoll GA, Sahgal A, Nair RC et al. Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. Am J Med 2002; **12**:110–114.
33. Bakris GL, Siomos M, Richardson D et al. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. Kidney Int 2000; **58**:2084–2092.
34. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet 1997; **349**:1857–1863.
35. Maschio G, Alberti Janin G, Locatelli F et al. Effects of angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med 1996; **334**:939–945.
36. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987; **316**:1429–1435.
37. Pitt B, Segal R, Martinez FA et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997; **349**:747–752.
38. Ponticelli C, Montagnino G, Aroldi A et al. Hypertension after renal transplantation. Am J Kidney Dis 1993; **21**:73–78.
39. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. J Am Soc Nephrol 1999; **10**:1606–1615.
40. Weir MR, Weber MA, Neutel JM et al. Efficacy of candesartan cilexetil as add-on therapy in hypertensive patients uncontrolled on background

therapy:a clinical experience trial. ACTION Study Investigators. Am J Hypertens 2001; **14**:567–572.
41. Russo D, Minutolo R, Pisani A et al. Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. Am J Kidney Dis 2001; **38**:18–25.
42. Ruilope LM, Barrios V, Volpe M. Renal implications of the renin-angiotensin-aldosterone system blockade in heart failure. J Hypertens 2000; **18**:1545–1551.
43. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int 1996; **50**:1641–1650.
44. Lebovitz HE, Wiegmann TB, Cnaan A et al. Renal protective effects of enalapril in hypertensive NIDDM: role of baseline albuminuria. Kidney Int Suppl 1994; **45**:S150–S155.
45. Nielsen FS, Rossing P, Gall MA et al. Impact of lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy. Diabetes 1994; **43**:1108–1113.
46. Bjorck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. BMJ 1992; **304**:339–343.
47. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; **329**:1456–1462. Erratum in: N Engl J Med 1993; **330**:152.
48. Zucchelli P, Zuccala A, Borghi M et al. Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. Kidney Int 1992; **42**:452–458.
49. Hannedouche T, Landais P, Goldfarb B et al. Randomised controlled trial of enalapril and beta blockers in non-diabetic chronic renal failure. BMJ 1994; **309**:833–837.
50. Levey AS. Short-term effects of protein intake, blood pressure, and antihypertensive therapy on glomerular filtration rate in the Modification of Diet in Renal Disease Study. Am J Soc Nephrol 1996; **7**:2097–2109.
51. Ihle BU, Whitworth JA, Shahinfar S et al. Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: a controlled double-blind trial. Am J Kidney Dis 1996; **27**:489–495.
52. Kamper AL, Strandgaard S, Leyssac PP. Effect of enalapril on the progression of chronic renal failure. A randomized controlled trial. Am J Hypertens 1992; **5**:423–430.

8

Lipid lowering and the progression of kidney disease

Robert D Toto

Introduction • Is chronic kidney disease a coronary risk equivalent? • Treatment: general aspects • Treatment of specific dyslipidemias • Reducing proteinuria and limiting lipogenic drug usage • Specific therapy for renal transplant recipients • References

1. INTRODUCTION

The incidence and prevalence of cardiovascular disease in patients with chronic kidney disease (CKD) is excessive. Lipid disorders are common in patients with CKD and may precede onset of overt nephropathy.[1] Dyslipidemia is believed to play a role in the development of both cardiovascular disease and progression of chronic kidney disease in pre end-stage renal disease (ESRD) and transplant recipients. CKD is associated with high prevalence of multiple risk factors including dyslipidemia, hypertension, proteinuria, metabolic syndrome, hyperhomocysteinemia, anemia, and elevated calcium phosphorus product. Therefore, it seems reasonable that CKD patients would benefit from reduction in cardiovascular risk afforded by appropriate treatment of dyslipidemia as occurs in non-CKD populations.

Several classes of lipoproteins exist including very low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and lipoprotein (a). The Adult Treatment Panel (ATP) III guidelines provide both a classification for dyslipidemias (Table 8.1), as well as treatment guidelines. Patients with CKD exhibit abnormalities in

Table 8.1 Adult Treatment Panel III classification of dyslipidemia

Lipid/Lipoprotein	*Concentration (mg/dL)*
LDL cholesterol	
Optimal	<100
Near optimal	100–129
Borderline high	130–159
High	160–189
Very high	≥190
HDL cholesterol	
Low	<40
High	>80
Triglycerides	
Normal	<150
Borderline high	150–199
High	200–499
Very high	>500
Atherogenic dyslipidemia	
Raised triglycerides	≥150
Low LDL	
Reduced HDL	<40 (men)
cholesterol	<50 (women)

LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

concentration and composition of all of these classes. Unfortunately, there are no cardiovascular outcome trials utilizing lipid lowering interventions in patients with CKD. Therefore treatment guidelines discussed in this chapter are based on the principle that patients with CKD and dyslipidemia are at the same or higher risk for cardiovascular disease as non-CKD patients. This chapter discusses the diagnosis and treatment of lipid disorders in patients with CKD in the context of current ATP III guidelines.

2. IS CHRONIC KIDNEY DISEASE A CORONARY RISK EQUIVALENT?

Coronary risk equivalent may be defined as the level of risk equivalent to clinical coronary heart disease in the absence of hard evidence of coronary heart disease. Although CKD is not yet considered a coronary risk equivalent, compelling evidence supports approaching management of dyslipidemia in patients with CKD according to the ATP III guidelines for coronary heart disease risk equivalent status. First, diabetes mellitus and essential hypertension account for more than 75% of incident ESRD cases in the United States.[2] Second, epidemiologic and clinical trial evidence indicates that the presence of CKD is an independent risk factor for increased cardiovascular morbidity and mortality.[3,4] For example, the rate of fatal and non-fatal myocardial infarction and stroke are increased in those with hypercreatininemia including diabetic and nondiabetic populations and those without prior myocardial infarction or cardiovascular accident.[3] Third, diabetes mellitus, hypertension, older age and low HDL cholesterol are common features of CKD and ESRD. Fourth, clinical trials in type 2 diabetics with overt nephropathy indicate that cardiovascular morbidity and mortality rates are excessive.[5,6] Fifth, patients with CKD have a high prevalence of traditional and non-traditional risk factors for coronary artery disease (Table 8.2). Finally, the prevalence and magnitude of major risk factors for coronary disease increase as renal failure progresses (e.g. hypertension, insulin resistance, hyperhomocysteinemia, and others).[7]

Table 8.2 Prevalent cardiovascular and coronary heart disease risk factors in patients with chronic kidney disease

Risk factor	*Traditional*	*Non-traditional*
Hypertension	×	
Diabetes	×	
LDL cholesterol	×	
Low HDL cholesterol	×	
Insulin resistance		×
Elevated lipoprotein (a)		×
Hyperhomocysteinemia		×
Increased serum calcium-phosphorus product		×
Anemia		×
Metabolic syndrome		×
Increased HDL		×

3. TREATMENT: GENERAL ASPECTS

3.1 ATP III guidelines for primary and secondary prevention of coronary heart disease

It is preferable to measure fasting plasma lipids in patients with chronic kidney disease to include total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels. For those patients with borderline abnormal levels, the fasting lipid profile should be repeated to confirm abnormalities prior to initiating interventions. The ATP III guidelines for primary and secondary prevention of coronary heart disease utilize a stepwise approach to assessing risk and selecting appropriate intervention with emphasis on LDL cholesterol (Table 8.3).[8]

Table 8.3 Adult Treatment Program III guidelines stepwise approach to management of coronary heart disease (CHD) risk

Step	*Action*			
1	Determine lipoprotein levels Obtain complete lipoprotein profile after 9–12 h fast			
2	Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent)			
3	Determine presence of major risk factors (other than LDL) which include: • Cigarette smoking • Hypertension • Low HDL cholesterol (<40 mg/dL) • Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years) • Age (men ≥45 years; women ≥55 years)			
4	If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalents, assess 10 year (short-term) CHD risk as follows using Framingham formula			
5	Determine risk category			
6	Initiate therapeutic lifestyle changes if LDL is above goal as shown			
7	Consider adding drug therapy if LDL exceeds levels as follows:			
	Risk category	LDL goal	LDL goal lifestyle	LDL drug Rx
	CHD or CHD equivalent >20%	≥100 mg/dL	≥100 mg/dL	≥ 130 mg/dL (100–129 mg/dL drug optional)
	2+ risk factors ≤20%	<130 mg/dL	≥130 mg/dL	10 yr risk 10–20% ≥130 mg/dL; 10 yr risk <10% ≥160 mg/dL
	0–1 risk factors	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL drug optional)
8	Identify metabolic syndrome and treat if present, after 3 months of TLC			
9	Treat elevated triglycerides (>150 mg/dL)			

Risk levels based on 10 year risk for CHD from Framingham scoring: >20% CHD equivalent; 10–20%, < 10%. The risk score is calculated based on age, total cholesterol, systolic blood pressure, HDL cholesterol, and smoking. The score can be calculated from the ATP III affiliated website: http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=pub

In addition, the guidelines include recommendations for treatment of the metabolic syndrome, hypertriglyceridemia and low HDL cholesterol that are common in CKD populations. Two important points should be kept in mind when developing a treatment program for patients with CKD. First, recognition that patients with CKD are a coronary heart disease risk equivalent group and second that metabolic syndrome is highly prevalent in the CKD population. One caveat to this approach arises when the treating physician believes that the

potential risk of therapy exceeds potential benefit in an individual patient.

3.2 Should all patients with CKD be treated with statin therapy?

Recent studies concerning the potential beneficial (pleiotropic) effects of statin independent of lipid lowering have raised the question of whether all patients with CKD should be administered these agents. For example, these agents exert powerful antiproliferative effects on tissues that promote both atherogenesis and progressive renal injury. Furthermore, because statins have been shown to confer cardiovascular benefit, even in individuals with normal plasma LDL cholesterol levels, and even in the absence of detectable lowering of plasma LDL levels, statins may be useful for reducing cardiovascular event rates particularly among dialyzed patients. The Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival (CHORUS) trial employed cerivastatin to test the hypothesis that statin therapy even in the presence of normal LDL levels reduced cardiovascular morbidity and mortality and all cause mortality in incident hemodialysis patients.[8] Unfortunately, the trial was stopped due to the removal of this drug from the market for reasons external to this clinical trial. However, hemodialysis patients treated with statins at onset of ESRD have reduced overall mortality over two years after beginning dialysis therapy.[9] To date, no studies have examined whether statin therapy reduces the risk of cardiovascular morbidity and mortality in patients with progressive renal disease. Therefore, statin therapy is not recommended for all patients with CKD. Instead, application of the ATP III guidelines for management of specific dyslipidemias encountered in CKD seems appropriate.

4. TREATMENT OF SPECIFIC DYSLIPIDEMIAS

The following discussion describes recommendations for treatment of specific dyslipidemias which may occur in many forms of CKD including nephrotic syndrome and ESRD (treated by dialysis or renal transplantation). A stepwise approach recommended by ATP III is illustrated in Table 8.3 and suggested algorithms for CKD/ESRD on dialysis, nephrotic syndrome, and transplantation are presented in Figures 8.1 and 8.2.

4.1 Hypercholesterolemia

Pre-ESRD and ESRD patients should be assessed for coronary artery disease (CAD) risk and treated according to ATP III guidelines as indicated in Table 8.3. For those individuals with a CAD risk ≥20% over 10 years the goal LDL cholesterol level should be ≤100 mg/dL. Whether this should be the goal for CKD patients with risk score of <20% remains to be determined. However, in individual cases the treating nephrologist may determine it desirable to achieve this goal utilizing dietary and/or pharmacologic intervention. Dietary management should include restriction of daily saturated fat consumption to less than 7% of total calories and cholesterol less than 200 mg. Ingestion of viscous (soluble) fiber (10–25 g/d) and plant sterols (up to 2 g/d) should be prescribed. For individuals with an LDL cholesterol >115 mg/dL, this diet should be combined with a statin as the first-line pharmacologic agent for achieving an LDL cholesterol goal of <100 mg/dL. After dose titration to a maximal dose of a statin, the addition of a bile acid sequestrant or nicotinic acid should be considered. Bile acid sequestrants can increase plasma triglyceride level, therefore repeating plasma lipid measures within 2–3 months after initiating treatment regimes.

Statins can be expected to lower LDL cholesterol by 25–50% which in many cases will result in optimal LDL cholesterol level (i.e. <100 mg/dL). This class of agents is effective and safe in chronic renal failure, nephrotic syndrome, and ESRD patients treated with dialysis or transplantation. Common side effects of statins include gastrointestinal (GI) distress and uncommon side effects include myopathy and liver disease. Rarely, overt rhabdomyolysis with myoglobinuric acute renal failure can

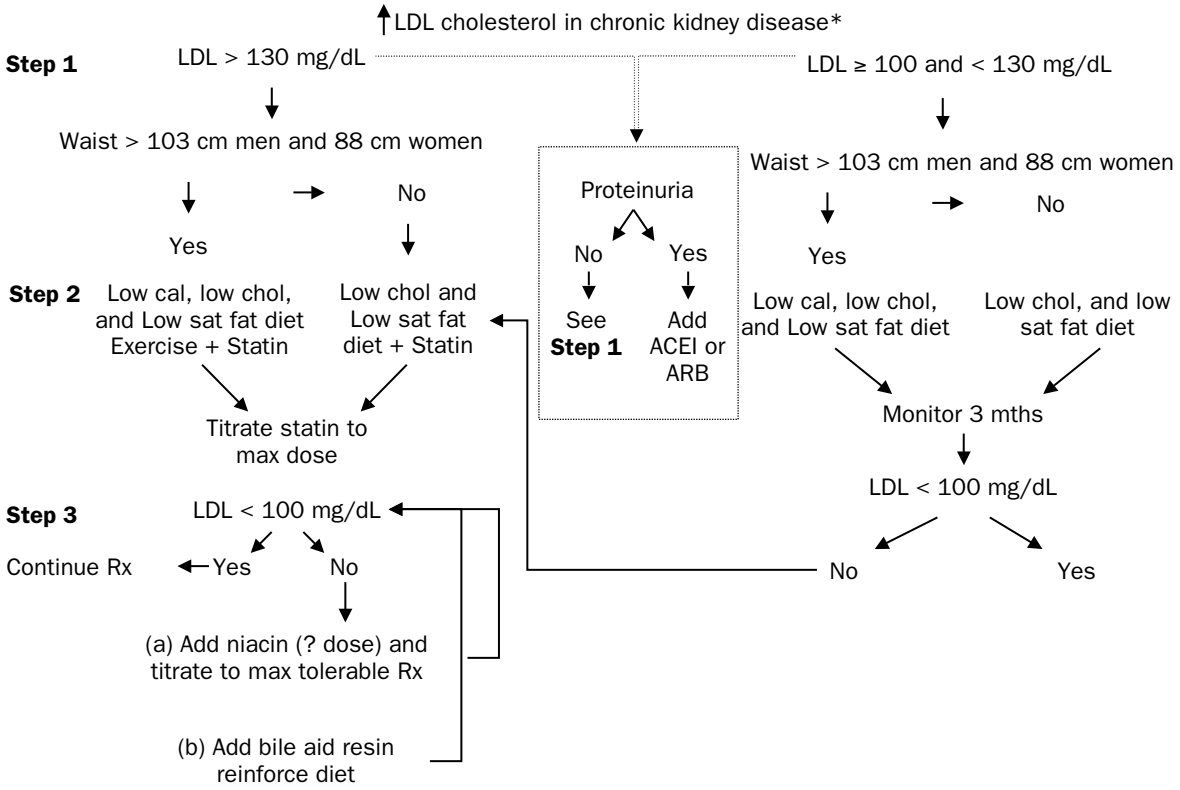

Fig. 8.1 Algorithm of suggested approach to chronic kidney disease. *For diabetics: target HbA_{1c} ≤7 mg/dL.

occur, but this is usually seen in patients on very high doses, those who are concomitantly treated with fibric acids or cyclosporin A. Other drugs that compete for hepatic metabolism via P450 pathway enzymes, such as macrolide antibiotics, may also increase risk of myopathy and subsequent rhabdomyolysis. Statins are contraindicated in patients with active and chronic liver disease.

If goal LDL cholesterol is not achieved with the combination of diet and statin therapy, bile acid resin or nicotinic acid should be added as second-line pharmacologic therapy. Cholestyramine (4–16 g/d) or colestipol (5–20 g/d) are effective in patients with CKD and can reduce LDL cholesterol an additional 15–20%. Bile acid resins also cause GI distress as well as constipation. In addition, these agents must be used with caution particularly in renal transplant patients as they may interfere with GI absorption of immunosuppressive agents, such as cyclosporin and tacrolimus (see below).

Bile acid sequestrants are absolutely contraindicated in patients with dysbetalipoproteinemia and those with serum triglyceride levels >400 mg/dL because they can increase very low-density lipoprotein (VLDL) synthesis thereby aggravating hypertriglyceridemia. Nicotinic acid or niacin compounds are very effective for further lowering of LDL cholesterol but are somewhat cumbersome to use in comparison to bile acid resins. Thus, the dose of nicotinic acid must be gradually increased from 50–100 mg/d up to 1.5–2.0 g/d. Also, the prevalence of adverse side effects including flushing, itching, orthostasis, hyperglycemia, hyperuricemia, worsening insulin resistance, GI distress, and hepatotoxicity limit its use.

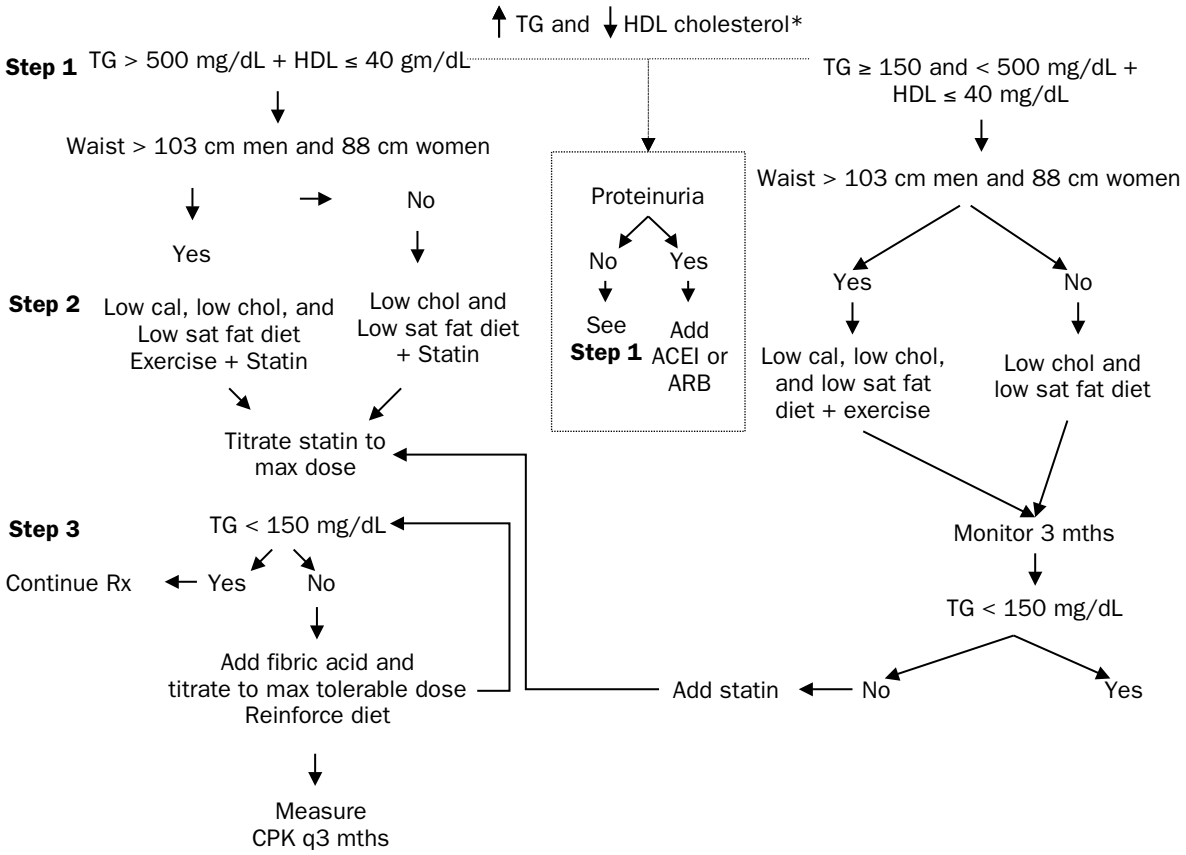

Fig. 8.2 Algorithm of suggested approach to end-stage renal disease. *For diabetics: target HbA_{1c} ≤7 mg/dL. TG, triglycerides.

Nevertheless, niacin is widely used and tolerated by most patients. Nicotinic acid is absolutely contraindicated in advanced liver disease and severe gout and is relatively contraindicated in diabetes, hyperuricemia, and peptic ulcer disease.

4.2 Hypertriglyceridemia and low HDL cholesterol

This is a very common abnormality in patients with chronic renal failure and those on dialysis, especially diabetics, the number one cause of ESRD. Hypertriglyceridemia is associated with increased risk of cardiovascular events in patients with CKD **(ASN abstracts 2001)**. The ATP III guidelines recommend treatment for triglyceride levels greater than 150 mg/dL but only after LDL goals are reached. This recommendation is based on the fact that lowering LDL cholesterol, particularly with statins, lowers triglyceride levels as well. Elevated plasma triglyceride and cholesterol levels (combined hyperlipidemia) are often observed in type 2 diabetes and nephropathy, nephrotic syndrome, and post-transplantation. Once LDL is in goal range, intensifying weight management and physical activity in overweight individuals with the metabolic syndrome is indicated for patients with combined hyperlipidemia with or without low HDL cholesterol. If fasting plasma triglyceride level remains in the range of 200–499 mg/dL after LDL goal is reached, intensifying therapy with LDL lowering drug or addition of nicotinic acid or a fibrate to further lower VLDL should be considered.

Fibrates are effective in reducing triglyceride levels in patients with renal disease and can reduce the level by 20–50%. However, these agents must be used with caution particularly in those on a statin and those with moderate to severe chronic renal insufficiency. The combination of a statin and a fibrate increases the risk of myopathy and rhabdomyolysis in such patients. The starting dose of a fibrate should be reduced by 50% from the normal dose because of cumulation of drug in blood and tissues in patients with moderate to severe renal failure. Therefore, the dose should be increased slowly over a period of weeks to months with monitoring of symptoms and signs (including muscle tenderness and muscle enzymes) of myopathy. Also, the dosing interval for fibrates in patients on maintenance hemodialysis or peritoneal dialysis should be every other day for the same reason. Fibrates and/or statins should be immediately discontinued in any patient suspected of myopathy or overt rhabdomyolysis until these disorders can be confirmed or excluded. Both statins and fibrates can produce modest increases (5–15%) in HDL cholesterol levels. However, at present neither class of drugs is indicated for increasing HDL cholesterol alone (i.e. in the absence of hypertriglyceridemia and/or hypercholesterolemia). Effective strategies aimed at lowering triglycerides and treating the metabolic syndrome generally result in some elevation of HDL cholesterol.

4.3 Treatment of metabolic syndrome

The metabolic syndrome consists of variable combination of physical and metabolic factors including obesity, hypertension, hyperlipidemia, insulin resistance, hyperuricemia, increased sympathetic activity, dyslipidemia, and elevated plasma markers of inflammation (e.g. elevated serum hsCRP). The typical dyslipidemia in the metabolic syndrome is hypertriglyceridemia and low HDL cholesterol. In some cases increased numbers of high-density LDL particles are also present. The latter are more susceptible to oxidation and are considered to be more atherogenic LDL particles as macrophage uptake of oxidized LDL by in atheromatous tissue is increased. The goal of treatment of the metabolic syndrome is to reduce obesity, lower triglycerides, blood pressure and fasting glucose, and to raise HDL cholesterol. Therapy should be aimed at treating underlying causes including obesity and diabetes mellitus as well as managing hypertension. Treatment regimes should therefore include intensifying weight reduction in men with a waist circumference >102 cm (>40 inches) and women with a waist circumference >88 cm (>35 inches) by diet and regular exercise (minimum of 30 minutes of aerobic exercise three times per week). It should be noted that physical activity programs are extremely important and can be applied to most patients with CKD. Amputees and blind individuals are exceptions to regular exercise; however, swimming is possible in blind individuals and wheelchair aerobics may be possible in some amputees.

5. REDUCING PROTEINURIA AND LIMITING LIPOGENIC DRUG USAGE

Several studies in patients with proteinuric nephropathies (including nephrotic syndrome, diabetic nephropathy, and transplant nephropathy) indicate that reducing proteinuria can improve plasma lipid and lipoprotein profiles.[10–13] Lowering blood pressure in hypertensive proteinuric patients can lower proteinuria; however, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are preferred agents for this purpose. These classes of agents more consistently reduce proteinuria as compared to other antihypertensive classes. Reducing blood pressure to levels of 120–130/70–80 mmHg is desirable in the proteinuric patient with progressive renal disease.[14] This lowering, when accompanied by reduction in proteinuria, may lower LDL and lipoprotein(a) levels. Thiazide diuretic agents and beta-blockers should be avoided or used with caution to mitigate dyslipidemia in patients with CKD.

In addition, several immunosuppressive agents cause or contribute to hypercholes-

terolemia and hypertriglyceridemia in transplant recipients (see below). Sevelamer HCl is a phosphate binder that has also been shown to reduce LDL and total cholesterol by about 20–30% in patients on hemodialysis.[15] This agent appears to work by acting as a bile acid/cholesterol binding agent thereby reducing plasma cholesterol level. This drug is indicated for lowering phosphorus, not for hypercholesterolemia, but this effect may provide an additional benefit in those patients with LDL cholesterol >100 mg/dL.

6. SPECIFIC THERAPY FOR RENAL TRANSPLANT RECIPIENTS

Dyslipidemia in renal transplant recipients is multifactorial resulting from immunosuppressives (corticosteroids, cyclosporin, and sirolimus), weight gain, dietary factors, loss of glomerular filtration rate (GFR) (e.g. rejection, drugs) and proteinuria (e.g. recurrent disease, chronic allograft nephropathy). Studies of discontinuation of corticosteroids or conversion from cyclosporin to tacrolimus demonstrate lowering of cholesterol and triglycerides and addition of sirolimus initiation increases cholesterol and triglyceride indicating that this is the case. In addition, allograft dysfunction, including proteinuria and loss of GFR as well as pre-transplant risk factors including diabetes mellitus and obesity, also contribute.[16–19] Treatment of dyslipidemia in the transplant patient involves treatment of the pathogenetic factors noted above. ATP III guidelines should be used with the goal of lowering LDL cholesterol to <100 mg/dL and lowering triglcyerides to <150 mg/dL. The reduction of lipogenic drugs when possible is beneficial. Thus, withdrawal of corticosteroids or conversion of cyclosporin to tacrolimus may be beneficial. However, changing or modifying the immunosuppressive protocols may not be feasible or possible in a given patient. This approach, although effective, must be undertaken with great precaution and done slowly, adhering to protocols used in studies in which this was safe and effective. Consideration of this approach should probably be limited to the high-risk patient. Discontinuation or dose reduction of other lipogenic agents including thiazide diuretics, beta-blockers should be considered.

Several studies indicate that reducing proteinuria with angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers are safe and effective for this purpose and often lower blood pressure as well.[19] Improving glycemic control and encouraging weight loss programs in obese patients should be undertaken. Drug therapy for management of the transplant patient should follow ATP III guidelines. Most transplant patients with hyperlipidemia require both dietary therapy and a statin. The effect of these agents on reducing cardiovascular risk in transplant is not established but their use is safe and effective in this population. Statins have also been reported in retrospective studies to reduce the risk of rejection which by preserving GFR may reduce risk of superceding uremic dyslipidemia. It is important to note that calcineurin inhibitors increase plasma levels of statins. Therefore, lower doses may be used in patients managed with these immunosuppressive agents in order to achieve the plasma lipid goals.[20]

REFERENCES

1. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int 2000; **58**:293–301.
2. USRDS. Incidence and Prevalence of ESRD. United States Renal Data Systems Report, Chapter 11. Ann Arbor, MI: University of Michigan 1998.
3. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med 2001; **134**:629–636.
4. Levey AS, Beto JA, Coronado BE et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis 1998; **32**:853–906.

5. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345**:861–869.
6. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; **345**:851–860.
7. Suliman ME, Qureshi AR, Barany P et al. Hyperhomocysteinemia, nutritional status, and cardiovascular disease in hemodialysis patients. Kidney Int 2000; **57**:1727–1735.
8. Grundy SM. United States Cholesterol Guidelines 2001: expanded scope of intensive low-density lipoprotein-lowering therapy. Am J Cardiol 2001; **88**:J23–J27.
9. Keane WF, Brenner BM, Mazzu A, Agro A. The CHORUS (Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival) protocol: a double-blind, placebo-controlled trial in patients with esrd. Am J Kidney Dis 2001; **37**(1 Suppl 2):S48–S53.
10. Seliger SL, Weiss NS, Gillen DL et al. HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. Kidney Int 2002; **61**:297–304.
11. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis, Kidney Int 2001; **59**:260–269.
12. O'Donnell MP, Crary GS, Oda H et al. Irbesartan lowers blood pressure and ameliorates renal injury in experimental non-insulin-dependent diabetes mellitus. Kidney Int Suppl 1997; **63**:S218–S220.
13. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med 1988; **84**:985–992.
14. Keilani T, Schlueter WA, Levin ML, Batlle DC. Improvement of lipid abnormalities associated with proteinuria using fosinopril, and angiotensin-converting enzyme inhibitor. Ann Intern Med 1993; **118**:246–254.
15. Klahr S, Levey A, Beck G et al. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. N Engl J Med 1994; **330**:877–884.
16. Chertow G, Burke S, Dillon J, Small M. Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of haemodialysis patients. Nephrol Dial Transplant 2002; **15**:559–565.
17. Vanrenterghem Y, Lebranchu Y, Hene R, Oppenheimer F, Ekberg H. Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. Transplantation 2000; **70**:1352–1359.
18. McCune T, Thacker L II, Peters T et al. Effects of tacrolimus on hyperlipidemia after successful renal transplantation. Transplantation 1998; **65**:87–92.
19. Kasiske BL, Chakkera HA, Luis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol 2000; **11**:1910–1917.
20. Bucher H, Griffith L, Guyatt G. Systematic review on the risk and benefit of different cholesterol-lowering interventions, Arterioscler Thromb Vasc Biol 1999; **19**:187–195.

9

Dose adjustment of drugs in kidney disease

Domenic A Sica

Introduction • Level of renal function wherein alterations in handling occur • Renal function determination • Considerations in renal failure pharmacokinetics • Diuretics • Alpha-blockers • Central alpha-agonists • Beta-blockers • Calcium-channel blockers • Angiotensin-converting enzyme inhibitors (ACEIs) • Angiotensin-receptor blockers (ARBs) • Conclusion • References

1. INTRODUCTION

Because of the magnitude of the chronic renal failure (CRF) population, it is important for physicians to be aware of the ways in which kidney disorders influence the handling of cardiovascular (CVR) drugs. Renal and cardiac diseases often coexist, and the pharmacokinetics of renally cleared drugs are influenced by the diverse hemodynamic and volume changes, which characterize many CVR illnesses. Many patients currently undergo chronic maintenance hemodialysis or peritoneal dialysis. The dialysis population exhibits a considerable CVR disease burden: thus, establishing them as candidates for a variety of CVR interventions of a pharmacologic nature. Finally, there is a growing population of patients who have undergone kidney, cardiac, or liver transplantation in whom the drugs making up their immunosuppressive regimens have the potential to reduce renal function and/or interact with co-administered CVR medications.

Whenever there are several drugs with the same therapeutic indication, it is prudent for the clinician treating the CRF patient to select one whose systemic handling is least affected by CRF. However, such an option is not always available. The clinician should have a working knowledge of the elimination profile of various medications and any interactions that may arise from drug accumulation. The literature concerning drug elimination in CRF is encyclopedic and the reader is referred to a number of authoritative reviews in this area for issues which are not covered in this chapter.[1–3]

2. LEVEL OF RENAL FUNCTION WHEREIN ALTERATIONS IN HANDLING OCCUR

The total body clearance (TBC) of a compound is influenced by multiple organs including the liver and kidney amongst other organs, such as skin, intestine, and muscle. Renal clearance is an important contributor to the TBC of a number of CVR compounds including angiotensin-converting enzyme inhibitors (ACEIs) certain beta-blockers, and most diuretics.[4–6] To be clinically relevant the renal clearance of a compound

need not be that high in absolute terms as long as the percentage contribution to the TBC from renal elimination is substantial (typically greater than 50%).

Renal drug clearance is comprised of various combinations of filtration, tubular secretion/passive reabsorption, and/or intrinsic renal metabolism. It is a commonly held belief that renal failure is a process characterized by simultaneous loss of all nephron components/functions. This is not always the case. Certain renal diseases may be predominantly tubulointerstitial and therein, at least in a relative sense, have a lesser impact on the renal clearance of drugs cleared predominantly by glomerular filtration. The opposite occurs and is even more pertinent clinically; that is, drug accumulation occurring with tubular-cleared drugs when tubulointerstitial disease exists *despite* a relatively normal glomerular filtration rate (GFR).[7]

Renally cleared compounds begin to accumulate at GFR values below 60 mL/min though the precise level of renal function at which clinically relevant changes in drug clearance occur is compound-specific.[4] A significant decline in drug clearance for a renally cleared drug can be expected by the time GFR falls below 30 mL/min. It is at GFR values below 30 mL/min that the issue of drug accumulation surfaces.

Drug accumulation is relevant in a number of ways for CVR compounds. First, if the compound administered has a *narrow therapeutic window* its accumulation can quickly exceed the boundaries of the desired pharmacologic effect with undesired consequences. For instance, accumulation of an antihypertensive compound can lead to an exaggerated fall in blood pressure (BP). If GFR falls as the result of such a drop in BP the renal clearance of a compound can be further reduced and with further accumulation a vicious cycle of events can ensue.[8] Second, if an administered compound has well-established *concentration-related side effects* they will occur more often and with greater severity when a drug accumulates. This is the case with renally cleared beta-blockers and the side effect of sedation. Finally, drug accumulation increases the *risk of drug–drug interactions* and thereby manufactures a risk from concurrent therapy that otherwise would be absent.

3. RENAL FUNCTION DETERMINATION

A means to accurately measure or estimate GFR would simplify the process of dose adjustment for medications in the presence of renal failure. Although there are a number of tests and prediction equations available to measure/estimate renal function problems exist with most of these methods. The reader is referred to more thorough reviews on this theme.[9–10]

Although serum creatinine remains the most commonly obtained measure of renal function an isolated value requires considerable interpretive skill since serum creatinine values can be significantly influenced by a patient's muscle mass. Because of this interdependency on muscle mass a serum creatinine value may lie within an established population range and it does not automatically follow that renal function is normal, since a specific serum creatinine value can be associated with a family of GFR values.

It becomes somewhat easier to interpret a serum creatinine value when it is one of several such determinations and/or it has been indexed to a carefully performed 24 hour creatinine clearance (CL_{creat}). This will establish a prevailing relationship between a serum creatinine value and measured CL_{creat} and thereby provide a landmark for subsequent interpretation of any change in serum creatinine. The renal clearance of creatinine is engineered by both filtration and tubular secretion. The latter occurs via the organic cation secretory pathway, a process that can be competitively interfered with by other organic cations, such as cimetidine and trimethoprim. The clinical corollary to the inhibition of creatinine tubular secretion is that serum creatinine values rise – by as much as 1–2 mg/dL – without a commensurate change in blood urine nitrogen values. When this happens, the serum creatinine is no longer a valid marker of renal function.

The amount of creatinine secreted defines the degree to which a CL_{creat} exceeds a gold-standard measurement of GFR. The contribution of tubular creatinine secretion to total

urinary creatinine fluctuates based on circadian factors and/or degree of renal insufficiency. Under normal circumstances, tubular creatinine secretion accounts for 10% of daily urine creatinine excretion; thus, a CL_{creat} can be expected to overestimate 'true' GFR by the same amount (10%). With progressive renal failure, as much as 40% of excreted urine creatinine can derive from tubular secretion; thus, seriously undermining the accuracy of a CL_{creat} determination. Moreover, this tendency for tubular creatinine secretion to increase in the face of declining renal function keeps serum creatinine values from increasing as much as might be expected in the face of progressive renal disease; thus the maxim that as much as 50–75% of renal function can be lost before there is a truly recognizable rise in serum creatinine. Alternatively, if tubular creatinine secretion is intentionally blocked with cimetidine, CL_{creat} will more closely approximate a patient's true GFR.[11] Although the optimal dose and timing of cimetidine for this purpose is still debated, a one time 1200 mg dose given 2 hours before the start of a urine collection will generally suffice.

The technical details of a CL_{creat} can prove a significant impediment to the accuracy of this testing method – 24 hour CL_{creat} measurements are routinely subject to patient error in the collection process. Because of this, carefully timed (2–4 h in duration), water-loaded CL_{creat} measurements are a preferred alternative. Overnight CL_{creat} determinations can simplify the issue of accurately timed urine collections. Unfortunately, nighttime CL_{creat} values systematically exceed daytime values in that nocturnal tubular creatinine secretion exceeds that observed in the daytime.[12] In addition to the timing inaccuracies for CL_{creat} measurements, body weight and surface area (which are indicative of the amount of muscle mass) and intrinsic day-to-day variation in renal function will influence results. These factors contribute to a variability of up to 30% in CL_{creat} values on repeat measurements.

In the light of the problems with available measurement methodologies for determination of the level of renal function any of the several urine-free formulae currently in use are probably of sufficient accuracy to guide the adjustment of drug dosing in renal disease.

4. CONSIDERATIONS IN RENAL FAILURE PHARMACOKINETICS

Drug kinetics in chronic renal failure (CRF) can be impacted by disease-related changes in any of a number of variables including drug absorption, distribution, protein binding, and excretion/metabolism (Box 9.1). For the most part alterations in renal clearance and/or metabolism – particularly in the CYP_{450} system – are the most important parameter changes that influence cardiovascular (CVR) medication dosing in the CRF patient. Drug accumulation will occur with repeated dosing of a renally cleared compound in the patient with CRF. The process of drug accumulation can exaggerate

Box 9.1 Factors known to affect drug kinetics in renal failure

Absorption
- Bioavailability
- Gastrointestinal disease

Distribution
- Partitioning among various aqueous compartments
- Lipophilicity

Protein binding
- Alteration of plasma protein levels in nephrotic syndrome
- Alteration of protein binding in renal failure

Excretion
- *Renal*
  - Filtration
  - Secretion
  - Direct metabolism
- Excretion of active or toxic metabolites
- *Hepatic*
  - Direct biliary excretion
  - Metabolism

Box 9.2 Criteria for drug dose adjustment in renal failure

- A substantial fraction (> 30–40%) of the drug dose is excreted by the kidney either unchanged or as either active or toxic metabolites. This is the case for angiotensin-converting enzyme inhibitors (ACEIs).
- The drug or its active metabolite has a narrow therapeutic window such that drug accumulation cannot be tolerated, as is the case for procainamide and *N*-acetylprocainamide.
- The kidney is a major site for the inactivation of the drug. This applies mainly to peptides like insulin, glucagon, and parathyroid hormone. In this regard, insulin requirements typically drop in parallel with declining renal function.
- There is a significant drop in the binding of the drug to plasma proteins. For instance, a decrease in the protein binding from 99% to 95% results in a 4-fold rise in the unbound, active drug concentration and the occasional need to decrease the amount of drug being administered.

the pharmacologic effect of drugs, most typically by extending the duration of pharmacologic effect. This is particularly the case with renally cleared antihypertensive medications. The pharmacodynamics of various CVR compounds has been sparingly studied in CRF patients and seldom prove the basis for specific dosage modification. Criteria for dosage adjustment of renally cleared compounds are listed in Box 9.2.

Medication dose adjustment in CRF may involve any of a combination of different approaches (Box 9.3). Reduced elimination of a drug prolongs its half-life as well as the time required to reach steady-state. Therefore, whenever it is clinically desirable to rapidly achieve a therapeutic steady-state level for a medication a loading dose should be administered. This is the case with digoxin when it is being given for rate control in the setting of a supraventricular tachycardia. To maintain a therapeutic level and, at the same time, avoid drug accumulation and toxicity in a patient with reduced renal function, the clinician must consider *reducing the size of the maintenance dose* or *extending the interval between doses*. In many instances, a combination of both approaches is used. In general, these changes should parallel the degree of renal impairment and consider adaptive or compensatory changes in the metabolism and excretion of the drug through non-renal routes.

Box 9.3 Factors influencing drug dose adjustment in renal failure

- Extension of the dosing interval
- Reduction in the maintenance dose
- Administration of a loading dose or not
- Monitoring serum drug levels

In addition, for a drug whose therapeutic serum level range is known and readily measured, dosage adjustments can be guided by serum drug levels and further refined by the patient's therapeutic response and/or side effect profile.

5. DIURETICS

5.1 Mannitol

This exerts a diuretic effect at the proximal tubule and loop of Henle. It must be filtered to be effective since it does not undergo tubular secretion. If it goes unfiltered, as in patients with renal insufficiency, it increases intravascular volume by an osmotic drag effect. The convective flux that occurs with high plasma mannitol concentrations will result in dilutional hyponatremia, increases in serum potassium

and if concentrations go high enough acute renal failure, which occurs secondary to afferent arteriolar vasoconstriction. The risks associated with mannitol, coupled with the availability of other highly effective diuretics, relegate its use to nondiuretic indications, such as cerebral edema.[13–14]

5.2 Thiazide diuretics

These are not the diuretics of choice in patients with renal insufficiency with the possible exception of the thiazide-like diuretic, metolazone. In the instance of metolazone it is often given together with a loop diuretic, particularly in diuretic-resistant states. In the process multiple nephron segments responsible for sodium resorption can be blocked and an effective diuresis often ensues. Metolazone is very poorly absorbed and this should be taken into account when both a dose and frequency of dosing are being determined.[15] Although a large dose of a thiazide diuretic will initiate a diuresis in patients with mild renal insufficiency, the response in patients with a CL_{creat} of less than about 50 ml per minute is poor. In the setting of CRF patients are not 'resistant' to a thiazide diuretic *per se*; rather, the basis for failure of a thiazide diuretic is an insufficient potency to meet the needs of such patients. Patients receiving fixed-dose combination antihypertensive therapy containing a thiazide diuretic should be considered for conversion to a loop diuretic (together with whatever was the other component of the fixed-dose combination) when CL_{creat} drops below 50 mL/min.

5.3 Potassium-sparing diuretics

These are generally used cautiously in patients with renal failure because of the risk of hyperkalemia. *Amiloride* is an organic cation, which is both filtered and extensively tubularly secreted. Renal disease prolongs its plasma half-life; accordingly, the dose should be reduced by 50% in patients with those with a CL_{creat} value below 50 mL/min.[16] Amiloride can compete for tubular secretion with other organic cations, such as cimetidine, metformin or trimethoprim.[17] Like all potassium-sparing diuretics the likelihood of its causing hyperkalemia is greatest in the CRF patient with diabetes.

The pharmacokinetics of *triamterene* are complicated, because it is hepatically converted to an active metabolite, which then undergoes tubular secretion. Renal disease impairs the tubular secretion of this metabolite and lengthening of the dosage interval to every 12 hours is suggested when CL_{creat} is below 50 mL/min.[18] Triamterene is also associated with crystalluria and occasionally with triamterene stones.[18] A final consideration with triamterene is its tendency to cause acute renal failure when given together with a nonsteroidal antiinflammatory drug (NSAID).[19] Triamterene can induce renal vasoconstriction and this stimulus triggers renal prostaglandin release, which, in turn restores renal blood flow. When NSAIDs are administered to a triamterene-treated patient this prostaglandin release is no longer possible and the prevailing renal hemodynamic environment becomes one of vasoconstriction and therein the likelihood of acute renal failure.[19] *Spironolactone* differs mechanistically from amiloride and triamterene in that it is an aldosterone receptor antagonist. This is the basis for its expanding use in congestive heart failure and more recently hypertension.[20] Dosage adjustment for spironolactone is not purely based on the level of renal function; rather, it is governed by the likelihood of clinically relevant hyperkalemia.[21] Spironolactone and/or its metabolites have a prolonged potassium-sparing effect which should be accounted for when it is prescribed.

5.4 Loop diuretics

These drugs are the most commonly used diuretics in renal failure. Approximately 50% of a dose of furosemide is excreted unchanged; the remainder is renally conjugated to glucuronic acid. Therefore, in patients with renal failure, the plasma half-life of furosemide is prolonged because both urinary excretion and renal conjugation are reduced. The two other loop diuretics available in the United States, bumetanide and torsemide, are largely hepatically metabolized

(50% and 80%, respectively) and their half-lives do not change appreciably in renal failure. However, renal insufficiency will impair their tubular delivery.[6] In addition to the routes of metabolism, the pharmacokinetic features of diuretics that assume clinical significance are bioavailability and half-life. The bioavailability of loop diuretics is not affected by renal insufficiency.

On average, furosemide is 50% absorbed, but within a range of 10–100%.[22] This wide range makes it a matter of some guesswork as to how much furosemide will be absorbed in an individual patient – particularly if congestive heart failure is present – and varied doses of furosemide must be tried before the drug is deemed ineffective. In contrast, absorption of the two other loop diuretics marketed in the United States, bumetanide and torsemide, is nearly complete, ranging from 80% to 100%. Consequently, there is probably less need for titration of these diuretics when converting from intravenous to oral therapy. The predictability of absorption with torsemide as well as its pattern of response is such that it may actually lower hospitalization rates in heart failure patients.[23]

The plasma half-life of a diuretic determines its frequency of administration. The plasma half-lives of loop diuretics are fairly short. This is of clinical import in that once a loop diuretic has been administered, its effect disappears fairly quickly and well before the next diuretic dose particularly when the loop diuretic is being given once daily. Shortly after a diuretic's effect has waned, the nephron becomes extremely sodium-avid, which may be sufficient to completely nullify the gain from the prior natriuresis. This rebound antinatriuretic effect and not the severity of the underlying disease state is the basis for many diuretic regimens requiring multiple daily doses.

Several pharmacodynamic features of diuretics are clinically important. In patients with a CL_{creat} below 20 mL/min, only 5–10% as much loop diuretic reaches the tubular fluid as occurs in normal subjects. Thus, a large dose must be given to attain a threshold quantity of diuretic in the tubular fluid. The relation between the rate at which the diuretic is excreted and the developed response in patients with renal insufficiency is similar to what is observed in normal subjects. Thus, the remaining nephrons in patients with renal insufficiency alone (and no significant sodium-retaining tendencies as occur in nephrotic syndrome) retain their responsiveness to diuretics; the problem is delivering adequate drug amounts to the site of action.

A frequently posed question in patients with severe renal insufficiency is, what is the largest single dose of a loop diuretic beyond which there is no additional yield? The maximal natriuretic response occurs with intravenous bolus doses of 160–200 mg of furosemide or the equivalent doses of bumetanide and torsemide, and nothing is accomplished by using larger doses. Some patients may require doses in the range of 160–200 mg several times a day to persist in their diuresis. Single intravenous bolus doses of 160–200 mg can cause transient tinnitus, but this effect can be minimized by administering the dose over a period of 20–30 minutes.

6. ALPHA-BLOCKERS

The peripheral alpha-blockers prazosin, terazosin, and doxazosin undergo extensive hepatic metabolism and their pharmacokinetics are not altered by the presence of renal insufficiency. Peripheral alpha-blockers do not require dose adjustment in the setting of renal failure. These drugs are not appreciably dialyzed. These compounds are used with some regularity in the hypertensive chronic renal failure (CRF) patient in that they are useful add-on compounds in the setting of resistant hypertension. Use of alpha-adrenergic antagonists in the treatment of hypertension has been limited by their tendency to increase plasma volume, a phenomenon which may be more evident at higher doses and in the CRF patient.

7. CENTRAL ALPHA-AGONISTS

Central alpha-agonists, such as clonidine and guanfacine, are frequently used in the management of hypertension in the CRF patient. Guanfacine is predominantly hepatically cleared and does not accumulate in CRF. Clonidine,

unlike guanfacine, undergoes modest renal clearance and its plasma half-life is somewhat prolonged in CRF although there are no specific recommendations for dosage adjustment in this population. CRF patients who suddenly stop oral clonidine can be expected to have less frequent rebound hypertension relating to this delayed clearance. Although clonidine is typically dosed to effect and can be expected to accumulate in the CRF patient its use seems not to be associated with so-called 'paradoxical hypertension', a phenomenon that occurs at very high plasma clonidine levels. Clonidine stimulates both $alpha_1$- and $alpha_2$-adrenergic receptors. At conventional doses the predominant effect of clonidine is to stimulate central $alpha_1$- and $alpha_2$-adrenergic receptors, which decreases sympathetic outflow; hence the fall in BP with clonidine. At very high plasma levels of clonidine peripheral alpha-receptor stimulation is interposed, which supplants the vasodepressor effect of central stimulation and thus the basis for the paradoxical rise in BP. This is most often seen in the setting of clonidine overdose. Also, patients with CRF and sinus node dysfunction are at risk of significant bradycardia with clonidine. In these patients clonidine is best avoided.

8. BETA-BLOCKERS

Beta-blockers are commonly utilized drugs in the patient with CRF being given either for the treatment of hypertension and/or for their cardioprotective effects.[24–25] The BP lowering effect of beta-blockers is somewhat unpredictable in the CRF patient unless combined with a diuretic. The selection of a beta-blocker in a CRF patient should occur with some knowledge of the elimination characteristics of the drug as well as whether the compound has active metabolites (Table 9.1).[25] Accumulation of a beta-blocker in a CRF patient does not generally improve BP control; alternatively, beta-blocker accumulation can be associated with more frequent side effects. If such side effects occur two options exist; first, to continue the offending beta-blocker with empiric dose reduction or second to convert to a hepatically cleared beta-blocker. The latter is generally the preferred clinical approach.

9. CALCIUM CHANNEL BLOCKERS (CCBs)

In general, the volume of distribution (V_d), protein binding, and plasma half-life of calcium channel blockers (CCBs) are comparable in CRF patients, and normal renal function subjects with a few notable exceptions (Table 9.2) and do not mandate dose adjustment based on pharmacokinetic considerations. One exception is nicardipine where hepatic metabolism and thereby plasma clearance is decreased in CRF patients when compared to normal subjects.[26] Although the mechanism of this defect in drug

Table 9.1 Elimination characteristics of beta-blockers

Drug	*Active metabolites*	*Accumulation in renal disease*	*Drug*	*Active metabolites*	*Accumulation in renal disease*
Acebutolol	Yes	Yes	**Metoprolol LA**	No	No
Atenolol	No	Yes	**Nadolol**	No	Yes
Betaxolol	No	Yes	**Nebivolol**	No	No
Bisoprolol	No	Yes	**Oxprenolol**	No	No
Carteolol	Yes	Yes	**Penbutolol**	No	No
Carvedilol	Yes	No	**Pindolol**	No	No
Celiprolol	Yes	No	**Propranolol**	Yes	No
Esmolol	No	No	**Propranolol-LA**	Yes	No
Labetalol	No	No	**Sotalol**	No	Yes
Metoprolol	No	No	**Timolol**	No	No

Table 9.2 Elimination characteristics of calcium channel blockers

Drug	*Trade name*	*Normal $T_{1/2}$ (h)*[a]	*Renal failure $T_{1/2}$ (h)*	*Dosage adjustment in renal failure*
Amlodipine[b]	Norvasc	40–50	50	No
Bepridil[c]	Vascor	26–64	na[c]	No: Close monitoring recommended
Diltiazem[d]	Cardizem	2–5	2–4	No
Felodipine	Plendil	11–16	18 ± 11.4	No
Isradipine	Dynacirc	8	3.1	No
Nicardipine	Cardene	11.5	na	No: Careful dose titration recommended
Nifedipine	Procardia	2.0	4.0	No
Nimodipine	Nimotop	2.8	22	No: Close monitoring recommended
Nisoldipine	Sular	15	na	No
Nitrendipine		3.6	4.1	No
Verapamil[e]	Calan, Isoptin Verelan, Covera	3–7 (acute) 8–12 (chronic)	11.4 ± 4.0 (15.2)	No

[a] Normal subject $T_{1/2}$ values are taken from populations studied simultaneously with renal failure subjects or from comparative studies in the literature.
[b] All data is from normal renal function individuals other than for renal failure $T_{1/2}$
[c] Bepridil has not been therapeutically studied in either renal failure or ESRD. Area-under-the-curve for bepridil is similar to that observed in normal volunteers
[d] Diltiazem has an active metabolite desacetyldiltiazem.
[e] Verapamil and norverapamil $T_{1/2}$ values are reported. Acute and chronic dosing $T_{1/2}$ values are reported in normal renal function subjects.

clearance remains unclear, as enzyme activity has not been specifically studied, this defect in plasma clearance is corrected by hemodialysis suggesting the presence of a dialyzable inhibitor of nicardipine clearance in renal failure. The cytochrome P-450 system is intimately involved in the presystemic clearance of CCBs, with the CYP3A family of enzymes playing a prominent role in this process. These enzymatic processes are variably suppressed in CRF patients a phenomenon, which may provide an alternative explanation for the reduction in CCB metabolism in some CRF patients.[27–29]

CCBs are commonly used drugs in the patient with CRF, which, in part, relates to the predictability of their BP-lowering response. Also, coronary artery disease is common in the CRF patient and drugs in this class are effective antianginal agents. Addition of a CCB to most other drug classes, with the possible exception of diuretics, produces an additive response. Dihydropyridine CCBs are not remarkably different in their ability to reduce BP in the CRF patient in comparison to non-dihydropyridine CCBs, such as verapamil and diltiazem.

CCB-related side effects have to be considered when these drugs are used in the CRF

patient. Many CRF patients tend to be constipated and this can be aggravated by verapamil. Also, CCBs can produce peripheral edema on a vasodilatory basis. This form of peripheral edema is not distinguished by weight gain. When a true volume-expanded form of peripheral edema exists – as is often the case in CRF – and a CCB is administered, any edema that develops cannot be viewed as an accurate reflection of the patient's volume state unless it is accompanied by some weight gain.

10. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

ACEIs are frequently administered drugs in the patient with chronic renal failure (CRF) being given either for the treatment of hypertension and/or for their cardiorenal protective effects. The BP-lowering effect of ACEIs is generally less in volume-expanded forms of hypertension as is often the case in CRF. In the CRF patient addition of a diuretic to an ACEI typically improves the BP-lowering response.

For most ACEIs, elimination is almost exclusively renal with varying degrees of filtration and tubular secretion occurring.[4] Tubular secretion as a mode of elimination for angiotensin-converting enzyme occurs via the organic anion secretory pathway. Dual route of elimination ACEIs are those whose active diacid is both hepatically and renally cleared. There are only two such compounds available in the United States, fosinopril and trandolapril. This property of combined renal and hepatic elimination minimizes accumulation in CRF, once dosing to steady state has transpired.[30] To date, a specific adverse effect has not been identified from ACEI accumulation although cough has been suggested, but not proven, to be an ACEI concentration-dependent side effect.

It is probable, however, that the longer drug concentrations remain elevated – once a response to an ACEI has occurred – the more likely it is that BP, renal function, and potassium (K^+) handling will be impacted. Some patients are very sensitive to the effects of an ACEI, particularly those who have an activated renin-angiotensin-aldosterone system (RAAS), thus, even minimal degrees of ACEI accumulation can present a problem.[31] The major adverse consequences of ACEI accumulation are prolonged BP reduction, an extended fall in GFR, and/or an increase in serum K^+ concentration. The mere fact that these physiologic and biochemical sequelae occur does not mandate permanent discontinuation of an ACEI; rather, cautious reintroduction of the offending ACEI, albeit at lower doses is recommended.[32]

The current product label recommendations, which suggest that ACEI doses should be reduced in moderate to severe CRF vary somewhat from compound to compound (Table 9.3). These differing dosage recommendations are inconsequential to the correct use of ACEIs in patients with CRF. ACEIs are typically titrated to effect when given to the CRF patient therefore it is contrary to clinical practice to reduce the dose of an ACEI merely if it accumulates. As previously mentioned, if the ACEI effect (i.e. BP reduction), or the side-effect drop in GFR and/or hyperkalemia occur then the dose should be reduced if not temporarily discontinued. When the dose of a renally cleared ACEI is reduced in the setting of an excessive BP drop or a significant fall in GFR the process of recovery can be a protracted one. This is consistent with the very slow elimination of such an ACEI when renal failure is present. Recovery of BP or renal function can often be accelerated by careful volume repletion if intravascular volume contraction exists. Whereas parameters, such as BP and renal function, are sensitive to the concentration of an ACEI, hyperkalemia may be less so. If hyperkalemia occurs with an ACEI a reduced dose or use of a non-accumulating ACEI can be considered. If hyperkalemia persists and ACEI remains vital (e.g. ACEI treatment in congestive heart failure) binding resins, which exchange sodium for potassium (Kayexalate®) can be tried.

11. ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

The ARBs have only recently been studied as to their renal and/or hepatic handling (Table 9.4). Like ACEIs, ARBs are generally less efficacious in the treatment of hypertension in the presence

Table 9.3 Elimination characteristics of angiotensin-converting enzyme inhibitors (ACEIs)

Drug	*Trade name*	*Usual total dose and/or range (mg) in renal failure* (Frequency/day) (CL_{creat} 10–30 mL/min)	*Usual total dose and/or range (mg) in renal failure* (Frequency/day) (CL_{creat} 0–10 mL/min)	*Recommended dose titration (mg), in renal failure* (Frequency/day)
Benazepril	Lotensin	5 (1)	Same	Titrate to max of 40 mg
Captopril	Capoten	75% of normal dose (CL_{creat} 10–50 mL/min)	50% of normal dose	
Enalapril	Vasotec			
Fosinopril	Monopril	No adjustment	No adjustment	Usual dose titration to effect
Lisinopril	Prinivil, Zestril	5 (1)	2.5 (1)	
Moexipril	Univasc	3.75 (1) (CL_{creat} <40 mL/min)	Same	Titrate to max of 15 mg
Perindopril	Aceon	2.0 (every other day) (CL_{creat} 15–29 mL/min)	2.0 (CL_{creat} <15 mL/min)	
Quinapril	Accupril	2.5 (1)	Same	
Ramipril	Altace	25% of normal dose (CL_{creat} <40 mL/min)	Same	
Trandolapril	Mavik	0.5 (1)	Same	Titrate to optimal response

Table 9.4 Mode of elimination for angiotensin II receptor antagonists (ARBs)

Drug	*Trade name*	*Renal*	*Hepatic*
Candesartan	Atacand	60	40
Eprosartan	Teveten	30	70 (unchanged)
Irbesartan	Avapro	1	99 (2C9)
Losartan	Cozaar	10	90 (2C9/3A4)
Olmesartan	Benicar	35–50	50–65 (unchanged)
E-3174	Metabolite of losartan	50	50
Telmisartan	Micardis	1	99 (unchanged)
Valsartan	Diovan	30	70 (unchanged)

of CRF and often require addition of a diuretic to maximize their BP-lowering effect. These drugs undergo significant hepatic elimination with the exception of candesartan, telmisartan, and the E-3174 metabolite of losartan, which are 40%, 60% and 50% hepatically cleared, respectively. Irbesartan and telmisartan undergo the greatest degree of hepatic elimination amongst the ARBs with each having >95% of their systemic clearance to be hepatic. Valsartan and eprosartan are both about 70% cleared by the hepatic route.[33]

On the surface, the mode of elimination for an ARB may seem like an unimportant issue. In reality, it proves to be an important variable in the renally compromised patient and may, in fact, dictate various elements of the acute change in renal function that occasionally occurs in the renal failure patient upon receipt of a compound, which interrupts the renin-angiotensin axis. In patients who develop a sudden change in renal function with a hepatically cleared ARB, the process will be to a degree self-limited by the ongoing hepatic disposition of the compound, a protective feature of drug elimination not present with renally cleared compounds. This is a phenomenon not dissimilar to what is observed with ACEIs with a dual route of elimination.[31] Not unlike ACEIs the dose of an ARB given a CRF patient should be adjusted according to the level of effect and not based on a predetermined plan to maintain an arbitrary blood level.

12. CONCLUSION

Chronic renal failure is a common condition and one that is hard to stage based on commonly used testing methods, such as the measurement of serum creatinine. Serum creatinine values typically lend themselves to an overestimate of renal function. Estimating renal function is an important clinical undertaking since a number of medications require dose adjustment based on the level of renal function. Antihypertensive medications are one such class of drugs. In this regard, diuretic dosing in renal failure patients should be predicated on a strong understanding of the physiology of diuretic effect. Other drug classes such as alpha-blockers and calcium channel blockers typically do not require dose modification in the presence of chronic renal failure. Several beta-blockers and ACE inhibitors undergo significant renal clearance and may require dose reduction either if the desired effect is excessive or if unacceptable side effects occur in relationship to high blood levels. Angiotensin II receptor blockers are typically not dose-adjusted in renal disease based on pharmacokinetic considerations; rather, any adjustment in their dose is based on an excessive physiologic effect having developed.

REFERENCES

1. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency. Drug Safety 1997; **16**:205–231.
2. Lam YW, Banerji S, Hatfield C, Talbert RL. Principles of drug administration in renal insufficiency. Clin Pharmacokinet 1997; **32**:30–57.
3. Olyaei AJ, De Mattos AM, Bennett WM. Prescribing drugs in renal disease. In: Brenner B, Rector F (eds), The kidney, 6th edn. Philadelphia: WB Saunders 2000, 2606–2653.
4. Sica DA. Kinetics of angiotensin converting enzyme inhibitors in renal failure. J Cardiovasc Pharmacol 1992; **20**(Suppl 10):S13–S20.
5. Carter BL. Dosing of antihypertensive medications in patients with renal insufficiency. J Clin Pharmacol 1995; **35**:81–86.
6. Brater DC. Diuretic therapy. N Engl J Med 1998; **339**:387–395.
7. Rodriguez-Iturbe B, Herrera J, Marin C, Manalich R. Tubular stress test detects subclinical reduction in renal functioning mass. Kidney Int 2001; **59**:1094–1102.
8. Sica DA. Renal considerations in the use of angiotensin converting enzyme inhibitors in the treatment of congestive heart failure. Clin Cardiol 1997; **20**:20–23.
9. Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. Curr Opin Nephrol Hypertens 2001; **10**:785–792.
10. Levey AS. Measurement of renal function in chronic renal disease. Kidney Int 1990; **38**: 167–184.
11. van Acker BA, Koomen GC, Koopman MG et al. Creatinine clearance during cimetidine

administration for measurement of glomerular filtration rate. Lancet 1992; **340**:1326–1329.
12. van Acker BA, Koomen GC, Koopman MG et al. Discrepancy between circadian rhythms of inulin and creatinine clearance. J Lab Clin Med 1992; **120**:400–410.
13. Warren SE, Blantz RC. Mannitol. Arch Intern Med 1981; **141**:493–497.
14. Borges HF, Hocks J, Kjellstrand CM. Mannitol intoxication in patients with renal failure. Arch Intern Med 1982; **142**:63–66.
15. Sica DA, Gehr TWB. Diuretic combinations in refractory oedema states: pharmacokinetic-pharmacodynamic relationships. Clin Pharmacokinet 1996; **30**:229–249.
16. Spahn H, Reuter K, Mutschler E et al. Pharmacokinetics of amiloride in renal and hepatic disease. Eur J Clin Pharmacol 1987; **33**:493–498.
17. Somogyi AA, Hovens CM, Muirhead MR, Bochner F. Renal tubular secretion of amiloride and its inhibition by cimetidine in humans and in an animal model. Drug Metab Dispos 1989; **17**:190–196.
18. Sica DA, Gehr TW. Triamterene and the kidney. Nephron 1989; **51**:454–461.
19. Favre L, Glasson P, Vallotton MB. Reversible acute renal failure from combined triamterene and indomethacin: a study in healthy subjects. Ann Intern Med 1982; **96**:317–320.
20. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; **341**:709–717.
21. Sica DA. Eplerenone: A new aldosterone receptor antagonist: Are the FDA's restrictions appropriate? J Clin Hypertens 2002; **4**:441–445.
22. Murray MD, Haag KM, Black PK et al. Variable furosemide absorption and poor predictability of response in elderly patients. Pharmacotherapy 1997; **17**:98–106.
23. Murray MD, Deer MM, Ferguson JA et al. Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. Am J Med 2001; **111**:513–520.
24. Frishman WH, Alwarshetty M. Beta-adrenergic blockers in systemic hypertension: pharmacokinetic considerations related to the current guidelines. Clin Pharmacokinet 2002; **41**:505–516.
25. McCullough PA, Sandberg KR, Borzak S et al. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. Am Heart J 2002; **144**:226–232.
26. Ahmed JH, Grant AC, Rodger RS et al. Inhibitory effect of uraemia on the hepatic clearance and metabolism of nicardipine. Br J Clin Pharmacol 1991; **32**:57–62.
27. Leblond F, Guevin C, Demers C et al. Downregulation of hepatic cytochrome P450 in chronic renal failure. J Am Soc Nephrol 2001; **12**:326–332.
28. Leblond FA, Giroux L, Villeneuve JP, Pichette V. Decreased in vivo metabolism of drugs in chronic renal failure. Drug Metab Dispos 2000; **28**:1317–1320.
29. Sica DA, Gehr TWB. Calcium channel blockers and end-stage renal disease: Pharmacokinetic and pharmacodynamic considerations. Curr Opin Nephrol Hypertens 2003; **12**:123–131.
30. Sica DA, Cutler RE, Parmer RJ et al. Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril, and enalapril in patients with chronic renal insufficiency. Clin Pharmacokinet 1991; **20**:420–427.
31. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS. Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation 2001; **104**:1985–1991.
32. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; **160**:685–693.
33. Sica DA, Gehr TW, Fernandez A. Risk-benefit ratio of angiotensin antagonists versus ACE inhibitors in end-stage renal disease. Drug Safety 2000; **22**:350–360.

10

Hypertensive urgencies

William J Elliott

Important definitions and examples • Epidemiology and risk factors • Diagnosis • Treatment • Outcomes • Summary • References

1. IMPORTANT DEFINITIONS AND EXAMPLES

A 'hypertensive urgency' is a clinical situation that falls between uncomplicated hypertension and a true hypertensive emergency.[1] The most common clinical presentations of patients who fit these criteria are listed in Table 10.1.[2] According to most authorities, a 'hypertensive urgency' may be diagnosed when the blood pressure (BP) should be reduced within hours, and there is *no* acute, severe target organ damage.[1,3] The absence of acute, severe target organ damage distinguishes a 'hypertensive urgency' from a true 'hypertensive emergency', for which the BP should be reduced within minutes, in order to prevent further acute and ongoing deterioration in end-organ function.[1] The distinction between stage 2 uncomplicated hypertension (systolic blood pressure >159 mmHg, or diastolic blood pressure >99 mmHg) and a 'hypertensive urgency' is somewhat more subjective. It should be based on the physician's assessment of the patient's short-term risk for adverse cardiovascular and renal consequences of untreated hypertension. The diagnosis of a 'hypertensive urgency' can be supported, and the process to reduce the BP safely over a few hours can be started, when two conditions are met. The physician must first believe, based on the patient's presentation, that there is a high short-term risk of complications, should the BP go untreated acutely. The physician must then also decide that the benefits of treatment are likely to outweigh the risks. These two conditions are probably not fulfilled as frequently as many physicians believe.[4]

The level of BP elevation at presentation is really not a sufficient criterion for these diagnostic labels. Although most physicians become concerned about the BP when faced with a patient with very elevated blood pressures, there are short-term risks associated with even stage 1 hypertension that may be worthy of treatment in certain settings. Obstetricians use a diastolic BP >90 mmHg (i.e. stage 1 hypertension) as one criterion for the diagnosis of preeclampsia, which is typically treated in hospital with antihypertensive medications, often including magnesium sulfate.[5] Similarly, many nephrologists would become alarmed when BP exceeds 160/100 mmHg (i.e. stage 2 hypertension) in a previously healthy young person with rapidly progressing glomerulonephritis. Thus, the level of BP at presentation is not a necessary condition for the diagnosis of 'hypertensive urgency', since the clinical scenario dictates the

Table 10.1 Common hypertensive emergencies and urgencies

Hypertensive emergency: Severe elevation in blood pressure accompanied by acute target organ damage, which must be reduced within ***minutes***, usually with parenteral drug therapy.

Neurologic emergencies
- Hypertensive encephalopathy
- Acute cerebrovascular accident
- Intracranial hemorrhage
- Cerebral embolism/thrombotic stroke
- Subarachnoid hemorrhage
- Acute head trauma/injury

Cardiac emergencies
- Cardiac ischemia/infarction due to coronary artery disease
- Acute left ventricular failure/pulmonary edema

Vascular emergencies
- Aortic dissection
- Recent vascular surgery
- Epistaxis unresponsive to anterior/posterior packing

Catecholamine excess state emergencies
- Pheochromocytoma
- Drug-related
  - –Tyramine-containing foods in patients on monoamine oxidase inhibitors
  - –Withdrawal of centrally acting α_2-agonists (clonidine, methyldopa, guanabenz, guanfacine, etc.)
  - –Phencyclidine or cocaine

Pregnancy-related emergencies
Eclampsia (and sometimes preeclampsia)

Hypertensive urgency: Severe elevations in blood pressure, with no acute target organ damage, which must be reduced within ***hours***, usually with oral medications in the outpatient setting:

- **Perioperative hypertension**
- **Hypertension after organ transplantation**
- **Hypertension associated with severe burns**

NOTE: **what was formerly called Stage 3 hypertension (>180/110 mmHg) without acute, severe target organ damage is NEVER an emergency and does not require parenteral drug therapy!**

Adapted from Elliott, 2001.[2]

level at which the physician becomes concerned, and may wish to consider giving antihypertensive drug therapy in a supervised fashion.

Since the definition of 'hypertensive urgency' excludes patients with acute, severe target-organ damage, it is important to search for these signs and symptoms (Table 10.2) when presented with a patient who has a higher than expected BP. If even one of these is present, the diagnostic algorithm usually leads to a 'hypertensive emergency', and quick initiation of a rapidly acting, easily titratable parenteral antihypertensive agent. The main exception is 'acute stroke-in-evolution', for which antihypertensive therapy is generally not recommended.[6]

At the other extreme, it is necessary to consider and rule out simple, uncomplicated hypertension when presented with a patient with a higher than

Table 10.2 Signs or symptoms of acute, severe target-organ damage associated with elevated blood pressure in various types of common hypertensive emergencies

Type of hypertensive emergency	*Typical symptom*	*Typical signs*	*Comment*
Acute stroke in evolution (thrombotic or embolic)	Weakness, altered motor skill(s)	Focal neurological deficit(s)	Hypertension not usually treated[6]
Subarachnoid hemorrhage	Headache, delerium	Altered mental status, meningeal signs	Lumbar puncture typically shows xanthochromia or red blood cells
Acute head injury/trauma	Headache, altered sensorium or motor skills	Lacerations, ecchymoses, altered mental status	Computed tomographic (CT) scan is helpful to determine extent of intracranial injury
Hypertensive encephalopathy	Headache, altered mental status	Papilledema	Usually a diagnosis of exclusion
Cardiac ischemia/ infarction	Chest discomfort, nausea, vomiting	Abnormal EKG (esp. T-wave elevations)	
Acute left ventricular failure/pulmonary edema	Shortness of breath	Râles auscultated in chest	
Aortic dissection	Chest discomfort	Widened aortic knob on chest x-ray	Echocardiogram, chest CT, or angiogram usually needed to confirm
Recent vascular surgery	Bleeding, tenderness at suture lines	Bleeding at suture lines	Often require surgical revision of vascular anastamosis
Pheochromocytoma	Headache, sweating, palpitations	Pallor, flushing, rare skin signs (phakomatoses)	Phentolamine is very useful
Drug-related catecholamine excess state	Headache, palpitations	Tachycardia	History regarding drug exposure is key
Preeclampsia/ Eclampsia	Headache, uterine irritability	Edema, hyperreflexia	New treatment guidelines exist[5]

expected BP, in whom one wishes to consider the diagnosis of a 'hypertensive urgency'. This involves a risk assessment of the specific patient, with the past history and mode of presentation carefully considered.[4] To have a 'hypertensive urgency', it is required that the patient be at increased risk for cardiovascular and/or renal complications in the near term, such that acute lowering of BP might improve the prognosis. This criterion is actually much more difficult to

fulfill, because there are currently *no* outcome data to show that acute lowering of BP in settings other than a hypertensive emergency confers an improved short-term prognosis.

There are nonetheless several common clinical scenarios that are typically used as illustrations of the principles delineated above. When BP levels reach levels of concern to surgeons that their handiwork might be at risk of suture failure or bleeding (e.g. within minutes to hours after a kidney transplant), many surgeons and transplant nephrologists begin antihypertensive drug therapy, in order to protect the suture line. Similarly, in the setting of a severe acute burn injury, hypertension is a known poor prognostic sign, perhaps because it exacerbates transdermal fluid loss. As a result, many burn units begin antihypertensive drug therapy (especially beta-blockers) when the BP increases only slightly; some now use beta-blockers prophylactically for all burn victims who might tolerate them. It could be argued that this practice helps control the adverse hyperadrenergic state commonly seen after an acute severe burn, rather than BP *per se*, but there is evidence that a beta-blocker in this setting improves prognosis.[7]

2. EPIDEMIOLOGY AND RISK FACTORS

Little formal research has been done regarding the incidence of hypertensive urgencies. Unlike hypertensive emergencies, which have specific diagnostic codes in both the International Classification of Disease (401.0) and Diagnosis-Related Groups (134 – Hypertension), medical documentation about hypertensive urgencies is typically not scrutinized with as much care by epidemiologists or health care economists. This is perhaps not surprising, as the economic burden of hypertensive emergencies is far greater than that of hypertensive urgencies. Many patients with hypertensive emergencies are treated in expensive intensive care units with specific or unusual parenteral therapies, whereas most hypertensive urgencies are treated as outpatients using less expensive oral medications already in common use. Furthermore, gathering retrospective data about hypertensive urgencies is difficult, as there is no specific reimbursable service that is cited in billing sheets; one must instead survey one-time oral antihypertensive drug use in an appropriate setting (e.g. emergency department, urgent care center, or in a hospital), which is time-consuming and often unrewarding.

Probably the biggest risk factor for the diagnosis of 'hypertensive urgency' is the local medical standard of care, as determined by tort law. In many jurisdictions, there have been legal precedents set by personal injury lawsuits filed after patients have been discharged from acute care settings with blood pressures that exceed certain arbitrary levels (typically $>180/110$ mmHg). Courts have occasionally held the treating physician liable for negligence after the patient suffered an adverse cardiovascular or renal event a few hours to days after discharge. As a result, many emergency departments affiliated with hospitals and free standing urgent care centers have a standing policy that no patient is allowed to leave the premises until or unless the blood pressure is below the arbitrary threshold (typically set by reference to local case law). There are essentially no data from the medical literature that support such a strategy, and it is based solely on deliberations of sympathetic juries in courts of law. There are, in fact, several older medical publications that argue *against* the idea that an elevated blood pressure, in the absence of acute target organ damage, is, *ipso facto*, a clear and present short-term danger to the patient. A very low short-term risk of the usual complications of hypertension was seen in a collection of 500 very hypertensive patients before the advent of modern drug therapy.[8] Similarly, in the first Veterans' Administration Trial on Antihypertensive Agents, the first stroke occurred *4 months* after the randomization to placebo among 143 hypertensive patients with diastolic blood pressures between 115 mmHg and 129 mmHg, measured in hospital after 6 days of bedrest and a low-salt diet.[9]

It is likely that hypertensive urgencies and hypertensive emergencies share a number of risk factors, as they are often considered within the same spectrum of disease. Perhaps the most common risk factor for uncontrolled hyperten-

sion in recent case series from emergency departments is nonadherence with previously prescribed antihypertensive drug therapy. In a large series from New York City, not having a primary care physician (available to refill antihypertensive medication prescriptions, even by telephone) was the most important risk factor for presenting to a hospital emergency department with severely elevated BP.[10] Occasionally, withdrawal of antihypertensive medications (especially alpha$_2$-agonists) or ingestion of substances that raise BP (Table 10.3) can be identified as a proximal cause of uncontrolled hypertension.[11] Recent studies of uncontrolled hypertension in young women, formerly thought to be due to oral contraceptive use, have exonerated the lower doses of estrogen used today, and instead suggested that previous hypertension during pregnancy is the most common risk factor.[12] In the state of Georgia,

Table 10.3 Common substances associated with hypertension in humans

CHEMICAL ELEMENTS AND OTHER INDUSTRIAL CHEMICALS

- Lead
- Mercury
- Thallium and other heavy metals
- Lithium salts, especially the chloride
- Chloromethane
- Carbon disulfide
- Polychlorinated (and polybrominated) biphenyls
- Parathion and other insecticides

FOOD SUBSTANCES

- **Sodium chloride**[a]
- Licorice
- Caffeine
- Tyramine-containing foods (with monoamine oxidase inhibiting drugs)
- Ethanol

STREET DRUGS

- Anabolic steroids
- Cocaine (?) and cocaine *withdrawal*
- Heroin *withdrawal*
- Methylphenidate
- Phencyclidine
- γ-Hydroxybutyric acid (and *withdrawal* from it)
- **Ma Huang, 'herbal ecstasy' and other phenylpropanolamine analogs**
- Nicotine (?) (and *withdrawal* from it)
- Ketamine
- Ergotamine and other ergot-containing herbal preparations

VENOMS AND TOXINS

- Spider bites (especially the brown recluse, 'fiddleback' spider)
- Scorpion bites (especially in the Middle East)
- Snake bites

PRESCRIPTION DRUGS

- **Cortisone and other steroids** (both cortico- and mineralo-)
- **Estrogens** (usually just oral contraceptive agents with high estrogenic activity)
- **Nonsteroidal antiinflammatory drugs**
- **Phenylpropanolamines and analogs**
- **Cyclosporine and tacrolimus**
- **Erythropoietin**
- Naloxone
- Ketamine
- Desflurane
- Bromocryptine
- Metoclopramide
- Antidepressants
- Buspirone
- Disulfuram
- *Withdrawal* from clonidine, a β-blocker (and maybe calcium antagonist)
- Pheochromocytoma: β-blocker in the absence of an α-blocker; glucagon
- Pentagastrin
- Digitalis
- Thyrotropin-releasing hormone (protirelin)
- Synthetic ACTH (corticotropin)
- Sibutramine
- Alkylating agents (typically used for cancer chemotherapy)

[a] Specific items in **bold** type have been studied more carefully and thoroughly than other entries. ACTH, adrenocorticotrophic hormone. Updated from Grossman and Messerli, 1995.[11]

African Americans insured by Medicaid have about twice the rate of claims submitted for 'malignant hypertension' as do whites.[13] Medical sociologists have suggested that nonadherence to chronic antihypertensive therapy (due to lack of a primary care physician or funds to pay for antihypertensive medications) is the primary reason for hypertensive emergencies in the United States; the same is probably true for hypertensive urgencies. A recent meta-analysis indicates more than a 15-fold reduction in the number of people in clinical trials whose BP progresses to a higher stage if essentially any single antihypertensive medication is taken continuously.[14]

3. DIAGNOSIS

The differential diagnosis of a patient with a very elevated blood pressure consists of three conditions that differ markedly in the need for rapidity of blood pressure lowering. These are, in descending order of the need for treatment: hypertensive emergency, hypertensive urgency, and uncomplicated hypertension.

The first and most important decision to be made in the management of the patient with a very elevated BP (e.g. systolic BP ≥180 mmHg; or diastolic BP ≥110 mmHg) concerns the rapidity with which the BP should be reduced (see Figure 10.1). The presence of severe, acute target-organ damage is best determined by

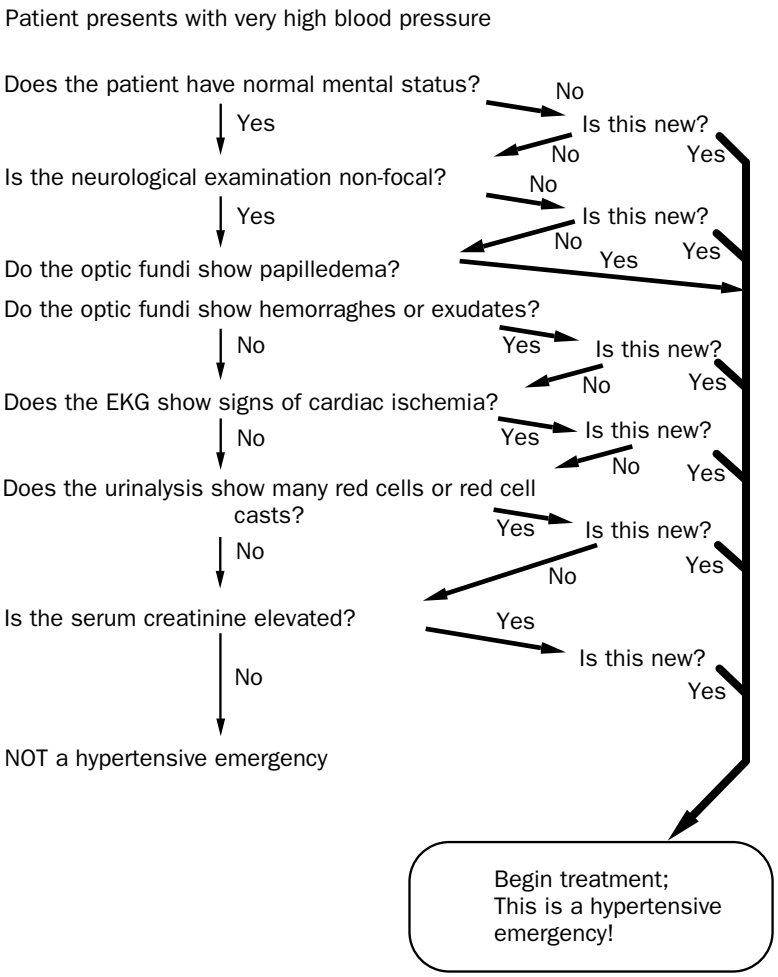

Fig. 10.1 Diagnostic algorithm for determining whether a patient with very high blood pressure has a hypertensive emergency. *Note*: If there is evidence of severe, acute target-organ damage, antihypertensive treatment may be started before and maintained during other indicated diagnostic procedures (e.g. computed tomographic scan of the head). Adapted from Elliott, 2001.[2]

careful examination of the patient and his/her urine, and by collecting other data regarding renal function (including a recent serum creatinine level). If this process discloses evidence of acute, severe target organ damage, the patient's diagnosis is a hypertensive emergency, and hospitalization and appropriate parenteral therapy are warranted. If, on the other hand, there is minimal or mild, or non-acute target organ damage, and a relatively normal physical examination and laboratory studies, a slower and less intense effort to lower the BP is appropriate.

When it is determined that the patient does not have evidence of severe, acute target organ damage, the next important question to be addressed is whether the patient is at high short-term risk of any cardiovascular or renal adverse event because of the elevated BP. This may be more of a 'judgement call' on the part of the physician, and probably would seldom lead to consensus, even among a panel of experts.

There are many reasons for the physician to make the diagnosis of a 'hypertensive urgency' under these circumstances. Probably the most common, discussed above, is an existing local policy mandating treatment and subsequent observation of all patients with a BP higher than a given threshold value (typically >180/110 mmHg). Another common motivation for the physician to give antihypertensive drugs in this setting is to demonstrate to the patient the importance of controlling BP. Unfortunately, many patients discontinue their antihypertensive drugs without a physician's recommendation to do so, and many of these appear in acute medical care settings with a BP that has returned to (or perhaps is even higher than) the original reading that prompted drug treatment. Perhaps because of this, many physicians perceive a duty to 'teach the patient a lesson' by acutely giving treatment and monitoring the patient thereafter. This does often impress patients about the importance of taking their routine drug therapy, and the consequences of not having done so before visiting the physician. The three most typical situations in which acute drug therapy is warranted for a 'hypertensive urgency' are discussed above and are listed in Table 10.1: perioperative hypertension (see Chapter 3), hypertension after organ transplantation, and hypertension associated with severe burns. In each of these settings there is a general agreement that antihypertensive drug therapy is a useful strategy, although no large randomized studies have been (or are likely to be) done to prove the benefits of acute antihypertensive drug therapy.

Another approach to evaluation of the patient with a very elevated BP but no evidence of severe, acute target organ damage would be that recommended by the Evidence-Based Medicine Working Group. This group, which is having a major impact on rational therapeutics in many medical care settings, asserts that the best medical decision-making should be based on published clinical trials that are pertinent to a given patient.[15] As noted above, there are no published outcome-based placebo-controlled clinical trials of antihypertensive drug therapy for patients with hypertensive urgencies. Nearly all our information comes from short-term (typically <1 week) follow-up, and the vast majority of clinical studies of antihypertensive drug therapy confine themselves to the course of BP reduction after acute administration of the test agents. Because there are no proven long-term benefits to the acute treatment of 'hypertensive urgencies', some would conclude that it is not warranted. These groups would generally agree with the usual recommendations for every therapeutic endeavor: the physician should weigh the relative benefits of therapy (even if not documented in clinical trials) against the potential risks of therapy (discussed below) and of no treatment (primarily medicolegal, discussed above).

Perhaps the most common presentation of all is that of the totally asymptomatic patient with what was formerly called stage 3 hypertension (BP ≥180/110 mmHg; but more typically BP ≥200/120 mmHg) who is seen in an acute medical care setting for a complaint unrelated to hypertension, who has a normal physical examination and stable (if not normal) laboratory results.[16] This patient is NOT having a hypertensive emergency, and requires only a prescription for an antihypertensive drug, and

an appointment for follow-up within 24 to 48 hours. In such cases, every effort should be made to ensure that the patient is seen as scheduled, and that the BP has been lowered out of a potentially dangerous range.

Although exceptions to this general policy for uncomplicated hypertension certainly exist, based on the opinion of the treating physician, one very important randomized study strongly supports this approach.[17] Sixty-four asymptomatic patients with severe hypertension visiting the Parkland Hospital Emergency Department were randomized to one of three treatment strategies. 'Clonidine loading' (discussed below) was used as the current standard of care regimen, and patients randomized to this arm of the trial received an initial 0.2 mg dose of oral clonidine, followed by another 0.1 mg dose every hour until the diastolic BP was reduced to predetermined threshold levels. A second group received the initial 0.2 mg oral dose of clonidine, but placebo tablets every hour thereafter. A third group received no acute therapy, but only a prescription for chronic oral antihypertensive medications, which was also given to the other two groups upon discharge from the emergency department. There was no significant difference in time to BP control between the first two groups, and all groups had similar BPs when measured 24 hours after discharge. In 44 patients who returned to the hypertension clinic a week after their emergency department visit, there was adequate control of BP in all groups, and no differences in average BPs between them. The authors interpreted their results to indicate that 'the common practice of antihypertensive loading to treat severe, asymptomatic hypertension should be reconsidered'.[17]

After the diagnosis of a hypertensive urgency is made, and successful treatment given, attention should be turned to the possibility of secondary hypertension. Both renovascular hypertension and pheochromocytoma are more common in patients who present with a hypertensive emergency or urgency. Appropriate diagnostic steps may be initiated for the evaluation of secondary causes after the patient returns to the medical office for follow-up after successful treatment of a hypertensive urgency or emergency.

4. TREATMENT

There are a number of antihypertensive drugs that have been found to be useful in research studies, and can be used to treat a hypertensive urgency (Table 10.4). The ideal drug would be one that had a predictable and relatively rapid onset of action (perhaps 10–30 min to peak effect) after oral administration, a relatively long duration of effect (perhaps as much as 24 h), require little monitoring after administration, and have no adverse effects. Unfortunately, the ideal drug with these properties does not currently exist. Each of the drugs in common use (discussed below) is effective in about 85–95% of hypertensive urgencies, and has a very similar tolerability profile.[18]

Table 10.4 Drugs often used for hypertensive urgencies

Oral drugs
- Nifedipine[a]
- Nicardipine
- Isradipine
- Clonidine
- Captopril
- Labetalol
- Hydralazine
- Minoxidil (when the patient is already taking a diuretic and β-blocker)
- Nitroglycerine

Intravenous drugs
- Labetalol
- Enalaprilat
- Hydralazine
- Urapidil (outside the USA)
- Nicardipine
- Fenoldopam iv
- Nitroglycerine

Percutaneous Drugs
- Nitroglycerine
- Clonidine

[a] Should be used 'with great caution, if at all' (according to the US Food and Drug Administration).[21]
Adapted from Grossman et al, 1998.[18]

4.1 (Short-acting) nifedipine capsules

Nifedipine was once the most popular drug used for hypertensive urgencies. There are good data from early clinical studies with nifedipine capsules that show impressive, but somewhat unpredictable, BP lowering after a 10 mg capsule of nifedipine is given orally.[19] Until the late 1980s, it was thought that the unpredictable efficacy of oral nifedipine during the first 30 minutes after oral administration was due to variability in drug delivery, perhaps due to different rates of hydrolysis of the gelatin capsule containing the nifedipine in solution. It became common practice to attempt to 'overcome' this by giving the liquid nifedipine solution either sublingually, or after biting the capsule to expel the oral solution from the broken capsule. Subsequent studies showed that the bioavailability of sublingual nifedipine was negligible, and that BP reduction occurred only after swallowing the nifedipine containing solution.[20] There is little need, therefore, to undertake elaborate instruction for the patient to hold the liquid under the tongue in order to make the BP-lowering effects of nifedipine capsules less erratic. Although there have been no clinical studies of the 'bite and swallow' technique compared to routine oral administration of nifedipine, there is probably little difference, as gastric acid and proteolytic enzymes routinely present in most people's stomachs quickly dissolve the gelatin capsule containing the nifedipine solution.

The major problem with nifedipine capsules for hypertensive urgencies is the low risk/benefit ratio in most clinical settings. Many systems of organized medical care have issued strong directives limiting or prohibiting the use of oral nifedipine capsules, based on a report of the dangers of short-acting nifedipine in 1996.[21] An accompanying editorial indicated that a New Drug Application was filed in 1985 with the US Food and Drug Administration (FDA) for the use of nifedipine capsules in hypertensive urgencies, and closed hearings held, but because of safety concerns, the FDA declined to approve the drug for this indication.[22] Although the total number of patients from which the sample was drawn is still unknown, 16 hypertensive patients received nifedipine capsules for acute BP lowering, 2 patients died, 4 had strokes, 9 had myocardial infarctions, and 1 pregnant woman required an emergency Cesarean section after her BP plummeted. The authors ascribed the acute target-organ damage to ischemia brought about by hypoperfusion, due to the unpredictable and precipitous declines in BP. There are no estimates of how commonly this occurs, but many experts put the risk at 1–5%. Most authorities feel that this risk is not worth taking, but recently, several obstetricians have published clinical studies with nifedipine capsules showing acceptable rates of adverse effects and good BP lowering efficacy.[23–25] Many hospitals and formulary committees have limited the use of nifedipine capsules to angiography suites and delivery rooms, because of concern that nifedipine was only 'cosmetically' lowering the BP, not controlling it long-term, and might *increase* target-organ damage, rather than *decrease* it. This was ostensibly the reason for the FDA's 1996 recommendation that nifedipine capsules should be used 'with great caution, if at all'.[21]

4.2 Other dihydropyridine calcium antagonists

Several other immediate-release dihydropyridine calcium antagonists have been reported to be effective in treating hypertensive urgencies. As might be expected from the known pharmacokinetic parameters of these drugs, both nicardipine and isradipine have a slightly longer onset of action, and the duration of their antihypertensive effects is also prolonged, compared to nifedipine. Neither has proven extremely popular, although probably each is theoretically less likely to cause the precipitous falls in BP seen occasionally with nifedipine. The sustained-release formulations of these and other dihydropyridine calcium antagonists are much more commonly used in the outpatient setting for chronic treatment of hypertension. These preparations are not as useful for hypertensive urgencies because, by design, sustained-release formulations delay the delivery of the drug from the tablet, usually by several hours.

4.3 Clonidine (and 'clonidine loading')

The centrally acting alpha$_2$-agonist, clonidine hydrochloride, has been used for hypertensive urgencies for many years. This drug has good oral bioavailability, a relatively rapid onset of action, and its effects on BP last for several hours. Transdermal clonidine is sometimes used to lower BP in post-surgical patients, but the onset of action of transcutaneously absorbed clonidine is too slow for it to be of much use for many other types of hypertensive urgencies. The major disadvantages of the acute use of clonidine are the progressive sedation, dry mouth, and somnolence that occur frequently at high (or repeated oral) doses, and the greater likelihood of 'rebound hypertension' after it is suddenly discontinued. These last two features of the drug have limited the enthusiasm for its widespread use for hypertensive emergencies. Since nonadherence to medications is a very common cause of severe, asymptomatic hypertension, the acute use of clonidine not only postpones the sequelae of nonadherence, but also may actually make the BP *higher* after the BP-lowering effects of clonidine wear off.

The most common treatment algorithm for the use of clonidine in hypertensive urgencies is the 'clonidine loading' sequence tested for long-term effects by Zeller et al. discussed above.[17] Oral clonidine is given to patients with hypertensive urgencies, beginning with a 0.2 mg dose, and thereafter every hour at 0.1 mg, until the BP meets a predetermined threshold. Frequently, the central side effects of clonidine (given at such a frequency) are so marked that the patient falls asleep, often about the time the BP reaches the target. This may confuse the medical personnel, as hypertensive encephalopathy is part of the differential; sedation may prohibit discharge of the patient from the emergency department setting to home if walking or driving is required.

Although there are more 'outcome results' with clonidine than with other drugs commonly used for hypertensive urgencies, the study by Zeller et al. suggests that clonidine loading is really not necessary for most patients. Similar BP-lowering results were obtained, at one day and one week, with either the costly and burdensome clonidine loading protocol or a simple prescription for an appropriate antihypertensive agent. These authors therefore suggest writing a simple prescription for a drug, followed by a rapid follow-up appointment in a setting where the BP can be monitored and controlled chronically.

4.4 Short-acting ACE inhibitors (ACEIs)

In many emergency departments outside the United States, oral captopril has become the primary drug for hypertensive urgencies. It is typically given in a 12.5–25 mg dose, crushed to hasten absorption. Several Brazilian and European centers have reported good success with this approach, and precipitous drops in BP are rare, although it can and does occur occasionally. Because oral captopril has a relatively short onset of action, repeating the dose at 30–60 minute intervals is also possible, but is usually not necessary. Intravenous enalaprilat also has been studied in this setting, and is typically started as a 1.25 mg dose intravenously every 6 hours.[26] Both drugs must be used with caution, since either can cause or exacerbate renal impairment in the occasional patient with critical renal artery stenosis; either can also precipitate or exacerbate hyperkalemia.

4.5 Labetalol

Although this combined alpha- and beta-blocker has been studied as an intravenous (iv) therapy mostly in the setting of hypertensive emergencies, it is often used in the latter setting as well.[27] The same escalating dose regimen used for emergencies is generally employed: at 20–30 minute intervals, depending on the response of BP, 10 mg of labetalol is given iv as a single dose, followed by 25 mg, then 50 mg then 100 mg, and finally 200 mg (if required). Because of its alpha-blocking properties, labetalol lowers BP more effectively if the patient stands; this may not be possible or appropriate in some intensive care units or clinical situations. Because of its beta-blocking properties, labetalol can cause bronchospasm or precipitate heart failure and/or heart block.

Based on the generally good results with iv labetalol in the treatment of both hypertensive emergencies and urgencies, some authors have suggested that oral labetalol might also be as useful, especially since this would avoid the time and expense of setting up an iv route of delivery for the drug. There are, however, some major differences in the bioavailability of the four diastereomers that make up the mixture given as labetalol, and oral labetalol seems to have somewhat less of the alpha-blocking properties (relative to the beta-blocking properties) of the iv administered compound. Because of this and its slower onset of action, oral labetalol seems to be somewhat less commonly used in many emergency departments than many other therapies for acute BP lowering.

4.6 Minoxidil and hydralazine

Minoxidil is a very powerful, direct vasodilator, and has been studied in the setting of hypertensive urgencies for patients presenting with severe hypertension, despite a recent dose of both a diuretic and a beta-blocker.[28] These drugs are generally required when minoxidil is given chronically, to combat the pedal edema and reflex tachycardia seen with continuous use. Although the onset of action of minoxidil is fairly long, compared to other drugs discussed above, it is a reasonable option for use in workday clinics. Many emergency departments have insufficient staffing to monitor BP frequently over a sufficiently long duration to observe the BP-lowering effects of an oral dose of minoxidil. Other options are therefore preferred in the emergency department setting.

Hydralazine is another direct-acting vasodilator that has been frequently used in hypertensive urgencies, both orally, intravenously, and intramuscularly. Probably its greatest use is in obstetrics, where it is routinely used when methyldopa does not reduce BP sufficiently in preeclamptic women. The flexibility of the route of delivery is sometimes an advantage in postoperative patients who cannot take oral medications. Its propensity for reflex tachycardia, pedal edema with long-term use, and the usual restriction of dose to <300 mg/d make it a less desirable alternative for many non-obstetrical patients.

4.7 Nitroglycerine and other nitrate preparations

Although not commonly used in the United States for the acute lowering of BP, South American and Central American physicians have extensive experience with oral, sublingual, buccal, and intravenous nitroglycerine and other nitrates as an antihypertensive drugs.[29] When the acute hypertensive episode is complicated by angina pectoris or acute myocardial infarction with persistent chest discomfort (i.e. a hypertensive emergency), this drug has been quite useful, despite its propensity to stick to plastic tubing and for patients to develop tolerance to its acute use. Nitroglycerine paste applied to the skin also has hypotensive properties, probably most well known to occur during its use for patients with acute pulmonary edema.

4.8 Other drugs used for hypertensive emergencies

It is likely that many of the drugs used in hypertensive emergencies would also be effective in reducing BP safely in patients with hypertensive urgencies. These drugs are generally not used often for hypertensive urgencies because of the need for intravenous lines, frequent monitoring of BP, and (in some hospitals) the need for an intensive care unit bed. Sodium nitroprusside is probably the drug with the longest track record of use; it is generally preferred because of its low cost, and when careful control of BP and very quick onset of action is required. Its specific disadvantages include light sensitivity and its toxic metabolites (both cyanide and thiocyanate). Intravenous nicardipine is effective and safe, and is often preferred when a calcium antagonist is indicated (e.g. in the setting of angina pectoris). Intravenous fenoldopam mesylate, a specific dopamine-1 agonist, lowers BP somewhat more slowly than nitroprusside, but has beneficial renal effects, giving it the edge in

patients with pre-existing renal impairment. In countries outside the USA, other drugs are available for hypertensive urgencies and emergencies, the most well-studied of which is urapidil, a complex molecule with alpha$_1$-blocking and probably some 5-hydroxytrypamine agonist activity.[30]

5. OUTCOMES

Unlike the situation in hypertensive emergencies, in which there are clear data showing the benefits of acute lowering of blood pressure, the long-term sequelae of hypertensive urgencies and their treatment are largely unknown. This may well be due to the fact that it is difficult to identify a cohort of people with this syndrome (due to problems in medical terminology and coding). Another contributor is that *many* patients probably would have to be studied to demonstrate a true, statistically significant difference in long-term outcomes across treatments (or even no treatment). This is even more likely given the data of Zeller et al., who were unable to demonstrate any difference in BP-related parameters even a week after intensive versus essentially no acute treatment of hypertensive urgencies.[17]

The risks of acute lowering of BP in the setting of a hypertensive urgency should not be overlooked. Although probably less common with hypertensive urgencies than with emergencies, a precipitous fall in BP following administration of a quick-acting antihypertensive drug can certainly lead to BP lowering beyond the ability of the autoregulatory capacity of many arterial systems. Thus, overaggressive and sudden lowering of BP has been associated with stroke, myocardial infarction, renal shutdown, and other catastrophes. These risks of 'overshoot' from hypotensive effects of medications have to be weighed in the decision about whether to treat a person with a hypertensive urgency.

There are nonetheless some very negative legal ramifications of a decision NOT to acutely treat an elevated BP in a person who presents to an emergency department for an unrelated reason. Well-documented case law now supports, in some jurisdictions, the practice of treating hypertensive urgencies before discharging a patient to outpatient medical care. Primarily because of this issue, hypertensive urgencies still deserve discussion in medical textbooks, even if 'evidence-based medicine' does not support their treatment with randomized, long-term outcome studies in hundreds or thousands of patients.

SUMMARY

'Hypertensive *urgencies*' are clinical situations in which the blood pressure should be reduced within hours, and are distinguished from true 'hypertensive *emergencies*' by the lack of acute, severe target-organ damage. The most common setting for a hypertensive urgency is the hospital emergency department, where elevations of blood pressure are often encountered in patients presenting with an unrelated complaint. Non-adherence to previously prescribed antihypertensive drug therapy is probably the most common cause, although others should be considered. After a suitable evaluation rules out acute target-organ damage, any of a number of oral antihypertensive agents can be given, with high probability of lowering blood pressure. This strategy is often followed in jurisdictions where it has become standard practice not to allow patients to leave the medical care setting with a blood pressure reading higher than an arbitrary level (e.g. diastolic BP > 110 mmHg). Unfortunately, there are no outcome studies to prove the merits of acute lowering of blood pressure in a setting other than a true hypertensive emergency; indeed, some treatments (e.g. nifedipine capsules) have occasionally been harmful. For most patients, therefore, the simple prescription for an antihypertensive agent with a reasonably short onset of action (e.g. 12–24 h) that may be suitable for long-term treatment, followed by a quicker-than-usual follow-up office visit, will be sufficient. This avoids hospital admission and the intensive monitoring of blood pressure and clinical status for several hours after drug administration. However, it also leaves open the possibility that the patient will not have the prescription filled at a phar-

macy, can decline follow-up in the medical office, and has not limited the physician's liability (should an untoward clinical event occur before an office visit). It is therefore likely that we will continue to provide acute treatment to patients with a hypertensive urgency, despite no evidence that such treatment confers any long-term benefit.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003; **289**:2560–2572.
2. Elliott WJ. Hypertensive emergencies. Critical Care Clinics 2001; **17**:435–451.
3. Currey R. Managing hypertensive urgencies in primary care. Lippincott's Primary Care Practice 1998; **2**:498–504.
4. Thach AM, Schultz PJ. Nonemergent hypertension. New perspectives for the emergency medicine physician. Emerg Med Clin North America 1995; **13**:1009–1035.
5. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; **183**:S1–S22.
6. Brott T, Bogousslavsky J. Drug therapy: Treatment of acute ischemic stroke. N Engl J Med 2000; **343**:710–722.
7. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. N Engl J Med 2001; **345**:1223–1229.
8. Perera GA. Hypertensive vascular disease: Description and natural history. J Chron Dis 1955; **1**:33–42.
9. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressure averaging 115 through 129 mmHg. JAMA 1967; **202**:1028–1034.
10. Shea S, Misra D, Francis CK. Predisposing factors for severe, uncontrolled hypertension in an inner-city minority population. N Engl J Med 1992; **327**:776–781.
11. Grossman E, Messerli FH. High blood pressure; A side-effect of drugs, poisons, and food. Arch Intern Med 1995; **155**:450–460.
12. Lip GY, Beevers M, Beevers DG. Malignant hypertension in young women is related to previous hypertension in pregnancy, not oral contraception. QJM 1997; **90**:571–575.
13. Sung JF, Harris-Hooker S, Alema-Mensah E, Mayberry R. Is there a difference in hypertensive claim rates among Medicaid recipients? Ethn Dis 1997; **7**:19–26.
14. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. J Am Coll Cardiol 1996; **27**:1214–1218.
15. Sackett DL, Rosenberg WMC, Muir Gray JA, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn't. BMJ 1996; **312**:71–72 [Editorial].
16. Wenzel UO, Stahl RA, Grieshaber M, Schweitzer G. [Diagnostic and therapeutic procedures by doctors for patients in a hypertensive crisis: An inquiry in 56 internal medicine clinics] (in German). Deutsche Med Wochenschr 1998; **123**:443–447.
17. Zeller KR, Von Kuhnert L, Matthews C. Rapid reduction of severe asymptomatic hypertension: a prospective controlled trial. Arch Intern Med 1989; **149**:2186–2189.
18. Grossman E, Ironi AN, Messerli FH. Comparative tolerability profile of hypertensive crisis treatments. Drug Safety 1998; **19**:99–122.
19. Bertel O, Conen D, Radu EW et al. Nifedipine in hypertensive emergencies. BMJ (Clin Res) 1983; **286**:19–21.
20. van Harten J, Burggraaf K, Danhof M, van Brummelen P, Breimer DD. Negligible sublingual absorption of nifedipine. Lancet 1987; **2**:1363–1365.
21. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA 1996; **276**:1328–1331.
22. Winker MA. The FDA's decisions regarding new indications for approved drugs. Where's the evidence? JAMA 1996; **276**:1342–1343 (Editorial).
23. Scardo JA, Vermillion ST, Hogg BB, Newman RB. Hemodynamic effects of oral nifedipine in preeclamptic hypertensive emergencies. Am J Obstet Gynecol 1996; **175**:336–338.
24. Scardo JA, Vermillion ST, Newman RB, Chauhan SP, Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. Am J Obstet Gynecol 1999; **181**:862–866.

25. Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. Am J Obstet Gynecol 1999; **181**:858–861.
26. Hirschl MM, Binder M, Bur A et al. Clinical evaluation of different doses of intravenous enalaprilat in patients with hypertensive crises. Arch Intern Med 1995; **155**:2217–2223.
27. Wilson DJ, Wallin JD, Vlachakis ND, et al. Intravenous labetalol in the treatment of severe hypertension and hypertensive emergencies. Am J Med 1983; **75**:95–102.
28. Alpert MA, Bauer JH. Rapid control of severe hypertension with minoxidil. Arch Intern Med 1982; **142**:2099–2104.
29. Vargas-Ayala G, Rubio-Guerra AF, Rodriguez-Lopez L et al. Comparison between isosorbide dinitrate in aerosol and in tablet form for the treatment of hypertensive emergencies in the elderly. Blood Press 2000; **9**:283–286.
30. Hirschl MM, Herkner H, Bur A, et al. Course of blood pressure within the first 12 hours of hypertensive urgencies. J Hypertension 1998; **16**:251–255.

Section III

Treatment – High-risk groups

11

Diabetes with and without proteinuria

Samy I Mcfarlane, John Shin, Reba Williams, and James Sowers

Diabetes and renal disease • Diabetic glomerulosclerosis and atherosclerosis as parallel entities • Proteinuria as a predictor of cardiovascular disease and renal risks • Treatment strategies that reduce vascular/glomerular disease in diabetes • Summary • References

1. DIABETES AND RENAL DISEASE

End-stage renal disease (ESRD) is a major public health problem that is approaching epidemic proportions. In the United States, diabetic nephropathy is the most common cause of ESRD, accounting for nearly 50% of the cases.[1] The economic burden of ESRD has also increased, reaching a current estimate of US$17.9 billion, an increase of 7.2% from 1998.[1]

Data from the United States Renal Data Systems (USRDS) indicates that the incidence of ESRD attributed to diabetes mellitus has increased more than 10-fold over the past two decades.[1] Furthermore, the prevalence of diabetes is also is also increasing as a result of increasing obesity, sedentary lifestyle, and aging population. Currently, diabetes afflicts over 16 million Americans, in whom about 5 million are not aware that they have the disease.[2] By the year 2020, it is estimated that diabetes will afflict over 250 million people worldwide.[2,3] Diabetes is the most common cause of ESRD in all ethnic groups and the incidence of diabetes is particularly high among minorities, such as African Americans, Hispanics, and native Americans. In these minority groups the rate of microvascular and macrovascular complication of diabetes is also highly increased compared to Caucasians.[4] For example, ESRD is currently the most common cause of mortality among Pima Indians.[1] Proteinuria is a marker for early diabetic nephropathy and its presence should dictate an aggressive therapeutic strategy to prevent the progression to ESRD.[4]

2. DIABETIC GLOMERULOSCLEROSIS AND ATHEROSCLEROSIS AS PARALLEL ENTITIES

There are many parallels between renal glomerular and vascular structure and function.[5] Endothelial cells line both glomeruli and vessels, mesangial cells are modified vascular smooth muscle cells (VSMCs) derived from the same progenitor cell line.[5,6] Mesangial cells also share many properties with VSMCs, such as contraction in response to agonists like vasopressin, angiotensin II (Ang II), and endothelin-1.[6,7] This is an important feature as the mesangium binds together capillary loops; contraction of the mesangial cells can alter glomerular capillary flow.[5] Both mesangial cells and VSMCs produce growth factors, such as Ang II, insulin-like growth factors (IGFs), and cytokines, as well as nitric oxide (NO), which counterbalances the biological effects of these growth factors.[5]

Abnormalities in both endothelial and mesangial cell function have been described in diabetes mellitus.[7] Specifically, there is decreased production and release of NO and prostaglandins (PGs) in the diabetic states,[8,9] both of which are known to attenuate the effects of various mitogens, such as Ang II.

The pathophysiologic changes that characterize glomerulosclerosis and parallel those of atherosclerosis include: mesangial cell hypertrophy/proliferation, foam cell accumulation, build up of extracellular matrix and amorphous debris with evolving sclerosis.[5] All these changes lead to glomerular extracellular matrix expansion and basement membrane abnormalities that result in loss of selective permeability, which in turn predisposes to proteinuria. Indeed, microalbuminuria reflects generalized transmembrane leakiness that is associated with endothelial cell dysfunction.[10,11]

3. PROTEINURIA AS A PREDICTOR OF CARDIOVASCULAR DISEASE AND RENAL RISKS

Microalbuminuria is defined as the presence of urinary albumin above the normal but below the detectable range with the conventional dipstick methodology. This is consistent with urinary albumin excretion rate of 20–200 μg/min (30–300 mg/24 h), as values within this range have been shown to predict the progression of diabetic nephropathy.[12] Furthermore, the degree of albuminuria is closely related to the progression of diabetic nephropathy,[13] with the fastest decline in glomerular filtration rate (GFR) in those patients with nephritic range proteinuria (>3500 mg/24 h). Those patients also have the shortest survival.[14,15] Microalbuminuria is also a predictor of cardiovascular disease (CVD) morbidity and mortality in both type 1,[16] and type 2 diabetes,[17,18] and is a marker of insulin resistance and endothelial dysfunction in patients with the metabolic syndrome as well as in people with diabetes.[10,18,19] Other cardiovascular and renal risk factors that cluster with microalbuminuria in patients with diabetes,[4] and the metabolic syndrome,[10] are listed in Box 11.1.

Box 11.1 Cardiovascular risk factors that cluster with microalbuminuria

- Central obesity
- Insulin resistance
- Low HDL cholesterol levels
- High triglyceride levels
- Small dense LDL particles
- Systolic hypertension
- Salt sensitivity
- Elevated C-reactive protein and other inflammatory markers
- Absent nocturnal drop in BP and heart rate
- Male sex and postmenopausal or diabetic women
- Increased cardiovascular oxidative stress
- Impaired endothelial function
- Abnormal coagulation/fibrinolytic profiles
- Left ventricular hypertrophy
- Hyperuricemia

HDL, high-density lipoprotein; LDL, low-density lipoprotein. Modified from McFarlane SI et al, 2001, with permission. [10]

For further discussion on proteinuria, refer to Chapter 3 of this book.

4. TREATMENT STRATEGIES THAT REDUCE VASCULAR/GLOMERULAR DISEASE IN DIABETES

In order to minimize the cardiovascular and renal disease risk in people with diabetes, factors that are involved in vascular disease development should be addressed comprehensively. These factors (Table 11.1) include hyperinsulinemia and hyperglycemia that create a milieu in which activation of cytokines, matrix protein, and other related factors accelerate cellular injury and destruction.[10,20] Elevated blood pressure (BP) leads to increased shear stress on the vessels and end-organs, which perpetuate cellular injury and destruction.[5,21–23] Thus, there is a synergy of adverse factors that ultimately lead to cardiovascular and renal injury that

Table 11.1 Factors that contribute to the pathogenesis of vascular and glomerular disease in diabetes

- **Hyperinsulinemia:** Increased activity of the renin angiotensin and sympathetic nervous systems, sodium retention, decreased activity of natriuretic hormones, and decreased steady state nitric oxide.
- **Hyperglycemia:** Increased apoptosis, adhesion molecules, glycation products. Increased permeability to molecules, increased cytokine and matrix protein production by cells. Intrarenal vasodilation, and loss of autoregulation (hyperfiltration).
- **Elevated blood pressure:** Increased intraglomerular pressure and shear stress.
- **Dyslipidemia:** Elevated triglycerides, low HDL cholesterol, increased small dense LDL cholesterol leading to accelerated atherosclerosis/glomerulosclerosis.
- **Coagulation abnormalities:** Increased plasminogen activator inhibitor, fibrinogen and decreased fibrinolytic activity.
- **Cigarette smoking:** Increases inflammation and cytokine production.

HDL, high-density lipoprotein; LDL, low-density lipoprotein. Modified with permission from Bakris and Sowers, Curr Diabetes Rep 2002.[24]

could be reduced with the optimal management of the contributing factors (Table 11.1).[24]

4.1 Glycemic control

The beneficial effects of glycemic control, as assessed by the hemoglobin A_{1c} (HbA_{1c}) measurements, on the microvascular complications of diabetes (nephropathy, neuropathy, and retinopathy) has been clearly documented in both type 1 and type 2 diabetes mellitus.[25–27] In the Diabetes Control and Complications Trial (DCCT), there was 54% reduction in the development of nephropathy when the HbA_{1c} was reduced from 9% to 7% in patients with type 1 diabetes. Furthermore, the incidence of microvascular complications was low if the HbA_{1c} level was maintained at 7%. The DCCT trial also showed dramatic increases in the development of microvascular complications when the HbA_{1c} level was above 8%. Based on these findings, the American Diabetes Association (ADA) recommends a goal HbA_{1c} of 7% and intensification of glycemic control if HbA_{1c} is above 8%.

In people with type 2 diabetes, prospective trials also have shown that the lower HbA_{1c}, the better the outcome in terms of microvascular complications.[26–28] The United Kingdom Prospective Diabetic Study (UKPDS) showed that when HbA_{1c} was lowered from 7.9% to 7.1%, there was a 24%–33% reduction in nephropathy.[26] There was no threshold HbA_{1c} below which a further reduction in diabetic complications did not occur.[26] In contrast to type 1 diabetes, lower HbA_{1c} is easier to achieve in people with type 2 diabetes, since these patients have a lower incidence of hypoglycemia, particularly with the use of thiazolidinedione and/or metformin.[29,30] Finally, despite the beneficial effects of glycemic control documented in the above trials, our recent report indicates that only 26.7% of people with diabetes achieved a target HbA_{1c} of $<7\%$.[31]

4.2 Blood pressure control

Hypertension is as twice as common in people with diabetes compared to those without the disease and accounts for up to 85% of excess cardiovascular disease (CVD) risk. Conversely, patients with hypertension are more prone to have diabetes than are normotensive patients.[4]

In type 1 diabetes, hypertension is usually a manifestation of diabetic nephropathy and both

hypertension and nephropathy appear to exacerbate each other. In type 2 diabetes hypertension usually clusters with the other components of the cardiometabolic syndrome (Box 11.1), such as microalbuminuria, central obesity, and insulin resistance.[10]

Hypertension in patients with diabetes, compared to those without diabetes, has unique features such as increased salt sensitivity, volume expansion, isolated systolic hypertension, loss of nocturnal dipping of BP and pulse, increased propensity to proteinuria, and orthostatic hypotension.[4] Most of these features are considered risk factors for CVD (Box 11.1) and are particularly important for selecting the appropriate antihypertensive medications, for example, low-dose diuretics for treatment volume expansion, and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) for proteinuria.

4.2.1 Blood pressure goal

Based on the results of several major randomized controlled trials, including the Hypertension Optimal Treatment (HOT) trial, the United Kingdom Prospective Diabetes Study (UKPDS), the Appropriate Blood pressure Control in Diabetes (ABCD) trial, and the Modification of Diet in Renal Disease (MDRD) trial, the Hypertension and Diabetes Executive Working Group of the National Kidney Foundation recommended lowering the BP goal level to 130/80 mmHg or less in patients with diabetes and/or renal impairment.[32] This treatment goal was also adopted by the Canadian Hypertension Society and by the American Diabetes Association (ADA).[33] However, despite the compelling evidence from these trials that lowering the BP significantly reduces CVD in people with diabetes, recent observation by our group indicates that, BP goal of 130/80 mmHg was achieved only in 25.6%.[31]

4.2.2 Pharmacological therapy

Drug therapy should be initiated in people with diabetes and BP above 130/80 mmHg (Figure 11.1), concomitantly with lifestyle modifications, such as weight loss, exercise, reduction of dietary sodium intake, and limitation of alcohol consumption, as an integral part in the management of hypertension in people with diabetes.

4.2.3 Angiotensin-converting enzyme inhibitors

The ability of ACEIs to attenuate albuminuria and renal disease progression initially led to their use as renoprotective agents in diabetic nephropathy.[34] More recently, randomized controlled trials have shown that ACEIs inhibitors provide cardiovascular benefits and may also improve insulin resistance and prevent the development of diabetes,[35] a finding that was also demonstrated most recently with the use of the angiotensin receptor blocker, losartan.[36] These reports suggest a negative role of Ang II in insulin resistance and vasorelaxation (Figure 11.2), and is being further investigated in the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial.

In patients with type 1 diabetes and proteinuria, ACEI treatment was associated with a 50% reduction in the risk of the combined end-points of death, dialysis, and transplantation.[34] In the MICRO-HOPE there was a 16% reduction in overt nephropathy.[35] With these clearly proven benefits, ACEIs are currently recommended as a first-line treatment and are the most prescribed antihypertensive medication for patients with both diabetes and hypertension.

4.2.4 Angiotensin II receptor blockers (ARBs)

ARBs selectively inhibit the binding of angiotensin II (Ang II) to the angiotensin II type 1 (AT_1) receptors and unlike ACEIs, ARBs have no effects on the bradykinin system; therefore they are very well tolerated with lower incidence of side effects, such as cough. ARBs are recommended as initial therapy for those who could not tolerate ACEIs (usually because of cough) and in whom ACEIs are recommended as first-line drugs, such as patients with diabetes and proteinuria, heart failure, systolic dysfunction, postmyocardial infarction, and those with mild renal insufficiency. However, three major studies, the Reduction of

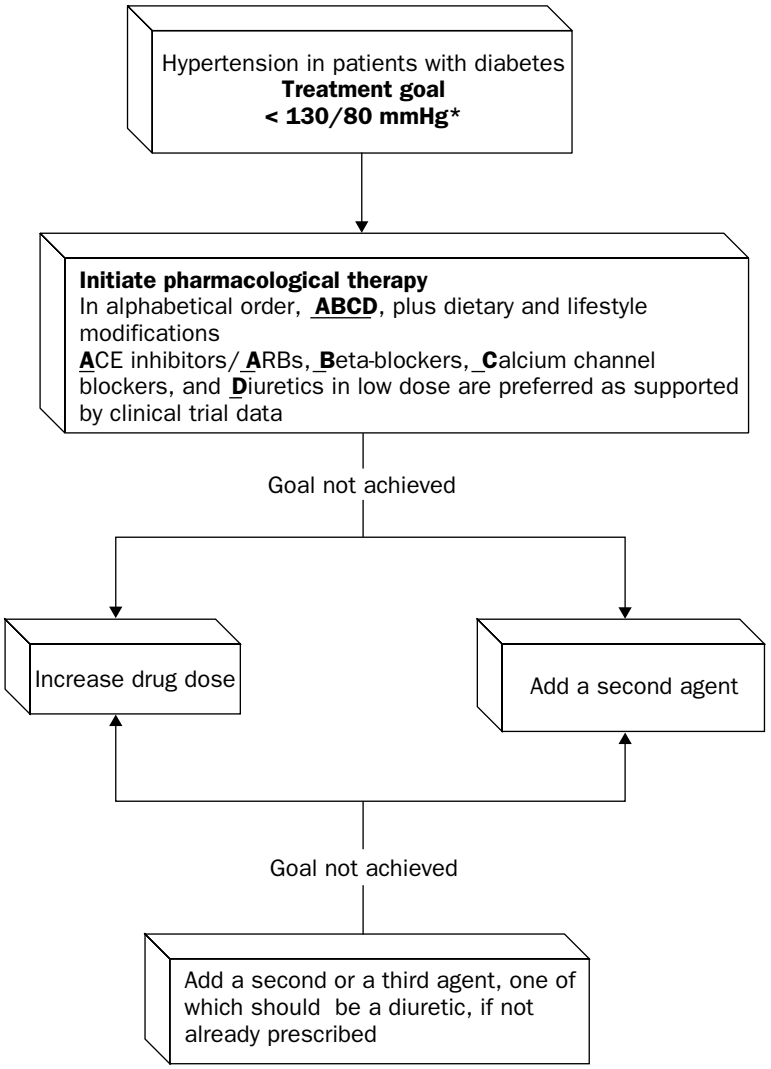

Fig. 11.1 Antihypertensive therapy in people with diabetes. *In patients with >1 g/d proteinuria and renal insufficiency the treatment goal is BP < 125/75 mmHg. ARBs, angiotensin II receptor blockers.

Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study, the Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients (IRMA II) Study, and the Irbesartan in Diabetic Nephropathy Trial (IDNT), showed that ARBs are effective in reducing the progression of renal disease in patients with type 2 diabetes and hypertension.[37–39] BP control was similar in the placebo and ARB-treated groups indicating that ARBs may protect the kidney independent of BP reduction. In the RENAAL trial, the risk of the primary end-point (a composite of doubling of serum creatinine, end-stage renal disease (ESRD) or death from any cause) was reduced by 16% with losartan. The risk of doubling of serum creatinine was reduced by 25% and the risk of ESRD was reduced by 28% over a follow up period of 3.4 years. This study also documented reduction in the initial hospitalization for heart failure. Recently, it was reported (LIFE trial), that losartan was statistically more effective than atenolol in reducing CVD morbidity and mortality in diabetic patients with hypertension and left ventricular hypertrophy (LVH). Losartan especially reduced fatal and non-fatal strokes by 25%, which is a major cause of death and disability in diabetic patients. Finally,

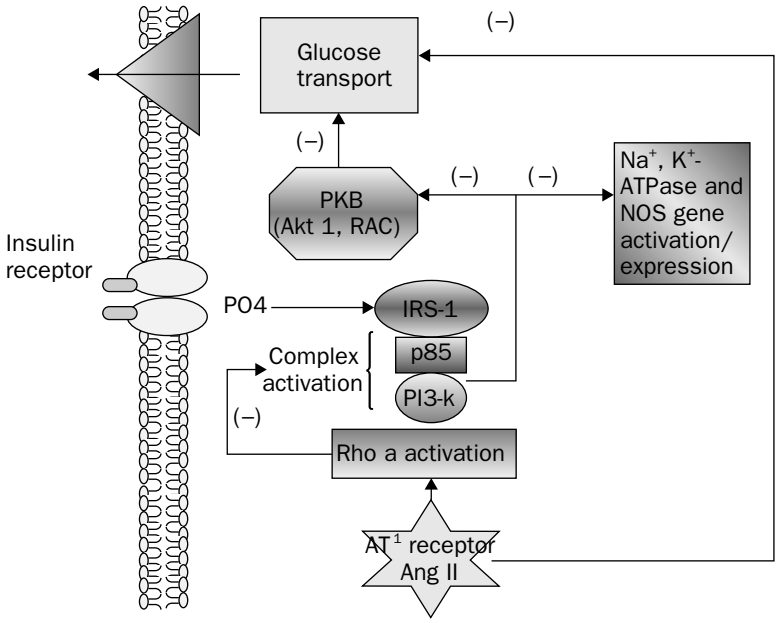

Fig. 11.2 Proposed interactions of insulin and angiotensin II (Ang II) in vascular tissue; (–) indicates insulin signaling steps that are inhibited by Ang II.

losartan reduced the new onset of diabetes by 25% compared to atenolol in the LIFE study. These benefits were above and beyond those attributable to BP reduction alone. Based on the evidence and because of the better tolerability, ARBs, in addition to ACEIs are recommended as a first-line therapy for patients with diabetes and hypertension. (Figure 11.1).

4.2.5 Beta-blockers

Beta-blockers are very useful antihypertensive agents in patients with diabetes.[20] In the UKPDS study, atenolol, reduced microvascular complications of diabetes by 37%, strokes by 44% and death related to diabetes by 32%. In that study the beta-blocker, atenolol, had equal efficiency compared to the ACEI, captopril, in reducing the micro- and macrovascular complications of diabetes, perhaps secondary to their ability to modulate the renin-angiotensin-aldosterone system (RAAS) system. Hypertensive patients receiving beta-blockers have a higher risk of diabetes than those on no medication or on other antihypertensive medications particularly those that interrupt the RAAS.[40] Despite this potentially adverse metabolic effect of beta-blockers, they have proved to have significant long–term favorable effects on CVD in hypertensive patients with diabetes and, therefore, should be used in patients with diabetes, particularly those with underlying ischemic heart disease.

4.2.6 Calcium channel blockers (CCBs)

To achieve a target BP of 130/80 mmHg, clinical trials suggest that at least 65% of patients require two or more different antihypertensive agents.[41] Additional therapies in people with diabetes (besides ACEIs and diuretics) may include long–acting CCBs. A non-dihydropyridine CCB, such as verapamil or diltiazem, may have more beneficial effects on proteinuria than a dihydropyridine CCB, such as nifedipine.[41] However, with the use of ACEIs (or ARBs) as a first-line treatment, together with a diuretic, the addition of a long-acting dihydropyridine, such as amlodipine, will help in achieving the target BP, especially in patients with isolated systolic hypertension not adequately responding to the addition of low-dose diuretic therapy.

4.2.7 Diuretics

Low-dose diuretics are effective antihypertensive agents in patients with diabetes as these patients often have expanded plasma volume.

Concerns regarding adverse metabolic effects, shown with the use of large doses (e.g. 50–200 mg of hydrochlorothiazide) were not substantiated with the use of low-dose diuretics.[4] Diuretics are also effective for the treatment of isolated systolic hypertension, which is common and occurs at a younger age in people with diabetes. The systolic hypertension in the elderly program (SHEP) trial showed that small doses of chlorothalidone, did not produce significant adverse metabolic effects and reduced the rate of major CVD events, fatal and non-fatal strokes and all cause mortality in patients with diabetes.[42] In addition, diuretics are often a necessary component of combination antihypertensive therapy in people with diabetes who usually require multiple drug therapy to achieve target BP.[41] They are critical components in the therapeutic strategy to reduce the elevated systolic BP, which is often significantly elevated in patients with type 2 diabetes.[4]

4.3 Lipid control

Dyslipidemia is a well-established risk factor for cardiovascular disease (CVD). Control of dyslipidemia can ameliorate macrovascular disease in people with diabetes, for whom the ADA recommends a treatment goal of LDL cholesterol of <100 mg/dL. Dyslipidemia is associated with microalbuminuria,[4] and statins have been shown to decrease urinary albumin excretion in patients with diabetes.[43] Statins inhibit key events in the inflammatory cascades that are associated with nephropathy and were shown to attenuate renal injury in both *in vivo* and *in vitro* studies.[44] In hyperglycemic insulin-deficient diabetic rats, statins ameliorated the structural and functional changes of diabetic nephropathy.[45] Clinical relevance of these findings and further characterization of the relationship between lipid control and diabetic nephropathy is yet to be determined by the ongoing interventional studies.

4.4 Smoking cessation

Cigarette smoking reduces renal plasma flow, probably by increasing synthesis of the vasoconstrictor endothelin and reducing generation of the vasodilatory endothelial nitric oxide.[46] Smoking also increases inflammation and cytokine production (Table 11.1) and is associated with microalbuminuria.[47] Smoking is a risk factor for nephropathy in both type 1 and type 2 diabetes,[48,49] and is a predictor of faster decline of renal function despite the use of ACEIs,[50] therefore, smoking cessation is an important part of the treatment and preventive strategies to reduce renal injury in people with diabetes (Table 11.1).

4.5 Antiplatelet therapy

Aspirin inhibits platelet aggregation, prostaglandin synthesis, smooth muscle cell proliferation, and thromboxane genesis and it has been shown to have beneficial effects in diabetic nephropathy.[51] Aspirin prevents early hyperfiltration and prevents the fall in GFR and glomerular basement membrane thickening that occurs over time in diabetic rats. Inhibition of prostaglandin-2 synthesis by aspirin may be responsible for the protection observed.[52] Based on the evidence that aspirin significantly reduces CVD events in people with diabetes, aspirin therapy is recommended as a primary as well as a secondary prevention strategy for prevention of CVD in people with diabetes.[53]

4.6 Dietary protein restriction

In patients with type 1 diabetes and nephropathy, dietary protein and phosphorus restriction has been shown to slow the progression of nephropathy.[54] In the Modified Diet in Renal Disease (MDRD),[55] among patients with moderate renal insufficiency, a slow decline in renal function started four months after the introduction of a low-protein diet suggesting a small benefit of this dietary intervention. Among patients with more severe renal insufficiency, a very-low-protein diet, as compared with a low-protein diet, did not significantly slow the progression of renal disease. In this study, only a small proportion (3%) of the patients were type 2 diabetics and none had type 1 diabetes. The ADA recommends 0.8 g/kg/day in people

with nephropathy with further restriction to 0.6 mg/kg/day once the GFR starts to decline.[56] Several concerns regarding the dietary protein restrictions remain including the lack of long-term information regarding benefits and consequences, such as protein malnutrition.

SUMMARY

Diabetes is the leading cause of end-stage renal disease (ESRD) that is currently approaching epidemic proportions. Proteinuria is a marker for early diabetic nephropathy and its presence should dictate aggressive therapeutic measures to prevent the progression to ESRD. Improving glycemic control, aggressive antihypertensive therapy and the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) will slow the progression of diabetic nephropathy. Additionally, strategies to control other risk factors that contribute to the vascular and glomerular disease in diabetes, such as smoking cessation, protein restriction, lipid control, and aspirin use, may have additional benefits in diabetic nephropathy.

REFERENCES

1. National Institutes of Health. Incidence and prevalence of ESRD. Excerpts from the United States Renal Data System's 2000 annual data report; atlas of end-stage renal disease in the United States. Am J Kidney Dis 2001; **38**(Suppl 3):38–52.
2. Mokdad AH, Ford ES, Bowman BA et al. Diabetes trends in the U.S.: 1990–1998. Diabetes Care 2000; **23**:1278–1283.
3. Mokdad AH, Serdula MK, Dietz WH et al. The continuing epidemic of obesity in the United States. JAMA 2000; **284**:1650–1651.
4. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. Hypertension 2001; **37**:1053–1059.
5. Bakris G, Palant CE, Walsh MF, Sowers JR. Analogy between endothelial and mesangial cells. In: Sowers JR (ed.), Endocrinology of the vasculature. Totowa, NJ: Humana Press 1996, 341–355.
6. Mene P, Simonson MS, Dunn MJ. Physiology of the mesangial cell. Physiol Rev 1989; **69**:1347–1424.
7. Standley PR, Bakir MH, Sowers JR. Vascular insulin abnormalities, hypertension, and accelerated atherosclerosis. Am J Kidney Dis 1993; **21**:39–46.
8. Tsukahara H, Gordienko DV, Tonshoff B, Gelato MC, Goligorsky MS. Direct demonstration of insulin-like growth factor-I-induced nitric oxide production by endothelial cells. Kidney Int 1994; **45**:598–604.
9. Doni MG, Whittle BJ, Palmer RM, Moncada S. Actions of nitric oxide on the release of prostacyclin from bovine endothelial cells in culture. Eur J Pharmacol 1988; **151**:19–25.
10. McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab 2001; **86**:713–718.
11. Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B. Atherosclerotic risk factors are increased in clinically healthy subjects with microalbuminuria. Atherosclerosis 1995; **112**:245–252.
12. Bakris GL. Microalbuminuria: what is it? Why is it important? What should be done about it? J Clin Hypertens (Greenwich) 2001; **3**:99–102.
13. Rossing P. Promotion, prediction, and prevention of progression in diabetic nephropathy. Dan Med Bull 1998; **45**:354–369.
14. Watkins PJ, Blainey JD, Brewer DB et al. The natural history of diabetic renal disease. A follow-up study of a series of renal biopsies. QJM 1972; **41**:437–456.
15. Kussman MJ, Goldstein HH, Gleason RE. The clinical course of diabetic nephropathy. JAMA 1976; **236**:1861–1863.
16. Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ 1996; **313**:779–784.
17. Muggeo M, Verlato G, Bonora E et al. The Verona diabetes study: a population-based survey on known diabetes mellitus prevalence and 5-year all-cause mortality. Diabetologia 1995; **38**:318–325.
18. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; **342**:145–153.
19. Sowers JR. Hypertension in type II diabetes: Update on therapy. J Clin Hypertens (Greenwich) 1999; **1**:41–47.

20. Cooper ME, Bonnet F, Oldfield M, Jandeleit-Dahm K. Mechanisms of diabetic vasculopathy: an overview. Am J Hypertens 2001; **14**:475–486.
21. Sowers JR, Lester MA. Diabetes and cardiovascular disease. Diabetes Care 1999; **22**(Suppl 3): C14–C20.
22. Ruggenenti P, Gambara V, Perna A, Bertani T, Remuzzi G. The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. J Am Soc Nephrol 1998; **9**:2336–2343.
23. Bakris GL. Pathogenesis of hypertension in diabetes. Diabetes Rev 1995; **3**:460–476.
24. Bakris GL, Sowers JR. Microalbuminuria in diabetes. Curr Diabetes Rep 2002; **2**:258–262.
25. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; **329**:977–986.
26. (UKPDS 33). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; **352**:837–853.
27. Ohkubo Y, Kishikawa H, Araki E et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; **28**:103–117.
28. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; **321**:405–412.
29. Bell DS. Chronic complications of diabetes. South Med J 2002; **95**:30–34.
30. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002; **137**:25–33.
31. McFarlane SI, Jacober SJ, Winer N et al. Control of cardiovascular risk factors in patients with diabetes and hypertension at urban academic medical centers. Diabetes Care 2002; **25**:718–723.
32. Bakris GL, Williams M, Dworkin L et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000; **36**:646–661.
33. Standards of medical care for patients with diabetes mellitus. Diabetes Care **24**(Suppl 1):S33–S43.
34. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; **329**:1456–1462.
35. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000; **355**:253–259.
36. Lindholm LH, Ibsen H, Dahlof B et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002; **359**:1004–1010.
37. Parving HH, Lehnert H, Brochner-Mortensen J et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001; **345**:870–878.
38. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345**:861–869.
39. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; **345**:851–860.
40. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med 2000; **342**:905–912.
41. Bakris GL. Maximizing cardiorenal benefit in the management of hypertension: Achieve blood pressure goals. J Clin Hypertens (Greenwich) 1999; **1**:141–147.
42. Hall WD. The Systolic Hypertension in the Elderly Program: Implications for the Management of Older Hypertensive Patients. Am J Geriatr Cardiol 1992; **1**:15–23.
43. Tonolo G, Melis MG, Formato M et al. Additive effects of Simvastatin beyond its effects on LDL cholesterol in hypertensive type 2 diabetic patients. Eur J Clin Invest 2000; **30**:980–987.
44. McFarlane SI, Muniyappa R, Francisco R, Sowers JR. Clinical review 145: Pleiotropic effects of statins: lipid reduction and beyond. J Clin Endocrinol Metab 2002; **87**:1451–1458.

45. Yokota T, Utsunomiya K, Murakawa Y, Kurata H, Tajima N. Mechanism of preventive effect of HMG-CoA reductase inhibitor on diabetic nephropathy. Kidney Int Suppl 1999; **71**: S178–S181.
46. Righetti M, Sessa A. Cigarette smoking and kidney involvement. J Nephrol 2001; **14**:3–6.
47. Krimholtz M, Thomas S, Viberti G. Cigarette smoking and diabetic nephropathy. Contrib Nephrol 2000; **130**:85–93.
48. Gambaro G, Bax G, Fusaro M et al. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. Diabetes Nutr Metab 2001; **14**:337–342.
49. Muhlhauser I, Bender R, Bott U et al. Cigarette smoking and progression of retinopathy and nephropathy in type 1 diabetes. Diabet Med 1996; **13**:536–543.
50. Chuahirun T, Wesson DE. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. Am J Kidney Dis 2002; **39**:376–382.
51. Winchester JF. Therapeutic uses of aspirin in renal diseases. Am J Kidney Dis 1996; **28**:S20–S23.
52. Moel DI, Safirstein RL, McEvoy RC, Hsueh W. Effect of aspirin on experimental diabetic nephropathy. J Lab Clin Med 1987; **110**:300–307.
53. Standards of Medical Care for Patients with Diabetes Mellitus. Diabetes Care **24**(Suppl 1):S62–S63.
54. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991; **324**:78–84.
55. Klahr S, Levey AS, Beck GJ et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994; **330**:877–884.
56. Diabetic nephropathy. American Diabetes Association. Diabetes Care 2001; **24**:S69–S72.

12

Treatment of hypertension in African Americans

Tariq Shafi, Bede Nnolim, and John M Flack

Introduction • Epidemiological considerations • Therapeutic considerations • Factors influencing BP responsiveness to antihypertensive drug therapy • Drug selection • Hypertensive urgencies and emergencies • Chronic hypertension in hospitalized patients • References

1. INTRODUCTION

Hypertension in African Americans, at the group level, is clearly different than hypertension in the general population. Hypertension prevalence is greater, it occurs earlier in life, is more often severe, and is linked to a greater burden of target-organ damage such as left ventricular hypertrophy (LVH), chronic kidney disease (CKD), heart failure, and stroke. Nevertheless, should the treatment of African American *individuals* with hypertension fundamentally differ as it relates to drug selection and overall therapeutic approach from that applied to whites or, for that matter, any other racial/ethnic group? We interpret the totality of available clinical evidence to support the thesis that the optimal approach to hypertension treatment and drug selection is minimally, if at all, affected by race or ethnicity. Clearly, this recommendation lies in the face of the long-standing paradigm that has highlighted race as an important consideration when choosing drug therapy.

Virtually all African American versus white comparisons of blood pressure (BP) responses showing racial differences in response have been to *single* antihypertensive drugs. It is our opinion that racial differences in BP response provide little insight into the selection of optimal drug therapy for either group. Furthermore, most patients will require multiple antihypertensive drugs to attain goal BP levels. There is virtually no difference in BP lowering, for example, between initiating therapy with an angiotensin-converting enzyme inhibitor (ACEI) or calcium antagonist in nondiabetic African Americans with reduced kidney function when complex drug regimens are prescribed. Also, the clinician should recognize the shortcomings of nonrandomized comparisons of racial patterns in BP response to single antihypertensive agents and avoid extrapolating these relatively small differences in group mean BP responses to all *individuals* in the contrasted groups. Multiple clinical trials have shown that African Americans, for example, respond less well to ACEIs and beta-blockers as monotherapy, than they do to calcium antagonists or diuretics. These and other studies have shown that African Americans manifest a lesser response than whites to single drug therapy with ACEIs, angiotensin II receptor blockers (ARBs), and beta-blockers than whites – particularly at low to moderate doses of

these agents. However, a close examination of these data does not support their utility in selecting drug therapy for individual African American patients. First, the racial differences in mean BP response are typically much less than the range of BP responses between the upper 25% and the lower 25% of responders (interquartile range) within either group. Thus, the variability of BP response is much greater within a racial group than between them. Furthermore, this variability in BP response can only be explained by factors that vary at the *individual* level. Second, even though racial differences in BP lowering have been demonstrated the BP response distributions for African Americans and whites significantly overlap. Also, regional (stroke-belt non-stroke belt) differences in BP response of a similar or even greater magnitude than racial differences also have been reported in men.[1] Third, BP responses to monotherapy leaves the majority of hypertensives, and particularly those with reduced kidney function, diabetes, and severe BP elevations, far above their minimum therapeutic BP target. Fourth, it is clear that in some hypertensive groups, such as persons with reduced kidney function and/or diabetes, that some of the therapeutic benefits are related to effects of the drugs that are independent of their BP lowering effects.[2–4]

Optimal hypertension treatment is not specific to any race or ethnic group. Although racial differences in BP response have been documented, they are seldom of sufficient magnitude to translate into different drug selections for different racial groups. We will discuss therapeutic approaches to optimal hypertension treatment that are applicable to all hypertensives, and will also consider the importance of various clinical settings in determining the route, timing, and BP treatment thresholds and minimum therapeutic goals.

2. EPIDEMIOLOGICAL CONSIDERATIONS

2.1 Systolic blood pressure is the principal mediator of BP- related complications

Epidemiological data supports the thesis that systolic blood pressure (SBP) is more important than diastolic blood pressure (DBP), especially after middle-age, in mediating cardiovascular disease (CVD) complications and mortality. Nevertheless, the therapeutic decisions suggest that clinicians actually place greater emphasis on DBP than SBP. This issue is particularly important amongst older higher risk persons with SBP elevations with 'normal' DBP (< 90 mmHg). The divergence of SBP and DBP occurs mostly in older persons and, to a degree, even in middle-aged persons with diabetes mellitus. Clearly, the clinician should persistently attempt to lower SBP in older persons even when DBP appears to be 'normal'.

2.2 Hypertension control rates

Even though three-quarters of African Americans are aware of their hypertension, it is untreated among a quarter and uncontrolled in the 57% that are under treatment. Interestingly, overall BP control rates to $< 140/90$ mmHg are relatively similar in African Americans and whites. There appears, however, to be little reason to systematically treat African Americans with hypertension differently in a qualitative sense, thus any differences in pharmacologic approach are most logically driven by factors that vary at the individual level. Ethnic group, *per se*, has not yet been used to justify a lower minimum therapeutic goal BP in African Americans.

2.3 Factors influencing BP control

Patients should routinely be asked about drug acquisition costs and medication bottles should be checked to avoid changes in medications due to automatic formulary interchanges. Other factors, such as use of oral contraceptives, nasal decongestants, and over-the-counter medications, as well as illicit drugs with sympathomimetic properties can contribute to poor BP control. Sleep apnea and occult ethanol abuse also can lead to poorly controlled hypertension.

Physician factors are important. Physicians sometimes become frustrated with their success in controlling elevated BP and reactively label the patient as noncompliant. Yet, there are considerable data suggesting that physicians often

make suboptimal therapeutic choices, do not use enough antihypertensive medications even in high-risk patients, and prescribe medications that interfere with BP control. Furthermore, physicians are often satisfied with BP levels far above the recommended minimum therapeutic goals and take no action when patients visit them with elevated BP – except to continue what has not worked.

When BP continues to remain elevated despite the use of three agents including a diuretic that is appropriate for the level of kidney function, then referral to hypertension specialists or nephrologist should be made with consideration of the most likely causes of secondary hypertension. Renal artery stenosis remains the most common treatable cause of secondary hypertension. Mineralocorticoid hypertension – hyperaldosteronism and glucocorticoid remediable aldosteronism – and sleep apnea, particularly the latter, are not infrequently encountered in ambulatory and hospital clinical settings. African Americans are at risk for all of these forms of secondary hypertension.

3. THERAPEUTIC CONSIDERATIONS

3.1 Rationale for antihypertensive drug therapy

Treatment of hypertension is both rewarding as well as challenging. Successful BP lowering reduces cardiovascular-renal morbidity and mortality, all cause mortality, and improves quality of life and a lower burden of subjective symptoms. These benefits have been demonstrated in both African Americans and whites in the United States, although the bulk of the data have been derived from whites. Nevertheless, the benefits of BP lowering have been widely demonstrated and there is little reason to doubt its benefits in African Americans or any other racial/ethnic group.

3.2 The myth of hypertension as an asymptomatic condition

Hypertension has long been assumed to be asymptomatic. Thus, the patients on treatment reporting symptoms have typically been thought to have drug-induced side effects. Hypertensives manifest a constellation of symptoms, such as headache, fatigue, weakness, dizziness, sleep disturbance, chest pain, and nervousness. Drug-treated hypertensives, with lower BP, report fewer side effects and better quality of life than placebo-treated patients with higher BP levels. It is highly likely that the symptoms of fatigue, dizziness, headache, and weakness reported by the hypertensive patients on treatment are more typically related to the BP level rather than to the medications *per se*. The attribution of these symptoms to the medications leads to erroneous clinical decisions such as discontinuation or down-titration of medications when, in fact, intensification of therapy is the clinical decision most likely to alleviate these complaints. Hypertensive patients have improved quality of life and report fewer subjective symptoms after successful BP lowering.

3.3 General therapeutic considerations

Figure 12.1 provides a suggested algorithmic approach to the management of hypertension in African American patients in the ambulatory clinic setting. Setting the appropriate goal BP is an important first step. For purposes of simplicity, the Joint National Committee (JNC) VI blood pressure goals will be utilized. Persons with 1 gram of proteinuria per 24 hours have goal BP $< 125/75$ mmHg. Those with diabetes, reduced kidney function (estimated glomerular filtration rate < 60 mL/min/1.73 m^2), and heart failure have a minimum therapeutic goal of $< 130/85$ mmHg. African Americans will more often have lower therapeutic BP goals because of their greater burden of comorbidities such as diabetes and reduced kidney function. All other hypertensives have a minimum therapeutic goal BP $< 140/90$ mmHg. Figure 12.1 illustrates that the minimum therapeutic goal BP depends on careful identification of the CVD risk factors, target-organ damage and presence of diabetes, and proteinuria. Estimation of glomerular filtration rate (GFR) (Figure 12.2), provides a means of more accurately determining the level of kidney function than solely using sex-specific

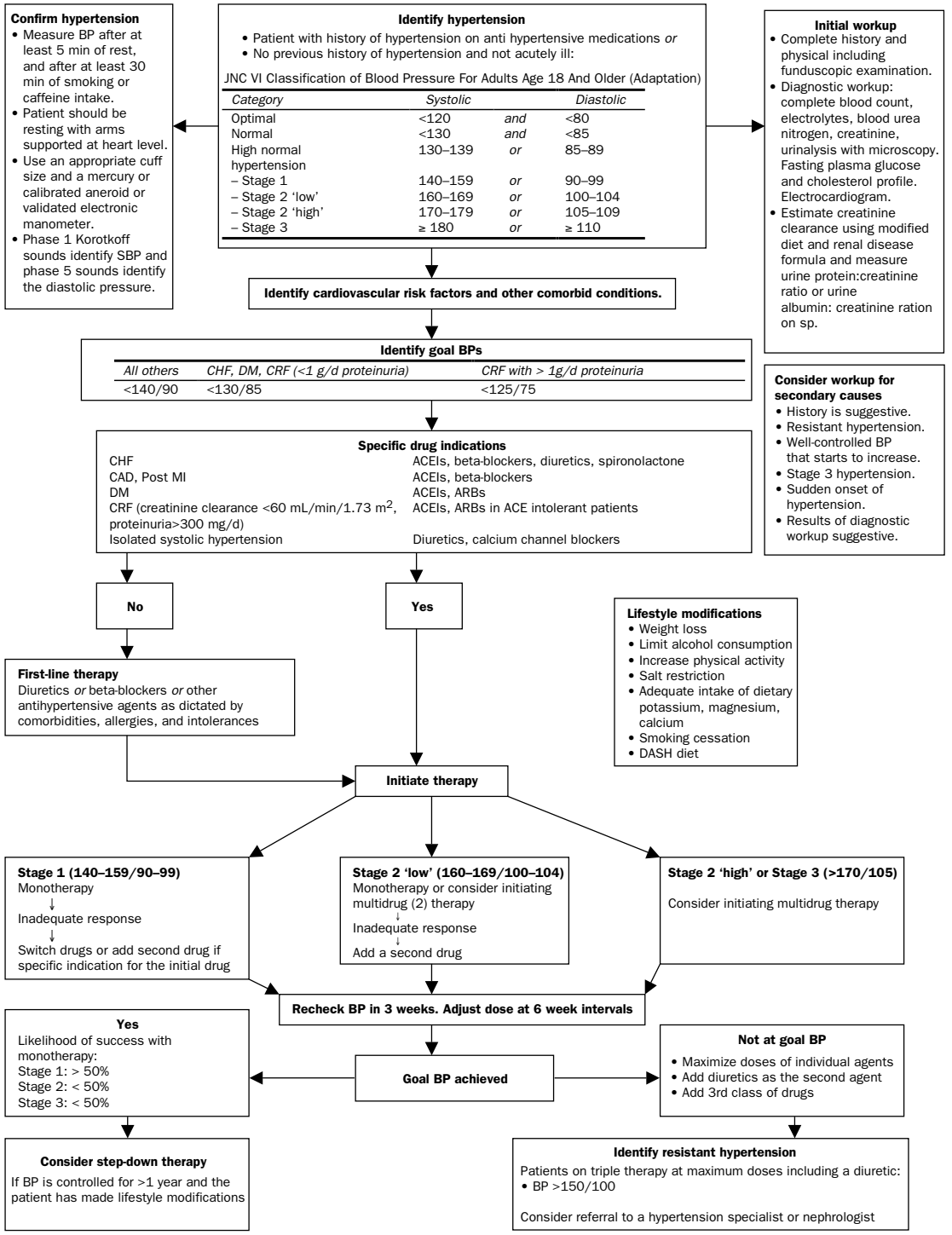

Fig. 12.1 A suggested algorithm for the management of hypertension in African Americans. CBC, complete blood count; BUN, blood urea nitrogen; MDRD, modified diet and renal disease; CHF, congestive heart failure; DM, diabetes mellitus; CRF, chronic renal failure; MI, myocardial infarction; DASH, dietary approaches to stop hypertension.

MDRD EGFR for black men

	SERUM CREATININE							
AGE	1.2	1.4	1.6	1.8	2	2.2	2.4	2.6
20 to 24	97.6	81.7	70	61.1	54.1	48.5	43.8	40
25 to 29	93.6	78.3	67.1	58.6	51.9	46.5	42.1	38.3
30 to 34	90.4	75.7	64.9	56.6	50.1	44.9	40.6	37
35 to 39	87.8	73.5	65	55	48.7	43.6	39.4	36
40 to 44	85.5	71.6	61.4	53.6	47.4	42.5	38.4	35
45 to 49	83.6	70	60	52.4	46.4	41.5	37.6	34.3
50 to 54	81.9	68.6	58.8	51.3	45.4	40.7	36.8	33.6
55 to 59	80.4	67.3	57.7	50.4	44.6	39.9	36.1	32.9
60 to 64	79	66.2	56.7	49.5	43.8	39.3	35.5	32.4
65 to 69	77.8	65.1	55.8	48.7	43.1	38.7	35	31.9
70 to 74	76.7	64.2	55	48	42.5	38.1	34.5	31.4
75 to 79	75.6	63.3	54.3	47.4	41.9	37.6	34	31
80 to 84	74.7	62.5	53.6	46.8	41.4	37.1	33.6	30.6
85 to 89	73.8	61.8	52.9	46.2	40.9	36.7	33.2	30.2
90 to 94	72.9	61.1	52.3	45.7	40.5	36.2	32.8	29.9
95 to 99	72.2	60.4	51.8	45.2	40	35.9	32.4	29.6

MDRD EGFR for black women

	SERUM CREATININE							
AGE	0.8	1	1.2	1.4	1.6	1.8	2	2.2
20 to 24	115.6	89.4	72.4	60.6	51.9	45.3	40.2	36
25 to 29	110.9	85.7	69.4	58.1	49.8	43.5	38.5	34.5
30 to 34	107.1	82.8	67.1	56.1	48.1	42	37.2	33.3
35 to 39	104	80.4	65.1	54.5	46.7	40.8	36.1	32.4
40 to 44	101.3	78.3	63.5	53.1	45.5	39.8	35.2	31.5
45 to 49	99	76.6	62	51.9	44.5	38.9	34.4	30.8
50 to 54	97	75	60.8	50.9	43.6	38.1	33.7	30.2
55 to 59	95.2	73.6	59.7	49.9	42.8	37.4	33.1	29.6
60 to 64	93.6	72.4	58.6	49.1	42.1	36.7	32.5	29.1
65 to 69	92.2	71.2	57.7	48.3	41.4	36.2	32	28.7
70 to 74	90.8	70.2	56.9	47.6	40.8	35.6	31.5	28.3
75 to 79	89.6	69.3	56.1	47	40.3	35.1	31.1	27.9
80 to 84	88.5	68.4	55.4	46.4	39.8	34.7	30.7	27.5
85 to 89	87.4	67.6	54.7	45.8	39.3	34.3	30.4	27.2
90 to 94	86.4	66.8	54.1	45.3	38.8	33.9	30	26.9
95 to 99	85.5	66.1	53.5	44.8	38.4	33.5	29.7	26.6

MDRD EGFR for non-black men

	SERUM CREATININE							
AGE	0.8	1	1.2	1.4	1.6	1.8	2	2.2
20 to 24	128.8	99.5	80.6	67.5	57.9	50.5	44.7	40.1
25 to 29	123.5	95.5	77.3	64.7	55.5	48.4	42.9	38.4
30 to 34	119.3	92.2	74.7	62.5	53.6	46.8	41.4	37.1
35 to 39	115.8	89.5	72.5	60.7	52	45.4	40.2	36
40 to 44	112.9	87.2	70.7	59.2	50.7	44.3	39.2	35.1
45 to 49	110.3	85.3	69.1	57.8	49.6	43.3	38.3	34.3
50 to 54	108.1	83.5	67.7	56.7	48.6	42.4	37.5	33.6
55 to 59	106.1	82	66.4	55.6	47.7	41.6	36.8	33
60 to 64	104.3	80.6	65.3	54.7	46.9	40.9	36.2	32.5
65 to 69	102.7	79.3	64.3	53.8	46.1	40.3	35.7	31.9
70 to 74	101.2	78.2	63.4	53	45.5	39.7	35.1	31.5
75 to 79	99.8	77.1	62.5	52.3	44.8	39.1	34.7	31.1
80 to 84	98.5	76.2	61.7	51.7	44.3	38.6	34.2	30.7
85 to 89	97.4	75.2	61	51	43.7	38.2	33.8	30.3
90 to 94	96.3	74.4	60.3	50.5	43.3	37.8	33.4	30
95 to 99	95.2	73.6	59.6	49.9	42.8	37.4	33.1	29.6

MDRD EGFR for non-black women

	SERUM CREATININE							
AGE	0.6	0.8	1	1.2	1.4	1.6	1.8	2
20 to 24	133.1	95.5	73.8	59.8	50.1	42.9	37.5	33.2
25 to 29	127.7	91.6	70.8	57.4	48	41.2	35.9	31.8
30 to 34	123.4	88.5	68.4	55.4	46.4	39.8	34.7	30.7
35 to 39	119.8	85.9	66.4	53.8	45.1	38.6	33.7	29.9
40 to 44	116.7	83.8	64.7	52.5	43.9	37.6	32.9	29.1
45 to 49	114.1	81.9	63.3	51.3	42.9	36.8	32.1	28.4
50 to 54	111.8	80.2	62	50.2	42	36	31.5	27.9
55 to 59	109.7	78.7	60.8	49.3	41.3	35.4	30.9	27.3
60 to 64	107.8	77.4	59.8	48.5	40.6	34.8	30.4	26.9
65 to 69	106.2	76.2	58.9	47.7	39.9	34.2	29.9	26.5
70 to 74	104.6	75.1	58	47	39.4	33.7	29.4	26.1
75 to 79	103.2	74	57.2	46.4	38.8	33.3	29	25.7
80 to 84	101.9	73.1	56.5	45.8	38.3	32.9	28.7	25.4
85 to 89	100.7	72.2	55.8	45.2	37.9	32.5	28.3	25.1
90 to 94	99.5	71.4	55.2	44.7	37.4	32.1	28	24.8
95 to 99	98.5	70.7	54.6	44.3	37	31.8	27.7	24.5

Fig. 12.2 An estimator of glomerular filtration rate (EGFR). MDRD, modified diet and renal disease.

creatinine cut-off points. This can lead to better therapeutic decision-making, for example, by allowing the practitioner to select the most appropriate diuretic or avoiding potentially deleterious drugs such as nonsteroidal antiinflammatory drugs (NSAIDs) in persons with reduced kidney function. Box 12.1 displays 10 suggested strategies that address common clinical scenarios that undermine attainment of goal BP.

3.4 Rapidity of BP lowering: What is the hurry?

There is little reason to pursue rapid BP-lowering in otherwise stable patients with hypertension. Most long-acting antihypertensive medications take approximately 4–6 weeks to achieve their maximal BP-lowering effects. Slower up-titration of medication (every 6 weeks) appears to improve BP control with fewer severe side effects than rapid up-titration (every 2 weeks).[5]

Box 12.1 Suggestions for attaining goal blood pressure

1. Wait 4–6 weeks, in most instances, to uptitrate BP medications.
2. Diuretic doses may need to be relatively high (i.e. 160 mg/d of furosemide) when kidney function is ↓.
3. Initiate lifestyle modifications: salt restriction to at least 2 g/d or lower, low saturated fat/cholesterol diet, appropriate aerobic exercise.
4. Consider using a dihydropyridine *and* a rate-limiting calcium channel block together if BP refractory to treatment.
5. Remember hypertension is NOT asymptomatic and that gradual BP lowering with drugs over time alleviates more side effects than it causes.
6. Minimize exposure to NSAIDs, including COX-II inhibitors, when kidney function reduced and refer to a nephrologist for evaluation when EGFR < 60 mL/min/1.73 m^2.
7. Multidrug therapy is the rule to attain goal BP when: (a) $>15/10$ mmHg above goal BPs or (b) diabetes and/or reduced kidney function (especially with proteinuria) is present.
8. Diuretics are essential to the multidrug 'cocktail' when >2 antihypertensives are prescribed.
9. Minoxidil use requires the concurrent use of a powerful diuretic (fluid retention) and an A-V nodal blocker (tachycardia) such as a beta-blocker or rate-limiting calcium antagonist.
10. If BP remains above goal on ≥3 antihypertensives (one of which is a diuretic) at near-maximal doses, consider referral to a clinical hypertension specialist or nephrologist.

However, in a patient with an insignificant reduction in BP to an adequately dosed therapeutic trial of sufficient duration the likelihood of achieving goal BP control is low. Thus, it may be reasonable to add another medication or switch to another drug as opposed to further up-titration of the initial ineffective drug. It is likely that the BP dose-response relationship of the second drug is steeper when added to the first drug compared to when the second drug replaces the first drug.

3.5 Lifestyle interventions

Lifestyle interventions are clearly effective treatments, at least in combination with drug therapy, in controlling BP. Weight loss, though difficult to maintain over the long-term, effectively lowers BP. Additionally, salt and alcohol restriction, also lower BP. In fact, one of the major causes of refractory hypertension is excessive consumption of dietary sodium. In hospitalized patients intravenous infusion of saline is a common, overlooked reason for difficult-to-control BP. Dietary prescription of <2 grams (87 mEq/d) of sodium and two or fewer drinks of alcohol per day is prudent. A diet enriched with fresh fruits, vegetables, and fiber but with reduced intake of saturated fat also has been shown to lower BP in African American hypertensives. Appropriate aerobic physical activity can also lower BP. Heavy weight lifting can raise BP both in the short- and long-term and therefore should be avoided. Practitioners should refer most patients encountered in the ambulatory clinic setting for

appropriate dietary counseling. The opportunity to either initiate and/or reinforce dietary counseling in hospitalized patients should not be overlooked. Although smoking does not chronically raise BP, the practitioner should offer counseling, referral, or therapeutic intervention for smoking cessation.

4. FACTORS INFLUENCING BP RESPONSIVENESS TO ANTIHYPERTENSIVE DRUG THERAPY

Salt sensitivity

Salt sensitivity occurs in the majority of hypertensive patients, including African Americans. Though there is no readily available means for the clinician to assess sodium sensitivity, overweight individuals, persons with diabetes mellitus and/or reduced kidney function, and older persons all are predisposed. The importance of salt sensitivity in antihypertensive treatment is that dietary sodium attenuates BP-lowering response to antihypertensive agents. This attenuation of BP-lowering response attributable to salt sensitivity can be overcome, at least partially, by increasing the dose of antihypertensive medications and/or by adding a diuretic. The antihypertensive effect of calcium antagonists and diuretics are relatively more resistant to the typical high levels of usual sodium excretion consumed by most free-living Americans than are drugs, such as ACEIs, ARBs, and beta-blockers. Persons taking NSAIDs, especially those with reduced kidney function, will likely retain more salt and water and experience an attenuation of the BP lowering effect of commonly used antihypertensive drugs.

4.2 Kidney function and proteinuria

We have previously reported that reduced estimated glomerular filtration rate (EGFR) and urinary protein excretion are both strong and independent predictors of attenuated BP responses to antihypertensive drug therapy in a largely African American cohort of drug-treated hypertensives.[6] Even microalbuminuria, levels of proteinuria below the dipstick positive range, were associated with reduced BP responsiveness to antihypertensive drug therapy. Higher levels of proteinuria predicted an even further attenuation of BP lowering. Proteinuria also predicts more rapid loss of glomerular filtration over time. Also, proteinuria cannot be maximally reduced in the setting of *ad libitum* sodium intake, even when profoundly antiproteinuric drugs, such as ACEIs and ARBs are prescribed.

Several clinical decisions require knowledge of the level of kidney function. If reduced kidney function is 'missed' because of reliance on serum creatinine elevations then minimum therapeutic BP targets may be set inappropriately high. Furthermore, drugs such as ACEIs or ARBs, drug classes with nephroprotective effects, also may not be prescribed. Finally, thiazide diuretics may be prescribed when there is inadequate glomerular function for these agents to be effective. Figure 4.2 displays a GFR estimator based on the modified diet and renal disease (MDRD) equation and depicts the EGFR range within which thiazides are most effective.

5. DRUG SELECTION

5.1 Monotherapy or combination therapy?

Most hypertensives, irrespective of race, will not attain their minimum therapeutic goal BP with single drug therapy. This is even more true for the African American hypertensive because of the high prevalence of JNC VI stage 3 hypertension (>180/110 mmHg), reduced kidney function, and salt sensitivity. A good rule of thumb is to anticipate the need for more than a single antihypertensive agent to lower BP to goal when BP is >15/10 mmHg above goal. Even when you anticipate the need for more than one antihypertensive agent, it is reasonable to initiate therapy with a single agent that will be up-titrated into the middle or even upper end of its dosing range. At that point a second agent can be added. Alternatively, two drugs can be prescribed initially, usually both at submaximal doses, as individual pills or as a combination formulation. Remember there is no hurry to normalize the BP.

5.2 Diuretics

Diuretics are important antihypertensive agents. These agents are indispensable in complex drug regimens, in part, because they antagonize the salt and water retention that occurs with other vasodilators and sympatholytic drugs when the patient is consuming an *ad libitum* sodium diet. That is when taking more than two antihypertensive agents, if one of the initial two agents was not a diuretic, then the third agent should be. The diuretic should be appropriate for the level of kidney function. Amongst persons with EGFR approximately 45 mL/min/1.73 m^2 thiazides are minimally effective to ineffective. Metolazone or loop diuretics do, however, effectively lower BP in these patients. A common mistake is to prescribe the loop diuretic furosemide to persons with relatively preserved EGFR. In this situation furosemide is not as effective as the thiazides in lowering BP. Furthermore, furosemide should be dosed at least twice daily because of its relatively short duration of action.

5.3 The renin-angiotensin-aldosterone-system is a valid therapeutic target in African Americans

The utilization of race as a pivotal consideration when choosing antihypertensive medications has been pervasive, yet in our opinion is an outdated concept. We have recently examined and discussed this topic in great detail.[7,8] Monotherapy with calcium channel blockers and diuretics has been shown to produce greater BP reductions in African Americans as compared to other drug classes. Nevertheless, African Americans do respond to treatment with ACEIs, beta-blockers, and ARBs, if given over a sufficient duration of time with adequate dosing. The addition of dietary salt restriction and/or diuretics to ACEIs can further reduce any racial differences in BP response to ACEIs. In nondiabetic African Americans with hypertension and reduced kidney function, the initial therapy with the ACE inhibitor ramipril was shown to be superior to amlodipine, a dihydropyridine calcium antagonist, and metoprolol, a beta-blocker in preserving kidney function. The benefit of the ACEI was greatest amongst persons with the highest level of proteinuria. It should be noted, however, that neither amlodipine or metoprolol were used in combination with each other or ramipril.

There are, however, several caveats regarding the use of ACEIs in African Americans. First, these agents can cause angioedema and dry cough to a greater degree than seen in whites. ARBs cause angioedema much less frequently and have not been linked to dry cough. The most common reason for a rise in serum creatinine during ACEI therapy is intravascular volume depletion, typically as a consequence of over-diuresis. Bilateral renal artery stenosis is an important cause of creatinine elevations during ACEI therapy, though it is much less common than over-diuresis. In patients with reduced kidney function it is not uncommon to see not only an initial rise in creatinine but also stabilization of the creatinine at a level higher than baseline. As long as the rise in creatinine is $<30\%$, the dose of the ACEI or ARB can be maintained.[9] Despite this small initial loss of GFR in some patients, they benefit over the long-term with less progression of their kidney insufficiency. Both ACEIs and ARBs can cause hyperkalemia, especially in hyperkalemia-prone patients – reduced kidney function, diabetes mellitus, use of NSAIDs in persons with reduced kidney function, those receiving heparin and/or potassium supplements and potassium-sparing diuretics. However, the ARBs appear to be less likely than ACEI to raise serum potassium levels.

6. HYPERTENSIVE URGENCIES AND EMERGENCIES

Sustained elevation of blood pressure $>215/115$ mmHg needs immediate attention and evaluation – although infrequently do these patients merit the intensive interventions that are commonly undertaken to bring their BP down within minutes to hours. Patients with severely uncontrolled hypertension fall into two broad categories.

6.1 Hypertensive urgencies

Severe uncontrolled hypertension in the absence of new or worsening target-organ damage (e.g. hematuria, proteinuria, heart failure, cerebral or coronary ischemia) is classified as hypertensive urgency. In this situation the physician is concerned that target-organ injury, however, is likely if BP remains elevated. Many different factors can lead to hypertensive urgencies including abrupt cessation of antiadrenergic medications, such as clonidine and beta-blockers, acute pain, cocaine abuse, poorly selected antihypertensive drug regimens, dietary indiscretions, and secondary causes of hypertension.

Most of these patients do not need acute interventions to bring down their BP. Many of them are already taking antihypertensive medication and either need dose adjustments and/or prescription of new medications with early follow-up over the next few days or so. Some physicians may opt to admit at least some of these patients to the hospital. Typically, a short-stay 23 hour admission with bedrest, sodium restriction, and reinstitution or intensification of prescribed medical therapy via the oral route is all that is necessary to lower BP levels below the dangerous range. Intravenous medications, such as labetalol, are often utilized in this situation but are infrequently necessary. The only possible exception to this is postoperative hypertension, which requires the use of parenteral medications much like hypertensive emergencies. The overarching goal is not normalization of BP but rather lowering the BP out of the danger zone where target-organ damage is thought to be imminent. Nevertheless, do not underestimate the risk of target-organ hypoperfusion occurring as a consequence of abrupt reductions in BP. A target pressure of no lower than 170/110 mmHg is reasonable, though when oral and most intravenous medications are used it is difficult to fine tune the magnitude of BP reduction.

6.2 Hypertensive emergencies

Sustained BP elevations associated with target-organ damage, such as acute aortic dissection, chest pain, pulmonary edema, acute renal failure, encephalopathy, and hemorrhagic or thrombotic cerebrovascular events, constitute life-threatening situations in which the BP needs to be lowered over minutes to hours. The goal of BP reduction in these situations also is not BP normalization but rather a gradual reduction in mean arterial pressure [(2 $\times$ diastolic blood pressure) + systolic blood pressure/3)] by no more than 15–20% to no lower than approximately 170/110 mmHg. This goal should be achieved by administration of intravenous medications, such as sodium nitroprusside or nitroglycerine. Both of these medications allow very precise titration of the BP-lowering effect. Overzealous BP lowering can precipitate or worsen target organ ischemia due to impaired autoregulation of blood flow into vital organs. After BP is better controlled a search for secondary causes of hypertension may be warranted.

7. CHRONIC HYPERTENSION IN HOSPITALIZED PATIENTS

Hypertensive hospitalized individuals may experience elevated BP for a variety of reasons, such as pain, anxiety, hypoxia, hypercarbia, hypoglycemia, status epilepticus, and antiadrenergic drug withdrawal. Another issue to consider is the ever increasing tendency to automatically substitute drugs within a therapeutic class because of restricted hospital formularies. This can contribute to poor BP control because of a delay in reaching steady state drug concentrations. Intravenous saline infusions should be minimized as they, like dietary sodium intake, can raise BP in salt-sensitive persons. Management of hypertension in the hospital is undermined by inaccuracies in BP determination because of inaccurate cuff size (usually too small), inexperienced personnel, and poorly calibrated automated BP measurement devices. Hospitalized patients are also prone to orthostatic changes due to prolonged bedrest.

A reasonable approach to treating chronic hypertension in hospitalized patients is to set the BP goals under levels likely to cause target organ ischemia. In other words most patients

do not need BP normalization during their hospitalization or even by the time of discharge. Furthermore, the BP triggering physician notification should be recorded in the admission orders and should be high enough (>215/115 mmHg) to avoid unnecessary interventions/therapeutic misadventures by cross-covering physicians who are unfamiliar with the patient. However, emphasis should be placed on patient evaluation in cases of severe BP elevations rather than over the phone, as required orders for acute BP-lowering therapy.

REFERENCES

1. Cushman WC, Reda DJ, Perry HM et al. Regional and racial differences in response to antihypertensive medication use in a randomized controlled trial of men with hypertension in the United States. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Arch Intern Med 2000; **160**:825–831.
2. Sica DA, Douglas JG. The African American Study of Kidney Disease and Hypertension (AASK): new findings. J Clin Hypertens (Greenwich) 2001; **3**:244–251.
3. Weekers L, Krzesinski JM. [Clinical study of the month. Nephroprotective role of angiotensin II receptor antagonists in type 2 diabetes: results of the IDNT and RENAAL trials] (in French) Rev Med Liege 2001; **56**:723–726.
4. Sleight P. The HOPE study (Heart Outcomes Prevention Evaluation). J Renin Angiotensin Aldosterone Syst 2000; **1**:18–20.
5. Flack JM, Yunis C, Preisser J et al. The rapidity of drug dose escalation influences blood pressure response and adverse effects burden in patients with hypertension: the Quinapril Titration Interval Management Evaluation (ATIME) Study. ATIME Research Group. Arch Intern Med 2000; **160**:1842–1847.
6. Duncan K, Ramappa P, Thornburg R et al. The influence of urinary albumin excretion and estimated glomerular filtration rate on blood pressure response in drug-treated hypertensive patients in an academic hypertension clinic. Am J Hypertens 2001; **14**(Suppl 2):196A.
7. Flack JM, Mensah GA, Ferrario CM. Using angiotensin converting enzyme inhibitors in African-American hypertensives: a new approach to treating hypertension and preventing target-organ damage. Curr Med Res Opin 2000; **16**:66–79.
8. Flack JM, Peters R, Mehra VC, Nasser SA. Hypertension in special populations. Cardiol Clin 2002; **20**:303–319.
9. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevation in serum creatinine: is this a cause for concern? Arch Intern Med 2001; **160**:685–693.

13

The kidney and hypertension in South and East Asians

Sunil Nadar and Gregory YH Lip

Introduction • The kidney and hypertension • The scope of the problem in south and east Asians • Implications for management • Summary • References

1. INTRODUCTION

South and East Asia is a large geographical area and encompasses a diverse ethnic mix. Although the main ethnic group in East Asia is Chinese, there is a sizeable population with origins in the Indian subcontinent. Even within this large area, there are considerable economic differences in the various regions.

It should also be remembered that many South and East Asian migrants are living in the Western world. In particular, countries such as the United Kingdom, are host to many first-generation migrants from South Asia. Certainly, hypertension is common amongst these ethnic groups, whether still living in their native land or host country – and hypertension brings with it the associated complications, such as renal disease, cardiovascular disease, and cerebrovascular disease.

2. THE KIDNEY AND HYPERTENSION

End-stage renal disease (ESRD) is a common complication of long-term hypertension and conversely, renal parenchymal disease is a common cause of hypertension, especially in the extremes of age, that is, amongst children and in the elderly. In the United States, hypertension ranks just below diabetes among causes of ESRD.[1] In other countries, hypertension may not be that significant and accounts for about 10% of ESRD.

In 1836, Bright first suggested a connection between abnormal kidney function and hypertension.[2] However, it was not until Goldblatt (1936) induced hypertension in dogs by causing renal ischaemia that the direct link was established.[3] The recognition of the existence of the renin angiotensin system finally proved without a doubt the important role of the kidney, both in maintaining normal electrolyte balance and blood pressure and in the pathogenesis of hypertension.[4,5]

Renal damage can lead to hypertension by various mechanisms. First, it can cause sodium retention,[6] and thereby volume expansion through the renin-angiotensin aldosterone system (RAAS),[7] and increased mineralocorticoid actions.[7] Second, renal disease increases the production of other vasopressors besides renin and angiotensin, such as the endothelins.[8] Finally, sympathetic overactivity is another common finding in renal failure, correlating

with the increase in both vascular resistance and systemic blood pressure.[9]

2.1 Hypertension and the progression of renal disease

Renal dysfunction is seen in many patients with long-term hypertension. However, clinical research amongst hypertensive patients, randomised controlled trials, and population studies confined to white communities all show scant evidence that 'essential' non-malignant non-proteinuric normo-creatininaemic hypertension leads to renal impairment.[10] Retrospective data from dialysis and transplantation units also tend to confirm this point. The only convincing exception is in studies of African Americans where there does appear to be a relationship between blood pressure at screening and the subsequent development of renal impairment, but it is not possible to be certain that those patients who develop renal impairment might not have had a low grade subclinical glomerulonephritis when first seen. Thus, if benign essential hypertension does damage the kidneys, it probably does so very rarely. Additional and novel risk factors need to be sought.

The proponents of the theory that hypertension leads to renal disease suggest that it does so through a series of haemodynamic and neuro-humoral mechanisms. Perhaps the major culprit relating hypertension and the progression of renal disease is the (RAAS).[11] This is evident by the fact that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) reduce the rate at which renal disease progresses.[12]

Progression to renal parenchymal damage and ESRD, which seems to be largely independent of the initial insult, is the final common pathway for chronic, proteinuric nephropathies in animals and humans. The key event is enhanced glomerular capillary pressure; this impairs glomerular permeability to proteins and permits excessive amounts of proteins to reach the lumen of the proximal tubule.[13,14] The secondary process of reabsorption of filtered proteins can contribute to renal interstitial injury by activating intracellular events, including up-regulation of the genes encoding vasoactive and inflammatory mediators. Both interstitial inflammation and progression of disease can be controlled by such drugs as the ACEIs, which alter the glomerular permeability barrier to proteins and thereby limit proteinuria and filtered protein-dependent inflammatory signals.[13,15]

In the setting of systemic hypertension, there is transmission of the elevated pressure to the glomerulus, leading to progressive damage. This phenomenon is dependent on afferent arteriolar resistance. In hypertension, there is resetting of tubuloglomerular feedback so that glomerular hypertension is sustained despite extensive loss of renal function (Figure 13.1). If glomerular hypertension produces progressive decline in renal function by way of progressive sclerosis of the glomeruli, it is glomerulosclerois that in turn leads to or aggravates hypertension by way of reduced renal mass, which results in an inability to perform a number of its usual functions or the appearance of one or more pressor mechanisms. Haemodynamically, when renal mass is reduced, blood pressure rises, first because of volume expansion and an increased cardiac output, but later because of elevated peripheral resistance.

Thus, it can be seen that the kidney can be both the victim and the culprit in hypertension associated with renal disease. Clinically, there is often a vicious cycle in which hypertension increases renal damage, which causes more hypertension.

3. THE SCOPE OF THE PROBLEM IN SOUTH AND EAST ASIANS

Hypertension continues to be a major health problem in the developing world. There are varying reports on the incidence of hypertension and its complications from the Asian continent. Furthermore, ethnic differences play as much a role in the progression of the illness as well as the geographical location itself.[16]

There are many studies that have shown that patients of ethnic minority groups in the United States,[17,18] and the United Kingdom,[19,20] who are exposed to the same environmental factors still have a different prevalence or incidence and

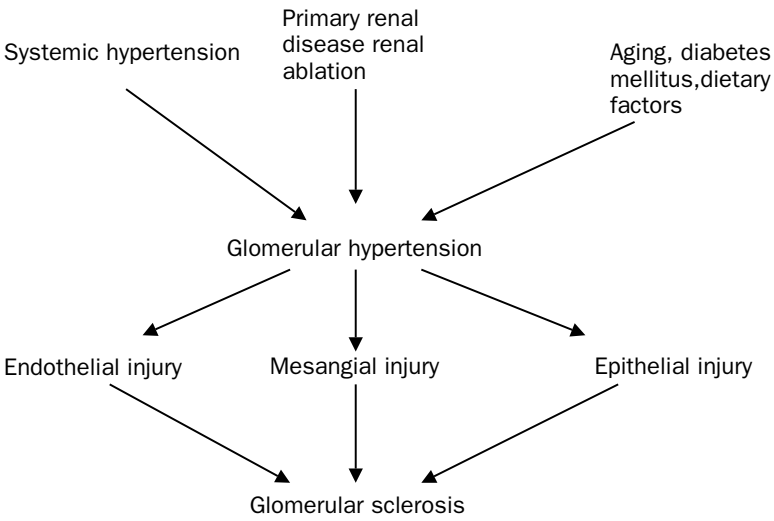

Fig. 13.1 Central role of glomerular hypertension in producing progressive structural renal damage.

etiologies of chronic renal failure. In the West Birmingham Malignant Hypertension register,[21] for example, Indo-Asians accounted for 41 out of a total of 315 patients, giving it a prevalence rate of 13%, although many of the clinical features (presenting blood pressures, prevalence of renal damage, prognosis, etc.) were similar to the Caucasian population; this is in contrast to Afro-Caribbeans, who had higher blood pressures and greater renal impairment at presentation, with an associated poorer prognosis.

Recently, the Study of Health Assessment and risk in Ethnic groups (SHARE) from Canada showed that south Asians had the highest prevalence of atherosclerosis, as compared to Europeans and Chinese (11%, 5%, and 2%, respectively).[22] These investigators also looked at various risk factors and felt that the differences in the risk factors specific to each ethnic group did not fully explain the differences in vascular complications, suggesting that genetic differences also accounted for some of the differences.

3.1 Prevalence of hypertension

There are different studies from various countries in the region quoting different prevalence rates for hypertension.

Studies from India have shown a prevalence of about 5.7% among the general population.[23] However, in a country as diverse as India, studies from different cities show different prevalence rates, depending on the geographical location, and also the ethnic background.[24–26] Interestingly, one study found that Takayasu's arteritis was the most common cause of renovascular hypertension in India, accounting for over 60% of all cases.[27] Another study from North India looked at 135 patients with malignant phase hypertension over a period of 11 years and reported that the underlying etiology was essential hypertension in 88 patients and a secondary cause in 47; of the latter, a renovascular etiology was present in 20 and renal parenchymal disease in 19.[28] Thus, 29% of patients with malignant phase hypertension in this series had a renal cause.

Data from East Asia are equally limited.[29–33] The Eastern Stroke and Coronary Heart Disease Collaborative Study reported the relationship between hypertension, CHD, and blood pressure in China and Japan, based on 13 cohorts from China and 5 from Japan, with 124 774 men aged between 18 and 98 years, with a mean blood pressure of 124/78 mmHg (with a range from 136/83 mmHg to 119/74 mmHg).[31] In this analysis, a different ratio between heart attacks and strokes is seen among Far Eastern populations, compared to data from Caucasian populations.

Isolated reports given some data on the prevalence of hypertension in different countries. One study from Taiwan found that the prevalence of

hypertension was 14.1% for the whole population, which increased to 33% in the elderly.[29] In mainland China, the prevalence of hypertension is about 11%.[30] One study from Malaysia reported that in the Malaysian population aged above 55 years, hypertension was present in about 38.7%.[32] A study from Mauritius showed that Indian Muslims appeared to have a lower prevalence of hypertension as opposed to Chinese and Indian Hindus.[33]

Asian hypertensives, with or without evidence of renal complications appear to have a higher vascular complication rate as compared to Caucasians, when followed up over time. For example, Khattar et al. followed up a mixed cohort of patients attending a district general hospital in London for about four years.[34] They found that the South Asians had the highest all cause event rate (including non-cardiovascular death, coronary death, cerebrovascular death, peripheral vascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation) of 3.46 events/100 patient-years, compared with 2.50 (not statistically significant) and 0.90 ($p = 0.002$) events/100 patient-years for white Caucasians and Afro-Caribbeans, respectively. This was because of an apparent excess of coronary events (2.86 vs 1.32 events/100 patient-years in South Asians vs white Caucasians, respectively; $p = 0.002$).

3.2 Prevalence of renal disease

The prevalence and pattern of renal disease vary widely in different geographical regions of the world and are greatly influenced by environmental, nutritional and socioeconomic conditions. The spectrum of community-acquired acute renal failure (ARF) in India and several other tropical countries is not comparable with the developed world. Indeed, medical conditions, such as diarrhoeal diseases, intravascular haemolysis, falciparum malaria, leptospirosis, snakebite, insect stings, etc., account for about 50% of the causes of ARF (Table 13.1).

The prevalence of nephritic syndrome in the tropics is about 60 to 100 times greater than seen in the United States or the United Kingdom.[35] Primary glomerular diseases constitute about 70% of the cases, with the most common primary glomerular disease being minimal change disease. Post-streptococcal glomerulonephritis is also a very common cause, accounting for about 25–39% of cases in Hong Kong, Singapore, and Taiwan.[36,37]

Chronic renal failure is also a common cause of morbidity in this region (Table 13.2). Studies from India show that glomerulonephritis was a common cause of ESRD.[38–40] Accelerated hypertension in these patients was a common cause of acute deterioration, accounting for up to a quarter of cases, with a poor prognosis.[39] Similar findings have been reported from Singapore and Malaysia.[37,41]

Even within the United Kingdom, the Indo-Asian population has a higher incidence of ESRD of undetermined cause,[42] with the relative risk of ESRD among Asians as compared with Caucasians being 1.76 (95% CI, 1.46–2.10).[42] The prevalence of hypertension with ischaemic nephritis is also much higher in the Indo-Asian population.[19]

Table 13.1 Causes of acute renal failure in the tropics

Etiology	*Naqvi et al.*[35]	*Prakash et al.*[36]	*Chugh et al.*[47]
• Diarrhoea	17.0%	35.2%	3.0%
• Drugs	13.0%	8.0%	
• Malaria	8.5%	4.2%	
• Antepartum haemorrhage	14.0%	10.5%	9.0%
• Postpartum haemorrhage	7.0%		
• Obstructive uropathy	12.0%	13.0%	11.0%

Table 13.2 Etiology of chronic renal failure in India

- Glomerulonephritis 26.8%
- Diabetic nephropathy 23.2%
- Intersitial nephritis 16.5%
- Obstructive nephropathy 6.4%
- Benign nephrosclerosis 4.1%
- Polycystic kidney 2.0%
- Unknown 16.2%

Causes of acute deterioration in patients with renal function

- Accelerated hypertension 26.1%
- Infection 22.4%
- Volume depletion 20.1%
- Drugs 14.9%

Adapted from Mittal et al. (1997).[39]

Another perspective is to look at morbidity and mortality amongst dialysis patients. For example, Pei et al. looked at the ethnic differences in survival of patients on dialysis, over a 14 year period, involving over 4700 patients on dialysis and found that the risk of death in Caucasian patients was significantly increased as compared to South and South East Asians: RR (95% CI) of 1.63 (1.36–1.97) and 1.36 (1.07–1.73), respectively.[43] These observations were confirmed by Wong et al. who examined data from the US Renal Data System census of ESRD patients treated in the United States, which included 84 192 white or Asian patients starting dialysis over a 2 year period. Adjusting for demography, diabetes, associated comorbidity, and nutritional factors, they found that in America, the mortality rates were much lower among Asian Americans, compared to Caucasians (RR for Asian Americans = 0.75, $p = 0.0001$) with the rates in Asian Americans being similar to those seen in Japan.

4. IMPLICATIONS FOR MANAGEMENT

There are substantial differences between different ethnic groups with regard to the prevalence of hypertension and renal failure. Renovascular problems are a common cause of hypertension in South and East Asians, which should be kept in mind whilst managing hypertension in these patients.

Although blood pressure control may be achieved by adequate ulltrafiltration and dialysis, recent reports have documented poor control in the majority of patients.[45] Since many dialysis patients have nocturnal hypertension, even those thought to be well controlled with daytime blood pressure measurements may still be at risk for hypertension-induced cardiovascular and stroke mortality and morbidity. Achieving dry weight by sufficient dialysis will either normalise the blood pressure or make it easier to control in the majority of hypertensive dialysis patients.

Furthermore, in many countries in South and East Asia, renal replacement therapies, such as dialysis and kidney transplantation, are not easily accessible due to cost constraints and cultural practices.[40,46] In these patients, conservative management in terms of fluid and salt restriction, calcium and iron supplementation, and drugs, such as diuretics, and antihypertensives play a very important role.

SUMMARY

South and East Asia is a large geographical area and encompasses a diverse ethnic mix. Hypertension secondary to renal diseases continues to be a major problem in this region. Management of hypertension should take into account the possible underlying renal problems, especially acute renal failure and renovascular causes. It should also be remembered that in some countries access to renal replacement therapy, such as dialysis and renal transplantation, is comparatively poor and often conservative management may be the only option.

REFERENCES

1. Brazy PC. Epidemiology and prevention of renal disease. Curr Opin Nephrol Hypertens 1993; **2**:211–215.
2. Bright T. Tubular view of the morbid appearance in 100 cases connected with albuminous

urine. With observations. Guys Hosp Rep 1836; **1**:380.
3. Goldblatt H, Lynch J, Hanzal RF. Studies on experimental hypertension: the production of persistent elevation of systolic blood pressure by means of renal ischaemia. J Exp Med 1934; **59**:347.
4. Peart WS. The isolation of a hypertension. Biochem J 1956; **62**:520.
5. Guyton AC. Physiologic regulation of arterial pressure. Am J Cardiol 196; **8**:401–407.
6. Preston RA, Singer I, Epstein M. Renal parenchymal hypertension: current concepts of pathogenesis and management. Arch Intern Med 1996; **156**:602–611.
7. Zuchelli P, Santoro A, Zuccala A. Genesis and control of hypertension in hemodialysis patients. Semin Nephrol 1988; **8**:163–168.
8. Markewitz BA, Kohan DE. Role of intrarenal endothelin in the generation and maintenance of hypertension. Miner Electrolyte Metab 1995; **21**:342–352.
9. Converse RL, Jacobsen TN, Toto RD et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med 1992; **327**:1912–1917.
10. Beevers DG, Lip GY. Does non-malignant essential hypertension cause renal damage? A clinician's view. J Hum Hypertens 1996; **10**:695–699.
11. Martinez-Maldonado M. Role of hypertension in the progression of chronic renal disease. Nephrol Dial Transplant 2001; **16**(Suppl 1):63–66 (Review, 46 refs).
12. Brenner BM, Cooper ME, Zeeuw DD et al. The losartan renal protection study. J Renin Angiotensin Aldosterone Syst 2000; **1**:328–335.
13. Remuzzi G, Ruggenenti P, Perico N. Chronic renal diseases: renoprotective benefits of renin-angiotensin system inhibition. Ann Intern Med 2002; **136**:604–615.
14. Ruggenenti P, Aros C, Remuzzi G. Renin-angiotensin system, proteinuria, and tubulointerstitial damage. Contrib Nephrol 2001; **135**:187–199.
15. Coats AJ. Angiotensin receptor blockers – finally the evidence is coming in: IDNT and RENAAL. Int J Cardiol 2001; **79**:99–102.
16. Rostand SG, Kirk KA, Rutsky EA, Pate BA. Racial differences in the incidence of treatment for end-stage renal disease. N Engl J Med 1982; **306**:1276–1279.
17. Feldman HI, Klag MJ, Chiapella AP, Whelton PK. End-stage renal disease in US minority groups. Am J Kidney Dis 1992; **19**:397–410 See comments.
18. Powers DR, Wallin JD. End-stage renal disease in specific ethnic and racial groups: risk factors and benefits of antihypertensive therapy. Arch Intern Med 1998; **158**:793–800 (Review, 79 refs).
19. Ball S, Lloyd J, Cairns T et al. Why is there so much end-stage renal failure of undetermined cause in UK Indo-Asians? QJM 2001; **94**:187–193.
20. Feehally J, Burden AC, Mayberry JF et al. Disease variations in Asians in Leicester. QJM 1993; **86**:263–269.
21. Lip GY, Beevers M, Beevers DG. Complications and survival of 315 patients with malignant-phase hypertension. J Hypertens 1995; **13**:915–924.
22. Anand SS, Yusuf S, Vuksan V et al. Differences in risk factors atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the study of Health Assessment and risk in Ethnic groups (SHARE). Lancet 2000; **356**:279–284.
23. Gupta R. Hypertension in India – definition, prevalence and evaluation. J Indian Med Assoc 1999; **97**:74–80 (Review, 25 refs).
24. Singh RB, Wander GS, Rastogi SS, Singh NK. Epidemiology of hypertension in rural and urban population of India. Indian J Hypertens 1997; **2**:23–27.
25. Gupta SP, Siwach SB, Moda VK. Epidemiology of hypertension based on total community surveys in a rural poplation of Haryana. Indian Heart J 1977; **29**:53–63.
26. Sharma BK. Hypertension among the industrial workers and professional classes in Ludhiana, Punjab. Indian Heart J 1985; **37**:380–385.
27. Chugh KS, Jain S, Sakhuja V et al. Renovascular hypertension due to Takayasu's arteritis among Indian patients. QJM 1992; **85**:833–843.
28. Sharma BK, Singh G, Sagar S. Malignant hypertension in north west India. A hospital based study. Jpn Heart J 1994; **35**:601–609.
29. Tseng WP. Epidemiology of hypertension among Chinese in Taiwan. J Hum Hypertens 1990; **4**:144–146.
30. Ueshima H, Zhang XH, Choudhury SR. Epidemiology of hypertension in China and Japan. J Hum Hypertens 2000; **14**:765–769 (Review, 51 refs).
31. Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Lancet 1998; **352**:1801–1807.
32. Srinivas P, Wong KS, Chia YC, Poi PJ, Ebrahim S. A profile of hypertension among rural elderly

Malaysians. Southeast Asian J Trop Med Public Health 1998; **29**:821–826.
33. Nan L, Tuomilehto J, Dowse G et al. Prevalence and medical care of hypertension in four ethnic groups in the newly-industrialized nation of Mauritius. J Hypertension 1991; **9**:859–866.
34. Khattar RS, Swales JD, Senior R, Lahiri A. Racial variation in cardiovascular morbidity and mortality in essential hypertension. Heart 2000; **83**:267–271.
35. Naqvi R, Ahmed E, Akhtar F et al. Analysis of factors causing acute renal failure. J Pak Med Assoc 1996; **46**:29–30.
36. Prakash J, Tripathi K, Malhotra V, Kumar O, Srivastava PK. Acute renal failure in eastern India. Nephrol Dial Transplant 1995; **10**:2009–2012.
37. Woo KT, Chiang GS, Edmondson RP et al. Glomerulonephritis in Singapore: an overview. Ann Acad Med, Singapore 1986; **15**:20–31.
38. Gulati S, Mittal S, Sharma RK, Gupta A. Etiology and outcome of chronic renal failure in Indian children. Pediatr Nephrol 1999; **13**:594–596.
39. Mittal S, Kher V, Gulati S, Agarwal LK, Arora P. Chronic renal failure in India. Ren Fail 1997; **19**:763–770.
40. Mani MK. Chronic renal failure in India. Nephrol Dial Transplant 1993; **8**:684–689 (See comments).
41. Zainal D, Monniaty M, Nazmi N. The pattern of chronic renal failure in Kelantan, northeastern state of Malaysia. Southeast Asian J Trop Med Public Health 1995; **26**:781–784.
42. Clark TJ, Richards NT, Adu D, Michael J. Increased prevalence of dialysis- dependent renal failure in ethnic minorities in the West Midlands. Nephrol Dial Transplant 1993; **8**:146–148.
43. Pei YP, Greenwood CM, Chery AL, Wu GG. Racial differences in survival of patients on dialysis. Kidney Int 2000; **58**:1293–1299.
44. Wong JS, Port FK, Hulbert-Shearon TE et al. Survival advantage in Asian American end-stage renal disease patients. Kidney Int 1999; **55**:2515–2523 (See comments).
45. Salem MM. Hypertension in the hemodialysis population: A survey of 649 patients. Am J Kidney Dis 1995; **26**:461–468.
46. Ikels C. Kidney failure and transplantation in China. Soc Sci Med 1997; **44**:1271–1283.
47. Chugh KS. Renal disease in India. Am J Kidney Dis 1998; **31**:Svii–Six.

14

Evaluation and management of hypertensive disorders in pregnancy

Jason G Umans and Lillian J Borrego-Conde

Introduction • Diagnosis and classification of hypertension in pregnancy • BP measurement, target BP goals, and benefits of antihypertensive therapy • Management of mild to moderate hypertension remote from delivery • Control of more severe hypertension near to term • Postpartum antihypertensive therapy in breastfeeding mothers • References

1. INTRODUCTION

Hypertension is the most common medical complication of pregnancy. Since the prevalence of chronic (essential) hypertension increases with age through the childbearing years and many women in developed countries now bear children at increasing ages, as many as 5% of pregnancies in the United States occur in this high-risk group of women.[1] In addition, approximately twice as many women (i.e. ~10%) develop hypertension during pregnancy.[2] Importantly, the diagnosis of hypertension during pregnancy, assessment of maternal (and fetal) risks, targets for blood pressure (BP) control, and choice of pharmacologic agents all differ considerably compared to hypertension in nonpregnant women. This chapter will focus first on diagnosis and classification of hypertension in pregnancy, on the morbidities associated with hypertension in pregnancy, and on the goals of antihypertensive therapy in these patients. Throughout, we pay special attention to preeclampsia, since it is pathophysiologically and hemodynamically unique, occurs uniquely in pregnancy, and accounts for much of the morbidity in these patients. While we touch on the physiology of maternal hemodynamic adaptation to normal and hypertensive pregnancy and current research into the mechanisms for and prevention of preeclampsia, our major focus is on diagnosis and therapy. We then review evaluation and medical management of chronic (mild to moderate) hypertension remote from delivery as well as antihypertensive and adjunctive management of more severe hypertension, often closer to term or in the setting of preeclampsia. Finally, we touch on antihypertensive selection in breastfeeding mothers.

2. DIAGNOSIS AND CLASSIFICATION OF HYPERTENSION IN PREGNANCY

Outcomes differ remarkably, depending on the specific and pathophysiologically distinct cause of hypertension during pregnancy. The literature has been ill-served by the use of various poorly defined terms (e.g. gestosis, pregnancy-induced hypertension – PIH, or toxemia), which have made it difficult to interpret inclusion criteria and outcomes of many treatment trials. The

recently updated report of the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Pregnancy,[2] endorsed a diagnostic scheme which is largely in agreement with those of several national societies and of the International Society for the Study of Hypertension in Pregnancy.[3] It recognizes four hypertensive entities in pregnancy: (1) chronic hypertension (essential and secondary); (2) preeclampsia-eclampsia; (3) preeclampsia superimposed on chronic hypertension; and (4) gestational hypertension.

2.1 Chronic essential hypertension

Many young women only seek medical care when pregnant and have had little or no medical evaluation, including blood pressure (BP) measurement, prior to conception. This can lead to surprising difficulty in the diagnosis of chronic hypertension. Blood pressure falls by approximately 10 mmHg early in normal pregnancy; even larger decrements (≥20 mmHg) are observed in women with pre-existing hypertension. This fall in BP occurs despite 30–50% increments in cardiac output (CO), pointing to even larger decreases in systemic vascular resistance (SVR). Therefore, normal-appearing BP values early in pregnancy may have been preceded by (undetected) frank hypertension prior to conception. Thus, while a history of hypertension or the documentation of elevated BP early in pregnancy establishes the diagnosis, these can often be missed, leading to the misdiagnosis of preeclampsia or gestational hypertension when BP rises (normally) nearer to term.

Decreased BP is but one of several important cardiovascular adaptations to normal pregnancy.[4] In addition to the early systemic vasodilation, there is specific renal vasodilation and glomerular hyperfiltration,[5] leading to approximately 50% increments in glomerular filtration rate (GFR), due apparently to increased effective renal plasma flow, without significant changes in glomerular capillary pressure. Not only is there systemic vasodilation in pregnancy, but there is a specific refractoriness to the vasopressor effect of several vasoconstrictors, most notably angiotensin II. Along with these vascular changes, pregnancy is characterized by the cumulative retention of 6–9 L of isotonic fluid, of which 4–7 L is in the extracellular space with an increase of approximately 50% in plasma water. These volume changes appear to be sensed as normal by the gravida, despite the expected occurrence of dependent edema (even in the absence of any disease) late in pregnancy.

Superimposed preeclampsia complicates at least 15–20% of pregnancies in women with baseline systolic (≥140 mmHg) or diastolic (≥90 mmHg) hypertension.[6–8] The incidence of superimposed preeclampsia increases with the severity of underlying hypertension and this disorder accounts for most, but not all, of the morbidity associated with chronic hypertension. Chronic hypertension is also associated with a doubling in the risk of placental abruption; this increased risk is then tripled in the setting of superimposed preeclampsia.[7] It is also associated with impaired fetal growth and with a threefold increase in fetal or perinatal mortality.[1] Accelerated hypertension can lead to hospitalization, target organ damage, or cerebrovascular catastrophe, the latter due to effects of moderately elevated pressures (≥170 mmHg systolic or ≥110 mmHg diastolic) on gestationally remodeled intracranial vessels. Finally, poorly controlled hypertension is the major cause of early delivery, with its attendant risks to the neonate, usually due to reasonable concerns regarding maternal safety.

2.2 Secondary hypertension

Secondary forms of hypertension other than preeclampsia are rare during pregnancy. However, they do occur and require a high degree of clinical suspicion in order to make a potentially life-saving diagnosis.[9] Hypertension in the setting of Cushing's syndrome, scleroderma, or periarteritis nodosa have such uniformly poor outcomes that women with these disorders should not contemplate pregnancy.

While data are limited, the incidence of superimposed preeclampsia and poor pregnancy outcome appears so high in women with renovascular hypertension, usually due to fibromuscular dysplasia, that diagnosis should

lead to corrective angioplasty, even during pregnancy, since long-term treatment with ACE inhibitors is contraindicated. Diagnosis is more difficult than in nonpregnant women since plasma renin is normally elevated in pregnancy, doppler ultrasound examinations of the renal arteries are technically difficult or unreliable in pregnancy, and it is often difficult to convince radiology colleagues to perform the gadolinium-enhanced magnetic resonance angiography or renal arteriography necessary for anatomic diagnosis. High clinical suspicion should lead first to measurement of plasma renin and to doppler ultrasound examination, though negative results should not deter further investigation. Magnetic resonance angiography is a reasonable next step as it may localize a stenosis with enough precision to limit the amounts of intravenous contrast and X-ray exposure required during a subsequent angiogram combined with angioplasty.[10]

The diagnosis of primary hyperaldosteronism is likewise difficult during pregnancy. Pregnancy is often accompanied by mild hypokalemia, irrespective of BP, often worse in women with clinically unremarkable degrees of emesis. Along with renin, serum aldosterone is also quite elevated in normal pregnancy and there are only rare case reports providing paired measurements of renin and aldosterone in gravidas with proven aldosteronoma.[11] The clinical course and presentation are made even more variable by the aldosterone-antagonistic effect of progesterone, which may antagonize both hypertension and hypokalemia in some women.[12] By contrast, a rare mineralocorticoid receptor mutation may lead to severe first or second trimester hypertension when progesterone acts, paradoxically, as an aldosterone-mimetic, also resulting in salt retention, hypokalemia, and suppressed aldosterone synthesis.[13] Localization of aldosteronoma during pregnancy is usually based on magnetic resonance imaging rather than computed tomography and adrenal vein sampling is avoided due to unavoidably large fetal X-ray exposure. Spironolactone is not used during pregnancy due to animal studies showing fetal virilization, and there are physiologic concerns, without any reassuring clinical experience, which weigh against use of amiloride. Blood pressure has most commonly been controlled with calcium entry blockers and adenomas have been successfully resected during the second trimester when antihypertensive therapy has failed.

Pheochromocytoma entails high mortality near to term or during labor. Therefore, any suggestive signs or symptoms should lead to aggressive diagnostic efforts. Screening for catecholamine excess is useful and management then includes alpha-adrenergic blockade, followed by beta-blockade and resection of the tumor (if it can be localized by magnetic resonance imaging) during the first or second trimester, or resection coupled with cesarian delivery when the fetus is viable and the tumor discovered during the third trimester.[9]

2.3 Preeclampsia-eclampsia

Preeclampsia, a form of secondary hypertension in its own right, is a generalized vasculopathy unique to human pregnancy which occurs most commonly in the latter half of first pregnancies, although it has been observed as early as 16 weeks gestation and in subsequent pregnancies as well. It is characterized by *de novo* hypertension and proteinuria, often associated with hyperuricemia and sometimes with thrombocytopenia or abnormalities of liver function or coagulation tests. Since it can have a variable course and explosive clinical evolution,[14] with real risks of maternal morbidity and mortality, one should err towards diagnosing preeclampsia, even in the absence of proteinuria (which can occur later in the evolution of the disorder), when hypertension is accompanied by abdominal pain, neurologic symptoms including headache or blurred vision, or any evidence of thrombocytopenia or liver function or coagulation abnormalities.[2] Preeclampsia can evolve rapidly to a convulsive phase, termed 'eclampsia'. An especially threatening variant of preeclampsia is the HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome, which may seem mild in its initial presentation, then evolve over hours

to microangiopathic hemolysis, severe thrombocytopenia, and hepatic necrosis.

2.4 Pathophysiology of preeclampsia and approaches to its prevention

Mechanisms leading to preeclampsia and to its attendant hypertension remain uncertain despite increasingly fruitful basic and translational research. Invasive hemodynamic measurements in hypertensive preeclamptic women reveal decreased or normal pulmonary capillary wedge pressures, decreased cardiac index, and markedly elevated systemic vascular resistance.[15] By contrast, serial noninvasive (echocardiographic) evidence suggests that, earlier in pregnancy, normal increments in cardiac output may have been exaggerated even further in women destined to preeclampsia, prior to the onset of systemic vasoconstriction.[16] One small trial suggested that early use of beta-blockers to interrupt these changes in cardiac output might prevent preeclampsia, a conclusion currently unsupported by meta-analysis of other beta-blocker trials.[17,18] Likewise, neither salt restriction nor prophylactic diuretics prevent preeclampsia, despite earlier claims, which were due to misdiagnosis of gravidas with non-proteinuric hypertension.[19] Despite observations of hypocalciuria in preeclamptic women, several large studies of calcium supplementation failed to demonstrate any significant prevention of proteinuric hypertension.[20,21] There remains the possibility of some benefit to women with extremely low dietary calcium, the subject of an additional trial in developing countries.

Among many studies of circulating vasoconstrictor factors in women with preeclampsia, several suggested an imbalance in arachidonic acid metabolism, favoring vasoconstrictor thromboxanes over prostacyclin, and leading to many studies of low-dose (60–100 mg/d) aspirin. Unfortunately, extraordinarily promising results of many early small studies have not been confirmed in subsequent well-designed large trials including >12 000 women and demonstrating only trivial effects on maternal or fetal outcome or on the occurrence of preeclampsia.[22,23] Additional studies of women at high risk for recurrent or superimposed preeclampsia (see below) also failed to demonstrate any prevention of proteinuric hypertension. Meta-analyses of trials including >30 000 women have suggested only minimal benefit and have failed to identify any aspirin-sensitive subgroups of women at risk.[24] Additional studies in which aspirin dose is increased, sustained release preparations utilized, or the dose schedule altered to take advantage of apparent circadian effects are now planned or underway.[25]

Preeclampsia is characterized by widespread endothelial dysfunction, including defective endothelium-dependent relaxation of vessels which contribute to regulation of systemic vascular resistance.[26] The endothelial dysfunction follows typical defects in placentation and may be mediated by increased oxidant stress or defective antioxidant mechanisms; this has led to a small study of vitamins C and E in women at high risk.[27] These antioxidant vitamins appeared to decrease proteinuria (and thus the diagnosis of preeclampsia) but not hypertension. Of concern, the incidence of low birthweight seemed to increase in the treatment group. Based on these early results, two large and hopefully definitive trials will soon be underway.

While recent studies appear to rule out inherited or acquired thrombophilias as a cause of recurrent or severe preeclampsia,[28] many obstetricians screen for and treat these disorders; usually with protocols based on low molecular weight heparin or aspirin, while patients with hyperhomocysteinemia receive high-dose folic acid. These strategies may prevent recurrent mid-trimester pregnancy loss, but effects on preeclampsia have not been demonstrated.

Finally, several studies have demonstrated changes in angiotensin receptor expression and activity,[29] or the occurrence of autoantibodies which activate angiotensin II type 1 (AT_1) receptors,[30,31] in women with preeclampsia. Due to specific fetotoxicity of AT_1 receptor blocking drugs (see below), these exciting mechanistic studies have not yet led to prevention or treatment trials.

2.5 Superimposed preeclampsia

While 'pure' preeclampsia occurs in approximately 6% of (usually primigravid) pregnancies, it can be superimposed on up to 20–40% of underlying cases of chronic hypertension, or other predisposing medical diseases including (even minor) renal disease of any cause, such as early diabetic nephropathy or microscopic hematuria,[32,33] or collagen vascular disease. Other risk factors include a family history of preeclampsia, multifetal gestation, and perhaps obesity with insulin resistance. It is important to note that, just as underlying hypertension is often obscured by early gestational vasodilation, the diagnosis of underlying renal insufficiency may be missed due to early renal vasodilation and hyperfiltration in pregnancy. Further, the presence of hypertension, proteinuria, or other suggestive laboratory abnormalities at baseline may make it extremely difficult to diagnose superimposed preeclampsia with any certainty. Indeed, proteinuria can be expected to worsen during pregnancy, often to nephrotic levels, in any woman with underlying glomerular disease. Because of these diagnostic uncertainties, we advocate a strategy of close monitoring, repeatedly re-establishing baseline data in order to detect interval changes in BP, proteinuria, symptoms, or blood test results which might suggest superimposed preeclampsia.

2.6 Gestational (transient) hypertension

These women develop mild to moderate hypertension after mid-pregnancy, usually close to term, without proteinuria or other manifestations of preeclampsia. The hypertension resolves with delivery, often recurs in subsequent pregnancies, and predicts essential hypertension later in life.[2]

3. BP MEASUREMENT, TARGET BP GOALS, AND BENEFITS OF ANTIHYPERTENSIVE THERAPY

Throughout pregnancy, BP should be measured at rest in the sitting position, using Korotkoff 5 (K5) as diastolic pressure. With rare exceptions,[34] most automated oscillometric devices, even those coupled with the noninvasive cardiotocographs used on labor wards, are notoriously inaccurate during pregnancy, and even more so in the setting of preeclampsia. The use of home BP monitors is based more on their ability to detect significant changes in systolic pressure than on accuracy of the data. An evolving literature suggests some promise in the use of ambulatory BP monitoring for risk assessment in pregnancy, though confirmatory and outcomes data remain lacking.[35]

While based on the results of several small and variable trials, treatment of chronic hypertension does not appear to prevent superimposed preeclampsia, placental abruption, or perinatal death.[1,18,36–38] As would be expected, antihypertensives decrease the occurrence of more severe hypertension later in pregnancy.[18,36–38] This more limited outcome may still be of considerable importance, since adverse perinatal outcomes seem most closely related to severity of maternal hypertension.[39] Also, while few studies specifically focus on either hospitalization or early delivery as end-points, severe hypertension is the major indication for each of these interventions and we might expect a major benefit of treatment. Even without clear outcomes data, it is well established that BPs as low as 170/110 mmHg can lead to cerebrovascular hemorrhage during pregnancy, making treatment of such pressures a medical emergency. The relative risks of 'hard' clinical end-points are low in mild hypertension and lower still over the short duration of a pregnancy; none of the available trials are either adequately powered or comprehensive enough to guide therapy, thus our continued dependence on consensus statements,[2,40,41] meta-analyses,[1,18,36,38,42,43] and clinical experience.[37]

There are no prospective studies that guide us in choosing BP targets for antihypertensive therapy. The Australasian Society for the Study of Hypertension in Pregnancy suggests maintaining BPs $< 140/90$ mmHg.[40] The Canadian Hypertension Society suggests similarly tight control only for some groups of women.[41] By contrast, the NHBPEP Working Group on Hypertension in Pregnancy suggests

(re)instituting drug therapy at pressures of 150–160/100–110, targeting lower pressures in selected patients with end-organ damage or underlying renal disease.[2] None of the BP treatment targets are as low as those recently advocated in nonpregnant patients with diabetic nephropathy or proteinuric renal disease.[44] There is controversy as to whether placental blood flow is autoregulated or if uteroplacental perfusion falls with progressive control of maternal hypertension. Of note, a recent 'meta-regression' of 14 trials suggested that fetal growth restriction worsened in proportion with tighter control of maternal hypertension, irrespective of the specific agents used.[45] Our lack of enthusiasm for tight control, in accord with that of the NHBPEP Working Group, is further tempered by the still limited information regarding fetal and remote childhood risks of exposure to most antihypertensive drugs *in utero*. Even the acknowledged long-term safety of methyldopa is based upon a single study with >7 year follow-up of only a small number of children.[46]

While no antihypertensive drugs have been proven safe in early pregnancy, this is seldom a problem. Since normal gestational vasodilation lowers mean arterial pressure by approximately 20 mmHg in most women with essential hypertension, we are usually able to discontinue some or all antihypertensives in gravidas with underlying stage 1 or 2 hypertension. Therapy can then be reinstituted, if necessary, when pressure rises later, usually during the second trimester. Women who fail to exhibit the expected early gestational vasodilation, renal hyperfiltration, and relative hypotension or who require multidrug antihypertensive therapy during the first trimester seem especially likely to have a stormy pregnancy with guarded outcome.

4. MANAGEMENT OF MILD TO MODERATE HYPERTENSION REMOTE FROM DELIVERY

While there are some small differences, each of the three recent consensus statements recognize methyldopa as a preferred agent with the greatest experience in pregnancy.[2,40,41] Methyldopa appears to be well tolerated,[1,2,36–38,40] does not impair either uteroplacental or fetal hemodynamics,[47] and is the best-studied drug in terms of subsequent childhood development.[46] The rationale for its efficacy is further supported by studies that used microneurography to demonstrate increased autonomic outflow in preeclamptic hypertension.[48] As expected, the efficacy of clonidine seems similar, however there have been reports that it may be embryopathic in early pregnancy or lead to postnatal sleep disturbance.[49] We must recall, though, that rare patients suffer methyldopa-induced hepatitis and many women will be unable to tolerate its common adverse effects of drowsiness or dry mouth. Of note, a recent meta-analysis along with a large retrospective single-center report suggested that other antihypertensive drugs might be superior to methyldopa in limiting perinatal morbidity and mortality.[38,50] Adequately powered prospective comparative trials are entirely lacking and should be required before we would be comfortable abandoning the long clinical experience and consensus support for use of methyldopa.

Beta-blockers are near to methyldopa in their wide use in pregnancy and are advocated by many as first-line therapy. They have been assessed in several randomized trials and in a Cochrane meta-analysis.[18] Early preclinical and clinical observations raised concerns of impaired uteroplacental perfusion, fetal growth restriction, and harmful cardiovascular effects on the fetus. However, most prospective studies, focusing on beta-blocker use in the third trimester, have shown effective BP control, prevention of more severe hypertension, and an absence of significant adverse effects on the fetus.[1,2,36–38,40,41] By contrast, early use of atenolol in one trial,[51] led to striking fetal growth restriction, a conclusion supported by several reviews and meta-analyses.[18,38,52] More recently, a large nonrandomized single-center series noted improved perinatal outcome with beta-blockers (primarily atenolol) compared with other agents (primarily nifedipine or methyldopa).[50] Finally, there was a suggestion in one recent meta-analysis of several small trials that beta-blockers might decrease (and calcium channel blockers increase) the

incidence of proteinuria or superimposed preeclampsia; this preliminary observation should provoke further study rather than a change in practice.[38] While atenolol may be the beta-blocker most commonly used in pregnancy, the NHBPEP Working Group advocates labetalol (a combined alpha- and beta-blocker) as an alternative to methlydopa, and the Australasian group advocates use of beta-blockers with intrinsic sympathomimetic activity, such as oxprenolol (not available in the US) or pindolol.[40,53]

Calcium channel blockers are widely used, effective in pregnancy, and appear not to be teratogenic.[2] Most studies have focused on nifedipine, although there are reports of other dihydropyridine and non-dihydropyridine agents as well, including a reassuring but small study with 18 months of infant follow-up.[54] Even though these are tocolytic agents, there are no data to suggest that use of calcium channel blockers for BP control interferes with labor or delivery. While data are limited, nifedipine is widely viewed as an acceptable alternative to methyldopa or beta-blockers for chronic use during pregnancy.

Hydralazine is the most commonly used second-line agent (following combinations of those discussed above); it is used in combination with either a beta-blocker or methyldopa to limit reflex tachycardia. There seems little basis for use of alpha-adrenergic blockers other than in the setting of suspected pheochromocytoma. Diuretics may be continued, if used before pregnancy, despite their effects on normal gestational volume expansion, and may be combined with other agents, especially when clinical volume overload is a problem. They appear safe in pregnancy, but are best avoided in preeclampsia, whose hemodynamics are characterized by decreased cardiac output and primary systemic vasoconstriction.[19]

Apparent activation of the renin-angiotensin system during pregnancy and evidence suggesting a role for angiotensin receptor activation in preeclampsia (see above) might seem to support use of angiotensin-converting enzyme inhibitors (ACEIs) or AT_1 receptor blockers in hypertensive gravidas. Indeed, these drugs are now widely used for 'renal protection' in young women of childbearing age with underlying diabetic nephropathy or proteinuric renal disease. Unfortunately, they are contraindicated during pregnancy, due to a specific fetopathy (including renal dysgenesis and calvarial hypoplasia) and the risk of (fatal) neonatal acute renal failure.[55] These drugs are often discontinued when pregnancy is planned but, since they are not teratogenic and all adverse outcomes appear due to fetal exposure in the second or third trimester,[56] reliable patients who are followed closely can continue these drugs through conception, discontinuing them in the first trimester if pregnancy is detected early. Table 14.1 summarizes those agents most commonly used for chronic BP control in pregnancy.

5. CONTROL OF MORE SEVERE HYPERTENSION NEAR TO TERM

As noted in Table 14.2, parenteral hydralazine, intravenous labetalol, and oral (immediate release) nifedipine are the agents most commonly used for urgent control of severe hypertension late in pregnancy with a meta-analysis suggesting little difference in outcome between them.[2,37,42] Hydralazine is used either in small (5–10 mg) repeated doses or as a continuous infusion, because larger doses or frequent dosing may lead to precipitous maternal hypotension and fetal distress. It is preferred by many obstetricians and by the NHBPEP Working group, based more on clinical experience than on compelling data. However, several small studies and a recent meta-analysis have highlighted concerns regarding excessive hypotension, oliguria or renal dysfunction, maternal side effects, placental abruption, Cesarian delivery, along with an excess of fetal distress in women receiving hydralazine as compared with other agents.[43] Parenteral labetalol, by continuous intravenous infusion or in repeated boluses, has replaced hydralazine at many centers and appears to have similar safety and efficacy, though comparative studies are few and it may result in less effective BP control.[43] Despite its lack of approval by the US Food and Drug Administration for the treatment of hypertension, the NHBPEP Working

Table 14.1 Oral antihypertensives in pregnancy

Drug (FDA risk)[a,b]	*Dose*	*Concerns/Comments*
Most commonly used first-line agents Methyldopa [C]	0.5–3.0 g/d in 2–3 divided doses	Preferred agent of the NHBEP working group; maternal side effects sometimes limit use.
Labetalol [C] or other β-receptor antagonists	200–2400 mg/d in 2–3 divided doses	Labetalol is preferred by NHBPEP working group as alternative to methlydopa. Atenolol most commonly used in Canada and β-blockers with intrinsic sympathomimetic activity are preferred by some in Australia. May cause fetal growth restriction, especially when started early.
Nifedipine [C]	30–120 mg/d of a slow-release preparation	Less experience with other calcium entry blockers.
Adjunctive agents Hydralazine [C]	50–300 mg/d in 2–4 divided doses	Few controlled trials, long experience with few adverse events documented; used only in combination with sympatholytic agent (e.g. methyldopa or β-blockers) to prevent reflex tachycardia.
Thiazide diuretics [C]	Depends on specific agent	Most studies in normotensive gravidas. May be useful in combination with methyldopa and vasodilator to limit compensatory fluid retention or control salt-sensitive hypertension.
Contraindicated ACEIs and AT_1 receptor antagonists [D[d]]		Leads to fetal loss in animals; human use associated with fetopathy, oligohydramnios, growth retardation, and neonatal anuric renal failure, which may be fatal.

[a] No antihypertensive has been proven safe for use during the first trimester (i.e. US Food and Drug Administrative Class A).
[b] FDA classifies risk for most agents as C: 'Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should only be given if the potential benefit justifies the potential risk to the fetus.' This nearly useless classification unfortunately still applies to most drugs used during pregnancy.

Group, along with many workers, advocated oral (or sublingual) nifedipine as an acceptable alternative to hydralazine or labetalol for urgent BP control during pregnancy.[2,57] Its efficacy and safety appear similar to the other agents, though data conflict regarding its effects on uteroplacental perfusion.[58,59] While the cerebrovascular pathophysiology of eclampsia remains controversial, several recent studies have hypothesized a role for increased cerebral perfusion pressure in most, but not all, cases;[60] in this regard, labetalol and magnesium, but not calcium channel blockers appear to decrease elevated cerebral perfusion pressure in hypertensive gravidas.[61] Nevertheless, despite any mechanistic or theoretical concerns, ongoing meta-analyses fail to favor one of these agents over the others and it seems reasonable, in the absence of new data, to choose amongst them based on the experience of the treating physician.[2,43]

Diazoxide is no longer favored, due to inferior outcomes in several small trials, difficult

Table 14.2 Antihypertensives for urgent blood pressure control near to delivery

Drug (FDA risk)[a]	*Dose and route*	*Concerns/Comments*[b]
Hydralazine [C]	5 mg, iv or im, then 5–10 mg every 20–40 min; or constant infusion of 0.5–10 mg/h	Preferred by NHBEP working group. Higher doses or more frequent administration often precipitate maternal or fetal distress, which appear more common than with other agents.
Labetalol [C]	20 mg iv, then 20–80 mg every 20–30 min, up to maximum of 300 mg; or constant infusion of 1–2 mg/min	Probably less risk of tachycardia and arrhythmia than with other vasodilators, likely less BP control than hydralazine.
Nifedipine [C]	5–10 mg po, repeat in 30 min if needed, then 10–20 mg every 2–6 h	Theoretical concerns regarding synergistic interaction with magnesium sulfate, but little supporting data. Parenteral calcium channel blockers seem reasonable alternatives, but less data.

[a] US Food and Drug Administration Class C, as noted in footnote to Table 14.1.
[b] Adverse effects for all agents, except as noted, may include headache flushing, nausea, and tachycardia (primarily due to precipitous hypotension and reflex sympathetic activation).

dose titration, and concerns regarding fetal toxicity. Ketanserin is used outside the United States, though BP control seems inferior to hydralazine.[42] Some favor intravenous nicardipine or other calcium channel blockers, which seems reasonable in the light of the larger experience with nifedipine, athough published reports remain limited.[62] Sodium nitroprusside remains a relatively contraindicated agent of last resort, usually reserved for urgent BP control in the minutes leading up to delivery.[63] Finally, while there have been reports of ACE inhibitor use as 'salvage therapy' during pregnancy,[64] there seems to be no justification for use of these agents or of angiotensin receptor blockers during the second or third trimester.

5.1 Clinical and adjunctive management of preeclampsia

Suspicion of preeclampsia should lead to hospitalization and inpatient evaluation. Near to term, if fetal maturity can be assured, delivery is the definitive treatment of choice for preeclampsia. Earlier in pregnancy, it may seem desirable to temporize, attempting to control BP, administer glucocorticoids to hasten fetal lung maturation, and monitor laboratory and clinical status closely so as to prolong pregnancy. The obstetric literature on such temporizing strategies often appears confusing and contradictory, but seems to agree that such approaches may result in days to weeks of additional fetal maturation; however, they are best reserved to tertiary centers and, regardless of gestational age, any of the ominous signs or symptoms noted in Box 14.1 should lead to delivery. As noted earlier, accelerated hypertension should be treated at systolic levels of >160 or diastolic of >105, to avoid the intracerebral bleeds which can occur at pressures of $\geq 170/110$. We advocate treatment at these somewhat lower pressures due to increased BP lability and uncertainty in BP measurement in women with preeclampsia. Central nervous system signs or symptoms (including even headache or blurred vision) should provoke treatment at even lower pressures.

Box 14.1 Ominous signs and symptoms in preeclampsia suggesting prompt delivery

- Inability to control BP (systolic ≤160 mmHg or diastolic ≤105 mmHg)
- Rapid increase in (nephrotic) proteinuria with decreasing serum albumin
- Any evidence of acute renal failure or progressive oliguria
- Falling platelets or thrombocytopenia $<10^5/mm^3$
- Any evidence of microangiopathic hemolysis or coagulopathy
- Upper abdominal (epigastric or right upper quadrant) pain
- Headache, visual disturbance, or any CNS signs
- Retinal hemorrhage or papilledema
- Acute congestive heart failure or pulmonary edema

Parenteral magnesium sulfate has long been favored by North American clinicians for treatment of eclamptic seizures, a practice validated in each of several well-designed comparative trials against the anticonvulsants phenytoin or diazepam.[65,66] Additionally, a recent randomized, placebo-controlled, double-blind study demonstrated the efficacy of 24 hours of magnesium therapy for primary prevention of eclamptic seizures in women with preeclampsia.[67] This study of over 10 000 gravidas was carried out largely in the developing world without monitoring of serum magnesium levels, and without significant short-term adverse effects to mother or baby. Interestingly, there was a strong trend towards decreased maternal death, apparently unrelated to the effect on convulsions. It remains unclear, however, which women with preeclampsia should be offered magnesium and for how long. In most centers, treatment usually entails a loading dose of 4–6 g magnesium sulfate (infused over 10 min, never as a bolus), followed by continuous infusion of 1–2 g/h to achieve plasma levels of 5–9 mg/dL. Magnesium is then usually continued until the patient stabilizes or for 24 hours following delivery. Lower doses should be used, with the greatest caution, in women with any degree of renal insufficiency, as magnesium is excreted renally. Finally, a vial of calcium gluconate should always be kept at the patient's bedside to treat magnesium toxicity, should it occur.

Table 14.3 summarizes our approach to evaluation, management, and treatment of pregnant women with underlying hypertension. It expands upon, but is largely in accord with recommendations made by the NHBPEP Working Group.[2] Our key objectives, to be carried out in close coordination with experienced high-risk obstetric colleagues, are to achieve BP control adequate to assure maternal safety, to carefully and serially monitor maternal BP, well-being, and laboratory data in order to facilitate early recognition of superimposed preeclampsia, and to proceed to expeditious delivery (± magnesium prophylaxis) in the face of preeclampsia or accelerated hypertension when it presents a threat to maternal safety.

6. POSTPARTUM ANTIHYPERTENSIVE THERAPY IN BREASTFEEDING MOTHERS

While the pharmacokinetic principles that govern drug distribution to milk and delivery to the infant are well understood, there are no well-designed studies assessing neonatal effects of maternally administered antihypertensive drugs delivered via breast milk.[68,69] Milk is essentially a suspension of fat globules in a protein-containing relatively acidic aqueous solution. Factors that favor drug passage into milk are a small maternal volume of distribution, low plasma protein binding, high lipid solubility and lack of charge at physiologic pH. Even when drugs are ingested by nursing infants, effective infant exposure depends on the volume of milk ingested, intervals between drug administration and nursing, oral bioavailability (in the infant), and the capacity of the infant to clear the drug.

Neonatal exposure to methyldopa via nursing is likely low and it is generally considered safe.

Table 14.3 Considerations in evaluation and management (in addition to usual high-risk obstetric care) of gravidas with underlying hypertension

Before pregnancy

1. Counsel regarding risks and need for close monitoring.
2. Assess hypertensive target organ damage, especially renal dysfunction and proteinuria.
3. Rule out secondary hypertension if any suspicion.
4. Consider screening for thrombophilia, especially if previous early superimposed preeclampsia or mid-trimester pregnancy loss.

Early in first trimester

1. Stop ACEIs and ARBs.
2. Monitor BP closely and attempt to discontinue all antihypertensives (if BP can be maintained <150/100). Note that failure to exhibit improved BP and increased GFR early in pregnancy may predict especially high risk of difficulties later in pregnancy
3. Baseline measurement of creatinine clearance, 24 h protein excretion, electrolytes, BUN and creatinine, uric acid, ALT, AST, LDH, albumin, CBC with platelets. These baseline values and repeated 'baselines' (usually only including blood tests and spot urine protein/creatinine ratios) obtained at 2–4 week intervals later in pregnancy may be key to diagnosis of superimposed preeclampsia.
4. If not done previously, encourage and instruct in home BP monitoring, otherwise check BP in office (by auscultation) at least every 2 weeks.

Later in pregnancy

1. If hypertension persists or recurs (≥150 mmHg systolic or ≥100 mmHg diastolic) restart and titrate therapy, favoring methyldopa or labetalol, then adding a second agent as needed. Second agents could be nifedipine or (if heart rate permits) the sympatholytic agent not used initially. Aim is BP <160/105 mmHg at all times, considering lower levels (140/90) if there is renal insufficiency or target organ damage.
2. Admit to hospital for evaluation and add a third agent (hydralazine ± a diuretic) if BP is inadequately controlled. Such severe hypertension occurring remote from term suggests a pregnancy that may not safely succeed in a live birth.
3. During the third trimester, increase frequency of visit to every 1–2 weeks.

Evaluation and management of (suspected) preeclampsia

1. Admit to hospital for evaluation of any clinical or laboratory evidence suggestive of accelerated hypertension, new target organ damage, or superimposed preeclampsia.
2. Diagnosis of superimposed preeclampsia near to term should lead to expeditious delivery.
3. Accelerated hypertension, or hypertension not controlled on a reasonable 2 or 3 drug oral regimen, should lead to admission, BP control using agents chosen from Table 14.2, and expeditious delivery.
4. One can delay delivery in cases of 'mild' preeclampsia remote from term only if patient can be monitored closely in a tertiary care setting, BP well controlled, and delivery effected for any fetal or maternal deterioration or for threatening findings as listed in Box 14.1.
5. Consider seizure prophylaxis with magnesium sulfate in all but mild preeclampsia.

AST; aspartate transaminase; LDH, lactate dehydrogenase.

Atenolol and metoprolol are concentrated in breast milk, whereas exposure to either labetolol or propranolol appears low.[70] While milk concentrations of diuretics are limited, these agents can decrease milk production significantly.[71] Calcium channel blockers are probably transferred into breast milk, apparently without adverse effects.[72] Due to concerns regarding

effects of ACE inhibitors and AT_1 receptor antagonists on neonatal renal function, these drugs are usually avoided, especially after very premature births; however, milk concentrations of captopril are quite low, suggesting use of this agent when an ACE inhibitor is required.[73]

REFERENCES

1. Ferrer RL, Sibai BM, Mulrow CD et al. Management of mild chronic hypertension during pregnancy: A review. Obstet Gynecol 2000; **96**:849–860. (Full report available at: http://www.ahcpr.gov/clinic/evrptfiles.htm).
2. Report of the National High Blood Pressure Education Project Working Group on High Blood Pressure in Pregnancy, NIH Publication No. 00-3029, July 2000, 38pp (Available at: http://www.nhlbi.nih.gov/health/prof/heart/hbp_preg.htm).
3. Brown MA, Lindheimer MD, DeSwiet M et al. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy. Hypertens Pregnancy 2001; **20**:ix–xiv.
4. McLaughlin MK, Roberts JM. Hemodynamic changes. In: Lindheimer MD, Roberts JM, Cunningham FG (eds), Chesley's Hypertensive Disorders in Pregnancy, 2nd edn. Stamford, CT: Appleton & Lange 1999 Ch.8, 69–102.
5. Conrad KP, Lindheimer MD. Renal and cardiovascular alterations. In: Lindheimer MD, Roberts JM, Cunningham FG (eds), Chesley's Hypertensive Disorders in Pregnancy, 2nd edn. Stamford, CT: Appleton & Lange 1999, Ch.8, 263–326.
6. Sibai BM, Abdella TN, Anderson GD. Pregnancy outcome in 211 patients with mild chronic hypertension. Obstet Gynecol 1983; **61**:571–576.
7. Sibai BM, Lindheimer M, Hauth J et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. N Engl J Med 1998; **339**:667–671.
8. Rey E, Couturier A. The prognosis of pregnancy in women with chronic hypertension. Am J Obstet Gynecol 1994; **171**:410–416.
9. August P, Lindheimer MD. Chronic hypertension. In: Lindheimer MD, Roberts JM, Cunningham FG (eds), Chesley's Hypertensive Disorders in Pregnancy, 2nd edn. Stamford, CT: Appleton & Lange 1999, 605–633.
10. Le TT, Haskal ZJ, Holland GA et al. Endovascular stent placement and magnetic resonance angiography for management of hypertension and renal artery occlusion during pregnancy. Obstet Gynecol 1995; **85**:822–825.
11. August PA, Seeley JE. The renin angiotensin system in normal and hypertensive pregnancy and in ovarian function. In: Laragh JH, Brenner BM (eds), Hypertension: Pathophysiology, Diagnosis, and Management, 2nd edn. New York: Raven Press 1995, 2225–2244.
12. Lindheimer MD, Richardson DA, Ehrlich EM et al. Potassium homeostasis in pregnancy. J Reprod Med 1987; **32**:517–532.
13. Geller DS, Farhi A, Pinkerton N et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science 2000; **289**:119–123.
14. Hauth JC, Cunningham FG. Preeclampsia-eclampsia. In: Lindheimer MD, Roberts JM, Cunningham FG (eds), Chesley's Hypertensive Disorders in Pregnancy, 2nd edn. Stamford, CT: Appleton & Lange 1999, Ch.5, 169–199.
15. Visser W, Wallenburg HCS. Central hemodynamic observations in untreated preeclamptic patients. Hypertension 1991; **17**:1072–1077.
16. Bosio PM, McKenna PJ, Conroy R et al. Maternal central hemodynamics in hypertensive disorders of pregnancy. Obstet Gynecol 1999; **94**:978–984.
17. Easterling TR, Brateng D, Schmucker B et al. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before onset of hypertension. Obstet Gynecol 1999; **93**:725–733.
18. Magee LA, Duley L. Oral beta blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2000; **4**:CD002863.
19. Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. BMJ 1985; **290**:17–23.
20. Belizan JM, Villar J, Gonzalez L et al. Calcium supplementation to prevent hypertensive disorders of pregnancy. N Engl J Med 1991; **325**:1399–1405.
21. Levine RJ, Hauth JC, Curet LB et al. Trial of calcium to prevent preeclampsia. N Engl J Med 1997; **337**:69–76.
22. Sibai BM, Caritis SN, Thom E et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. N Engl J Med 1993; **329**:1213–1218.

23. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of preeclampsia among 9364 pregnant women. Lancet 1994; **343**:619–629.
24. Duley L, Henderson-Smart D, Knight M et al. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. BMJ 2001; **322**:329–333.
25. Hermida RC, Ayala DE, Fernandez JR. Administration time-dependent effects of aspirin in women at differing risk for preeclampsia. Hypertension 1999; **34**:1016–1023.
26. Pascoal IF, Lindheimer MD, Nalbantian-Brandt C et al. Preeclampsia selectively impairs endothelium-dependent relaxation and leads to oscillatory activity in small omental arteries. J Clin Invest 1998; **101**:464–470.
27. Chappell LC, Seed PT, Briley AL et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. Lancet 1999; **354**:810–816.
28. Morrison ER, Miedzybrodzka ZH, Campbell DM et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review. Thromb Haemost 2002; **87**:779–785.
29. AbdAlla S, Lother H, el Massiery A et al. Increased AT(1) receptor heterodimers in preeclampsia mediate enhanced angiotensin II responsiveness. Nat Med 2001; **7**:1003–1009.
30. Wallukat G, Homuth V, Fischer T et al. Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. J Clin Invest 1999; **103**:945–952.
31. Xia Y, Wen H, Bobst S et al. Maternal autoantibodies from preeclamptic patients activate angiotensin receptors on human trophoblast cells. Hypertens Pregnancy 2002; **21**(Suppl 1): 119(Abstract).
32. Ekbom P, Damm P, Nogaard K et al. Urinary albumin excretion and 24-hour blood pressure as predictors of pre-eclampsia in Type I diabetes. Diabetologia 2000; **43**:927–931.
33. Stehman-Breen CO, Levine RJ, Qian C et al. Increased risk of preeclampsia among nulliparous pregnant women with idiopathic hematuria. Am J Obstet Gynecol 2002; **187**:703–708.
34. Golara M, Benedict A, Jones C et al. Inflationary oscillometry provides accurate measurement of blood pressure in pre-eclampsia. BJOG 2002; **109**:1143–1147.
35. Hermida RC, Ayala DE. Prognostic value of office and ambulatory blood pressure measurements in pregnancy. Hypertension 2002; **40**:298–303.
36. Magee LA, Ornstein MP, von Dadelszen P. Management of hypertension in pregnancy. BMJ 1999; **318**:1332–1336.
37. Sibai BM. Treatment of hypertension in pregnant women. N Engl J Med 1996; **335**:257–265.
38. Abalos E, Duley L, Steyn DW et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2001; **2**:CD002252.
39. Buchbinder A, Sibai BM, Caritis S et al. Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. Am J Obstet Gynecol 2002; **186**:66–71.
40. Brown MA, Hague WM, Higgins J et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust NZ J Obstet Gynecol 2000; **40**:139–155.
41. Rey E, LeLorier J, Burgess E et al. Report of the Canadian Hypertension Society consensus conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. Can Med Assoc J 1997; **157**:1245–1254.
42. Duley L, Henderson-Smart DJ. Drugs for rapid treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev 2000; **2**:CD001449.
43. Cham C, von Dadelszen P, Magee L. Is hydralazine the drug of choice for severe hypertension in pregnancy? Hypertens Pregnancy 2002; **21**(Suppl 1):32 (Abstract).
44. Bakris GL, Williams M, Dworkin L et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J Kidney Dis 2000; **36**:646–661.
45. von Dadelszen P, Ornstein MP, Bull SB et al. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet 2000; **355**:87–92.
46. Cockburn J, Moar VA, Ounsted M et al. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children, Lancet 1982; **1**(8273):647–649. (Earlier follow-up papers from this trial were by Mutch, Moar, Ounsted, and Redman, appearing in: Early Hum Dev 1977; **1**:47–57; 59–67.)
47. Montan S, Anandakumar C, Arulkumaran S et al. Effects of methyldopa on uteroplacental

and fetal hemodynamics in pregnancy-induced hypertension. Am J Obstet Gynecol 1993; **168**:152–156.
48. Schobel HP, Fischer T, Heuszer K et al. Preeclampsia – a state of sympathetic overactivity. N Engl J Med 1996; **335**:1480–1485.
49. Huisjes HJ, Hadders-Algra M, Touwen BC. Is clonidine a behavioural teratogen in the human? Early Hum Dev 1986; **14**:43–48.
50. Ray JG, Vermeulen MJ, Burrows EA et al. Use of antihypertensive medications in pregnancy and the risk of adverse perinatal outcomes: McMaster outcome study of hypertension in pregnancy 2 (MOS HIP 2). BMC Pregnancy Childbirth 2001; **1**:6.
51. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. BMJ 1990; **301**:587–589.
52. Lip GY, Beevers M, Churchill D et al. Effect of atenolol on birthweight. Am J Cardiol 1997; **79**:1436–1438.
53. Gallery EDM, Ross MR, Gyory AZ. Antihypertensive treatment in pregnancy: analysis of different responses to oxprenolol and methyldopa. BMJ 1985; **291**:563–566.
54. Bortolus R, Ricci E, Chatenoud L et al. Nifedipine administered in pregnancy: effect on the development of children at 18 months. Br J Obstet Gynaecol 2000; **107**:792–794.
55. Sedman AB, Kershaw DB, Bunchman TE. Recognition and management of angiotensin converting enzyme inhibitor fetopathy. Pediatr Nephrol 1995; **9**:382–385.
56. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy – United States, Canada, and Israel, 1987–1995. MMWR Morb Mortal Wkly Rep 1997; **46**:240–242.
57. Gallery ED, Gyory AZ. Sublingual nifedipine in human pregnancy. Aust NZ J Med 1997; **27**:538–542.
58. Visser W, Wallenburg HC. A comparison between the hemodynamic effects of oral nifedipine and intravenous dihydralazine in patients with severe preeclampsia. J Hypertens 1995; **13**:791–795.
59. Fenakel K, Fenakel G, Appelman Z et al. Nifedipine in the treatment of severe preeclampsia. Obstet Gynecol 1991; **77**:331–337.
60. Belfort MA, Varner MA, Dizon-Townson DS et al. Cerebral perfusion pressure, and not cerebral blood flow, may be the critical determinant of intracranial injury in preeclampsia: a new hypothesis. Am J Obstet Gynecol 2002; **187**: 626–634.
61. Belfort MA, Tooke-Miller C, Allen JC et al. Labetalol decreases cerebral perfusion pressure without negatively affecting cerebral blood flow in hypertensive gravidas. Hypertens Pregnancy 2002; **21**:185–197.
62. Aya AG, Mangin R, Hoffet M et al. Intravenous nicardipine for severe hypertension in preeclampsia – effects of treatment on mother and foetus. Intensive Care Med 1999; **25**:1277–1281.
63. Shoemaker CT, Meyers M. Sodium nitroprusside for control of severe hypertensive disease of pregnancy: a case report and discussion of potential toxicity. Am J Obstet Gynecol 1984; **149**:171–173.
64. Easterling TR, Carr DB, Davis C et al. Low-dose, short-acting, angiotensin-converting enzyme inhibitors as rescue therapy in pregnancy. Obstet Gynecol 2000; **96**:956–961.
65. The Eclampsia Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. Lancet 1995; **345**:1455–1463.
66. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 1995; **333**:201–205.
67. The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; **359**:1877–1879.
68. Atkinson HC, Begg EJ, Darlow BA. Drugs in human milk: clinical pharmacokinetic considerations. Clin Pharmacokinet 1988; **14**:217–240.
69. Beardmore KS, Morris JM, Gallery EDM. Excretion of antihypertensive medication into human breast milk: a systematic review. Hypertens Pregnancy 2002; **21**:85–95.
70. Atkinson H, Begg EJ. Concentrations of beta-blocking drugs in human milk. J Pediatr 1990; **116**:156.
71. White WB. Management of hypertension during lactation. Hypertension 1984; **6**:297–300.
72. Ehrenkranz RA, Ackerman BA, Hulse JD. Nifedipine transfer into human milk. J Pediatr 1989; **114**:478–480.
73. Devlin RG, Fleiss PM. Captopril in human blood and breast milk. J Clin Pharmacol 1981; **21**:110–113.

15

Evaluation and management of hypertension in children

Susan R Mendley

Introduction • Defining pediatric hypertension • Technique of blood pressure measurement • Tracking high blood pressure • Causes of hypertension in children • Evaluation of hypertension in children • Therapy • Conclusion • References

1. INTRODUCTION

Our understanding of the prevalence, significance, and etiology of hypertension in childhood is evolving rapidly. New and ongoing epidemiologic research has demonstrated the presence of high blood pressure as well as other cardiovascular risk factors at young ages.[1–5] Studies of children using ambulatory blood pressure measuring devices has provided new blood pressure norms and confirmation of normal and pathologic blood pressure patterns previously found in adults.[6] Target-organ damage has been demonstrated by echocardiography, interpreted with age-appropriate pediatric norms.[7,8] Thus, the earliest indicators of hypertensive cardiomyopathy can be shown to begin in childhood, giving new significance to its diagnosis and treatment. Treatment of high blood pressure in children has evolved with new US Food and Drug Administration (FDA) mandated testing of pharmaceutical agents in children, which should provide better pharmacokinetic, efficacy, and safety data of a growing number of antihypertensive agents.

The overall view of high blood pressure in children differs importantly from that in adults. It is much less common in children than adults; an estimated 1–3% of children have high blood pressure, although that varies by age and by population studied. A larger percentage of children have secondary (and potentially correctable) causes of hypertension than do adults. Nonetheless, essential hypertension is increasing in prevalence and represents an important public health concern, particularly in light of changes in obesity rates noted in large surveys.[9,10] We recognize these trends as having very significant implications for early development of cardiovascular disease.

2. DEFINING PEDIATRIC HYPERTENSION

Blood pressure (BP) rises with age in the first two decades of life, even in non-industrialized societies.[11] Extensive data on BP measurement have been accumulated to allow definitions of normal values for age and sex, initially reported in 1977.[12] Subsequent analysis of BP data by quintile showed a significant relationship of systolic BP with markers of physical maturity including height, bone age, and number of permanent teeth.[3] This is most clearly demonstrated when markers are expressed as *Z*-score

(number of standard deviations above or below the mean for age, i.e. *Z*-score = 0 is the mean, *Z*-score = −1 is 50th percentile below the mean) as shown in Figure 15.1. Children in the lowest quintile of BP were significantly shorter and less mature by bone age and dentition; those in the highest quintile of BP were the most physically mature. In fact, the differences in BP quintile due to physical maturity can be largely accounted for by adjusting for height. Thus, height is considered the most useful measure for adjusting age-derived BP norms. In the Update of the 1987 Task Force Report on High Blood Pressure in Children and Adolescents data were again analysed with regard to height and new tables created (see Tables 15.1 and 15.2) to permit clinicians and researchers to define normal and elevated blood pressure values for children of different ages.[13] Blood pressures >90th percentile for age and height were considered high normal and those ≥ 95th percentile were hypertensive.

Equally apparent from Figure 15.1 is the relationship of systolic BP quintile with weight, body weight index (weight/height^2), skinfold thicknesses and hip and waist circumferences. This is

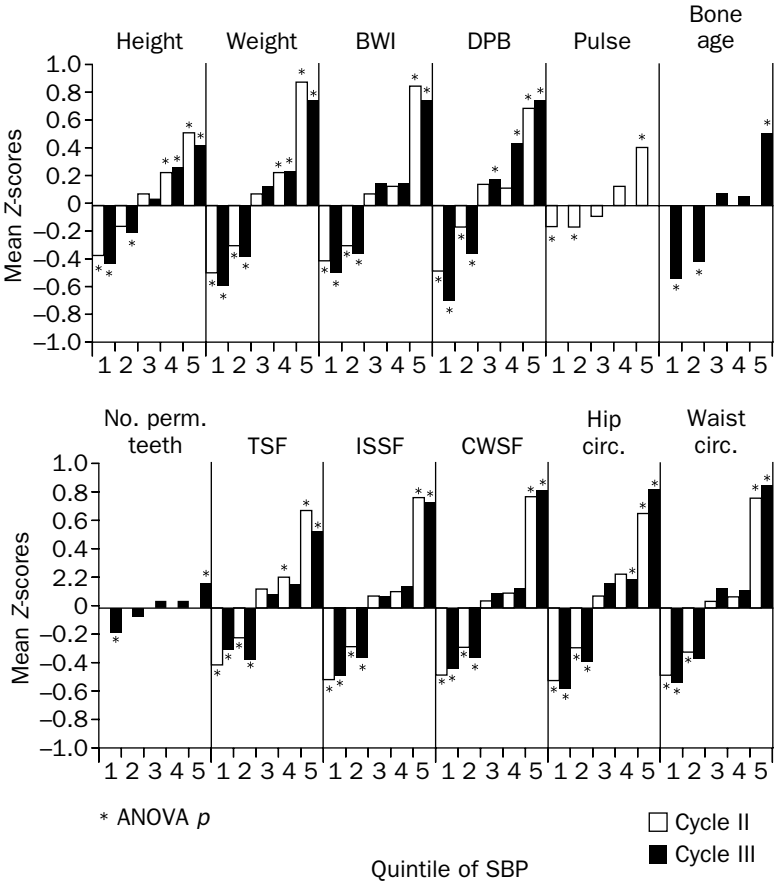

Fig. 15.1 Mean *Z*-scores of subjects remaining in the same quintile of systolic blood pressure in both Cycle II (1963–5) and III (1966–70) examinations (from the US Health Examination Surveys, National Center for Health Statistics). BWI, body weight index (weight/height^2); SBP, systolic blood pressure DBP, diastolic blood pressure; TSF, triceps skinfold thickness; ISSF, infrascapular skinfold thickness; CWSF, chest wall skinfold thickness; Hip Circ., hip circumference; Waist circ, waist circumference. $p = 0.05$; most were <0.001. The numbers remaining in the 1st, 2nd, 3rd, 4th, and 5th quintiles were 166, 110, 104, 120, and 209, respectively. *Note*: Those with pressures in highest quintiles of BP are the most mature with respect to dentition and bone age; they are also taller and more obese. Adapted with permission from Rahman et al, Am J Kidney Dis 2000.[3]

Table 15.1 Blood pressure (BP) levels for the 90th and 95th percentiles of BP for boys aged 1–17 years by percentiles of height

Age (yrs)	*BP percentile*[a]	*Systolic BP by percentile of height (mmHg)*[b]							*Diastolic BP by percentile of height (mmHg)*[b]						
		5%	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*	*5%*	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*
1	90th	94	95	97	98	100	102	102	50	51	52	53	54	54	55
	95th	98	99	101	102	104	106	106	55	55	56	57	58	59	59
2	90th	98	99	100	102	104	105	106	55	55	56	57	58	59	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	111	112	113	63	63	64	65	66	67	67
4	90th	102	103	105	107	109	110	111	62	62	63	64	65	66	66
	95th	106	107	109	111	113	114	115	66	67	67	68	69	70	71
5	90th	104	105	106	108	110	112	112	65	65	66	67	68	69	69
	95th	108	109	110	112	114	115	116	69	70	70	71	72	73	74
6	90th	105	106	108	110	111	113	114	67	68	69	70	70	71	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	90th	106	107	109	111	113	114	115	69	70	71	72	72	73	74
	95th	110	111	113	115	116	118	119	74	74	75	76	77	78	78
8	90th	107	108	110	112	114	115	116	71	71	72	73	74	75	75
	95th	111	112	114	116	118	119	120	75	76	76	77	78	79	80
9	90th	109	110	112	113	115	117	117	72	73	73	74	75	76	77
	95th	113	114	116	117	119	121	121	76	77	78	79	80	80	81
10	90th	110	112	113	115	117	118	119	73	74	74	75	76	77	78
	95th	114	115	117	119	121	122	123	77	78	79	80	80	81	82
11	90th	112	113	115	117	119	120	121	74	74	75	76	77	78	78
	95th	116	117	119	121	123	124	125	78	79	79	80	81	82	83
12	90th	115	116	117	119	121	123	123	75	75	76	77	78	78	79
	95th	119	120	121	123	125	126	127	79	79	80	81	82	83	83
13	90th	117	118	120	122	124	125	126	75	76	76	77	78	79	80
	95th	121	122	124	126	128	129	130	79	80	81	82	83	83	84
14	90th	120	121	123	125	126	128	128	76	76	77	78	79	80	80
	95th	124	125	127	128	130	132	132	80	81	81	82	83	84	85
15	90th	123	124	125	127	129	131	131	77	77	78	79	80	81	81
	95th	127	128	129	131	133	134	135	81	82	83	83	84	85	86
16	90th	125	126	128	130	132	133	134	79	79	80	81	82	82	83
	95th	129	130	132	134	136	137	138	83	83	84	85	86	87	87
17	90th	128	129	131	133	134	136	136	81	81	82	83	84	85	85
	95th	132	133	135	136	138	140	140	85	85	86	87	88	89	89

[a] Blood pressure percentile was determined by a single measurement.
[b] Height percentile was determined by standard growth curves.
Adapted from Blacher et al, Curr Opin Nephrol Hypertens 2002.[13]

Table 15.2 Blood pressure (BP) levels for the 90th and 95th percentiles of BP for girls aged 1–17 years by percentiles of height

Age (yrs)	*BP percentile*[a]	*Systolic BP by percentile of height (mmHg)*[b]							*Diastolic BP by percentile of height (mmHg)*[b]						
		5%	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*	*5%*	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*
1	90th	97	98	99	100	102	103	104	53	53	53	54	55	56	56
	95th	101	102	103	104	105	107	107	57	57	57	58	59	60	60
2	90th	99	99	100	102	103	104	105	57	57	58	58	59	60	61
	95th	102	103	104	105	107	108	109	61	61	62	62	63	64	65
3	90th	100	100	102	103	104	105	106	61	61	61	62	63	63	64
	95th	104	104	105	107	108	109	110	65	65	65	66	67	67	68
4	90th	101	102	103	104	106	107	108	63	63	64	65	65	66	67
	95th	105	106	107	108	109	111	111	67	67	68	69	69	70	71
5	90th	103	103	104	106	107	108	109	65	66	66	67	68	68	69
	95th	107	107	108	110	111	112	113	69	70	70	71	72	72	73
6	90th	104	105	106	107	109	110	111	67	67	68	69	69	70	71
	95th	108	109	110	111	112	114	114	71	71	72	73	73	74	75
7	90th	106	107	108	109	110	112	112	69	69	69	70	71	72	72
	95th	110	110	112	113	114	115	116	73	73	73	74	75	76	76
8	90th	108	109	110	111	112	113	114	70	70	71	71	72	73	74
	95th	112	112	113	115	116	117	118	74	74	75	75	76	77	78
9	90th	110	110	112	113	114	115	116	71	72	72	73	74	74	75
	95th	114	114	115	117	118	119	120	75	76	76	77	78	78	79
10	90th	112	112	114	115	116	117	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	90th	114	114	116	117	118	119	120	74	74	75	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	79	79	80	81	81
12	90th	116	116	118	119	120	121	122	75	75	76	76	77	78	78
	95th	120	120	121	123	124	125	126	79	79	80	80	81	82	82
13	90th	118	118	119	121	122	123	124	76	76	77	78	78	79	80
	95th	121	122	123	125	126	127	128	80	80	81	82	82	83	84
14	90th	119	120	121	122	124	125	126	77	77	78	79	79	80	81
	95th	123	124	125	126	128	129	130	81	81	82	83	83	84	85
15	90th	121	121	122	124	125	126	127	78	78	79	79	80	81	82
	95th	124	125	126	128	129	130	131	82	82	83	83	84	85	86
16	90th	122	122	123	125	126	127	128	79	79	79	80	81	82	82
	95th	125	126	127	128	130	131	132	83	83	83	84	85	86	86
17	90th	122	123	124	125	126	128	128	79	79	79	80	81	82	82
	95th	126	126	127	129	130	131	132	83	83	83	84	85	86	86

[a] Blood pressure percentile was determined by a single reading.
[b] Height percentile was determined by standard growth curves.
Adapted from Blacher et al, Curr Opin Nephrol Hypertens 2002.[13]

a clear demonstration of the relationship of BP in childhood with obesity. Such a relationship has been demonstrated in adults and, since obesity in childhood (particularly in the second decade) is associated with continued obesity into adulthood, the significance of these findings cannot be overemphasized.[14] Further, the increasing prevalence of obesity among children (Table 15.3) will have a dramatic effect on BP and cardiovascular health in young adulthood.[15] This risk factor is potentially modifiable, but there are clearly no easy solutions to the problem.

Thus, the working definition of hypertension is an average systolic or diastolic BP reading ≥ 95th percentile for age and height on at least three occasions. The norms provided for pediatric BPs are important guidelines, but certain limitations should be recognized. Most of the datasets used to produce these norms represent single measurements while clinical recommendations are to repeatedly confirm elevated BP readings; often, subsequent BP readings normalize once patients become more familiar with the procedure. (This explains the statistical tautology that only ~1% of children will have BP readings ≥95th percentile.) The norms do not make any attempt to address the more fundamental question of what level of BP is associated with the development of target organ damage. Therefore, while the guidelines are important for defining high BP, they are less useful in directing clinical decision making, particularly with regard to a level at which to treat hypertension. We will look at other approaches to that critical question.

3. TECHNIQUE OF BLOOD PRESSURE MEASUREMENT

The well-recognized effect of inappropriate cuff sizes on blood pressure measurement means a wider range of cuffs must be available to a clinician to fit children of varying size. Ideally, one chooses a cuff whose width is 40% of the circumference of the patient's arm measured between the acromion and the olecranon; in practice, one chooses from among the wide range of commercially available cuffs using the suggested markings.[13] An inappropriately small cuff may falsely elevate the BP reading, while a slightly large cuff may result in a lower reading, but is unlikely to obscure the diagnosis of true hypertension. Blood pressure should be measured after 3–5 minutes of rest in the seated position. Systolic BP is defined as the onset of the first Korotkoff sound (K1) and diastolic is now defined as the fifth Korotkoff sound (K5) for children of all ages. The choice of K5 is somewhat controversial and arises from the 1996 Update of the Task Force Report.[13] In some children, Korotkoff sounds can be heard to 0 mmHg, which effectively excludes diastolic hypertension.

Automated oscillometric devices have gained favor in many settings for ease of use, particularly in infants and toddlers. These devices measure systolic and mean arterial BP and calculate diastolic BP by various (proprietary) software programs. Few of the devices have been validated in children and thus diastolic BP readings from such devices should be viewed with skepticism.

Table 15.3 Prevalence of overweight among children and adolescents aged 6–19 years, for selected years 1963–65 through 1999–2000

Age (yrs)	*1963–65 1966–70*	*1971–74*	*1976–80*	*1988–94*	*1999–2000*
6–11	4	4	7	11	15
12–19	5	6	5	11	15

Data for 1963–65 are for children aged 6–11 years; data for 1966–70 are for adolescents aged 12–17 years, not 12–19 years. Adapted from Zoccali et al, Circulation 2002.[9]

'White coat' hypertension is a real entity among children and adolescents. Repeated measurement of BP will often result in normalization of modestly elevated readings. This is particularly important to avoid stigmatizing otherwise normal children with a diagnosis of hypertension and to prevent unnecessary evaluation and therapy.

Ambulatory blood pressure monitoring (ABPM) using oscillometric devices has been useful in differentiating white coat hypertension from true elevated BP.[16] Consistently normal systolic and diastolic values outside the office setting are diagnostic of white coat hypertension; such patients are more likely to present with BP elevations only 10% above the 95th percentile for age and height.[17] Reference data for height-normalized ABPM in healthy children and adolescents have been published.[6] Using ABPM devices, the nocturnal fall of BP ('dipping') was demonstrated at 13% ± 6% for systolic ABP and 23% ± 9% for diastolic ABP.

ABPM also permits better definition of the degree of hypertension by the calculation of average BP, BP load (the percentage of BP readings greater than a threshold value, typically the 95th percentile for height) and BP index (average BP divided by reference ambulatory BP 95th percentile for height). These ABPM-derived measures are associated with echocardiographic evidence of left ventricular hypertrophy and are, thus, more predictive of target organ damage than are casual BPs obtained in the office setting.[7]

Children receive more consistent routine health care than adults, which provides a valuable opportunity to identify and treat early manifestations of disease. Current American Academy of Pediatrics recommendations call for yearly measurement of blood pressure in children over age 3 years, recognizing the importance of identifying correctable causes of hypertension.[18] Further, recognizing the prevalence of obesity and obesity-associated hypertension among children offers the possibility of intervening early in a modifiable cause of cardiovascular disease.

4. TRACKING HIGH BLOOD PRESSURE

Convincing evidence is available to show that BPs measured in childhood are predictive of BP in adulthood; this phenomenon is known as tracking.[1–3,19] In particular, the risk of adult hypertension is significantly greater in those whose systolic and diastolic BPs were >80th percentile on even a single measurement during childhood or adolescence.[2] Figure 15.2 shows the prevalence of hypertension at age 20–31 in subjects who had BPs measured in childhood. The prevalence of hypertension (>140/90) in those whose childhood BP was in the highest quintile (>80th percentile) was 18% (systolic) and 15% (diastolic) and was significantly different from those with BP in the lower percentiles. Multiple readings >80th percentile in childhood are even better predictors of adult hypertension, as is shown in Figure 15.3. Noting the change in scale, individuals with multiple high readings in childhood were even more likely to develop hypertension as adults.

Just as blood pressure tracks from childhood into adulthood, weight in childhood has a strong relationship to weight in adulthood. Obese adolescents are at strikingly greater risk of obesity in young adult years and children of obese parents face an increased risk of obesity in adulthood.[14] In addition, the rate of weight gain from childhood through adulthood may be of central importance as it appears to correlate significantly with systolic BP, as well as with fasting insulin and lipid levels.[5] When followed over many decades, overweight adolescents have greater morbidity and mortality in adulthood.[20] Recent National Health and Nutrition Examination Survey (NHANES) data show a dramatic increase in obesity among US children (Table 15.3) in the past decade with 15% of these children considered overweight in the most recent reassessment.[9] Additional studies demonstrate a concomitant increase in systolic BP among children that can be explained by the increase in weight.[21] The phenomenon of an increasingly obese, hypertensive cohort of children entering adulthood clearly portends an increase in cardiovascular disease over the next several decades and

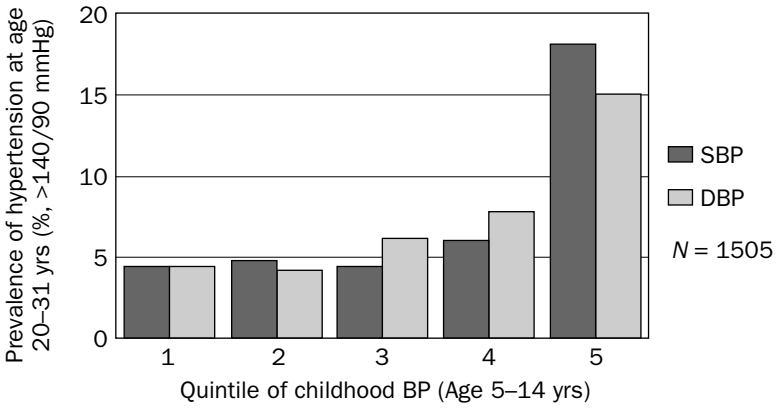

Fig. 15.2 Association between childhood blood pressure (BP) and prevalence of adult hypertension over 15 years in the Bogalusa Heart Study (n = 1505)[2]. It was the subjects who ranked in the highest age-, race-, and sex-specific quintiles of baseline BP developed hypertension even when they were 20–31 years old. SBP, systolic blood pressure; DBP, diastolic blood pressure. Adapted from System USRD, Am J Kidney Dis 2003.[2]

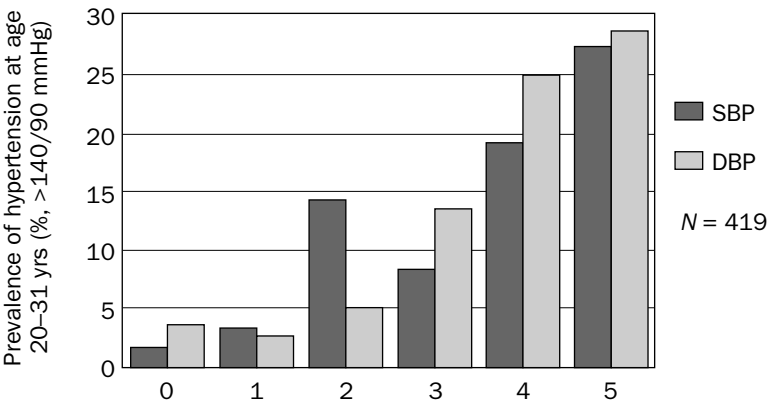

Fig. 15.3 Prevalence of adult hypertension related to the frequency of blood pressure (BP) elevations (within the top 20% rankings by age, race, and sex) in five previous surveys of Bogalusa Heart Study. Individuals detected at multiple times were more likely to develop hypertension even at age 20–31 years. SBP, systolic blood pressure; DBP, diastolic blood pressure. Adapted from System USRD, Am J Kidney Dis 2003.[2]

threatens to reverse recent improvements in cardiovascular death rates achieved with better medical management. While National Institutes of Health initiatives are being weighed to address this urgent public health concern, there does not appear to be a simple response to this growing problem.

5. CAUSES OF HYPERTENSION IN CHILDREN

The etiologies of elevated blood pressure in children differ significantly from those seen in adults. The search for secondary or correctable causes has a much higher yield and deserves more vigorous pursuit. In truth, patients with hypertension diagnosed in childhood who move into adulthood on antihypertensive therapy are unlikely to be re-evaluated for a secondary cause. Thus, we are obligated to be appropriately complete in their initial evaluation. A general caveat holds: the higher the blood pressure, the younger the child, the greater the likelihood of secondary hypertension.

The urgency of evaluation and treatment will depend upon the degree of hypertension detected and the presence of symptoms which can be attributed to high BP (see Box 15.1). As shown in Table 15.4, the level of blood pressure considered severe or emergency varies with the age of the child and is quite different from the level which would elicit concern in an adult. While good pediatric practice generally requires confirmation of an initial elevated blood pressure reading by at least two more readings, some elevations are extreme enough (approximately 40% over the 95th percentile or with symptoms) to consider immediate treatment or hospitalization while evaluation is undertaken.

Box 15.1 Symptoms of high blood pressure in infants and children

- Lethargy
- Irritability
- Growth failure
- Feeding disorder, vomiting
- Headache
- Seizure
- Stroke
- Congestive heart failure

Many of the common etiologies of secondary hypertension are unique to the pediatric setting.[13] They vary by age groups and this provides direction in the search for underlying disease. These are briefly summarized in Box 15.2.

Hypertension in the neonate is usually caused by a limited range of pathology. Indwelling umbilical artery catheters can cause thrombosis of main renal arteries or small intrarenal branches producing renovascular hypertension. Renovascular hypertension may also occur in the setting of congenitally small or atretic renal arteries.[22] Recessive polycystic kidney disease (PKD) and congenital obstructive uropathy can cause neonatal hypertension with palpable kidneys; these diagnoses are made ultrasonographically. Coarctation of the aorta produces upper extremity hypertension with pulse and blood pressure disparity in the lower extremities; an echocardiogram confirms and localizes the coarctation. Bronchopulmonary dysplasia and its attendant glucocorticoid therapy are also

Table 15.4 Significant or severe high blood pressure in infants and children

Age	*Significant hypertension (≥95th percentile)*	*Severe hypertension (≥99th percentile)*
Newborn–7 days	Systolic ≥ 96	Systolic ≥ 106
8–30 days	Systolic ≥ 104	Systolic ≥ 110
<2 years	Systolic ≥ 112 Diastolic ≥ 74	Systolic ≥ 118 Diastolic ≥ 82
3–5 years	Systolic ≥ 116 Diastolic ≥ 76	Systolic ≥ 124 Diastolic ≥ 84
6–9 years	Systolic ≥ 122 Diastolic ≥ 78	Systolic ≥ 130 Diastolic ≥ 86
10–12 years	Systolic ≥ 126 Diastolic ≥ 82	Systolic ≥ 134 Diastolic ≥ 90
13–15 years	Systolic ≥ 136 Diastolic ≥ 86	Systolic ≥ 144 Diastolic ≥ 92
16–18 years	Systolic ≥ 142 Diastolic ≥ 92	Systolic ≥ 150 Diastolic ≥ 98

Box 15.2 Most common etiologies of hypertension by age group

Infants
- Renovascular disease
- Coarctation of the aorta
- Congenital renal disease
- Bronchopulmonary dysplasia

First decade of life
- Renal parenchymal disease
- Coarctation of the aorta
- Renovascular disease

Second decade of life
- Renal parenchymal disease
- Renovascular disease
- Essential hypertension

Adapted from Blacher et al, Curr Opin Nephrol Hypertens 2002.[13]

common causes of hypertension in the neonatal intensive care unit.

The causes of hypertension in the infant and toddler are similar to those found in the neonate. Renal disease, both urologic and parenchymal, is the most likely etiology. PKD may present with hypertension and flank masses. Acute post-infectious glomerulonephritis is a common cause of hypertension in young children and may cause seizures or congestive heart failure because of its sudden onset in previously normotensive children. Coarctation of the aorta is most often discovered in this age group. Renovascular hypertension remains an important (and potentially correctable) cause of high BP in this age group.

School-aged children (6–10 years) have a similar spectrum of diseases causing hypertension as those described above. Renal parenchymal disease is a significant cause, including congenital urologic problems, such as reflux nephropathy with scarring and obstructive uropathy. Acquired glomerular diseases cause hypertension in this age group; acute post-infectious glomerulonephritis and focal segmental glomerulosclerosis are the most common etiologies, but the range of possible diseases is very broad and often require renal biopsy. PKD of both the dominant and recessive types causes hypertension in this age group and older patients. Renovascular disease presents in this age range as well, usually caused by fibromuscular dysplasia.

By the adolescent and teen years, essential hypertension is the most frequent diagnosis encountered, often coincident with obesity. Renal parenchymal disease remains the most likely secondary cause of hypertension. The renal scarring of reflux nephropathy may present with hypertension in this age group as do the late effects of obstructive uropathy which may have been due to posterior urethral valves or ureteropelvic junction obstruction. Hypertension may be seen from congenital urologic disease even after successful surgical correction earlier in life. Primary glomerular disease is seen in this age group; most common is focal segmental glomerulosclerosis, but Alport's syndrome, IgA nephropathy and numerous other renal diseases are seen in this age group and kidney biopsy is needed to differentiate them. Hypertension is often part of the presentation of systemic lupus erythematosis or systemic vasculitis. Renovascular disease, usually from fibromuscular dysplasia, remains an important and correctable etiology. Glucocorticoid excess causes hypertension in children of all ages. Cushings syndrome is rare: steroid therapy is a much more common cause. Drug-induced hypertension may arise from oral contraceptives or illicit drugs including diet pills, methamphetamines, and anabolic steroids.

The increasing effect of childhood obesity on BP and the impact of parental obesity on childhood obesity often muddy our recognition of the hereditary components of BP regulation. In fact, high BP is a polygenetic condition which is far from fully elucidated. Twin studies demonstrate a clear genetic component to BP regulation: concordance of systolic BP is much greater for monozygotic twins ($r = 0.55$, or rather 55% of systolic blood pressure can be explained by the identical twin's BP) than for dizygotic twins

($r = 0.25$, i.e. 25% of systolic BP can be explained by the fraternal twin's BP).[23] Nonetheless, noting that monozygotic twins do not have identical BP, implies there must be an environmental effect nearly as great as the genetic effect. Adoption studies provide a further glimpse of environmental effects on BP. Siblings adopted separately were shown to have greater concordance of BP with their adoptive parents than with their siblings who lived apart.[11] Socioeconomic factors also appear to affect BP.[24]

A small subset of patients will be found to have single gene defects which result in hypertension; they are highly informative and teach us much about the normal regulation of BP and sodium balance.[25] Often, a child is the index case for a kindred with a rare monogenetic hypertensive disorder when the diagnosis of elevated BP in the youngster sparks an evaluation that sheds light on an entire family. These rare disorders include syndromes of excess mineralocorticoid activity where hypokalemic metabolic alkalosis and suppressed plasma renin activity would be expected. The first to be recognized were the congenital adrenal hyperplasias, in particular 11β-hydroxylase and 17α-hydroxylase deficiency.[26] In addition, glucocorticoid-remediable aldosteronism (GRA) is known to cause early onset hypertension in children.[27] In this condition, aldosterone is produced under the control of adrenocorticotrophic hormone (ACTH) rather than under control of angiotensin II because of an unequal crossing over event such that the ACTH-responsive regulatory sequence of the steroid 11β-hydroxylase gene (11-OHase) has been fused to the coding sequences of the aldosterone synthase gene. As a result, normal regulation of aldosterone is disrupted and volume expansion, hypertension and a suppressed plasma renin occur. Suppression of ACTH production by glucocorticoids stops the inappropriate secretion of aldosterone. The syndrome of apparent mineralocorticoid excess (AME), an autosomal recessive mutation of the renal isoform of 11β-hydroxysteroid dehydrogenase, has been recognized in children in several kindreds.[28] In those patients cortisol binds freely to the mineralocorticoid receptor and functions like unregulated aldosterone. In Liddle's syndrome, an autosomal dominant hypertensive disorder seen in children and adults, a mutation in a subunit of the epithelial sodium channel (ENaC) causes unregulated sodium reabsorption in the distal tubule.

Other endocrine disorders, such as hyperthyroidism or glucocorticoid excess, cause hypertension in children. Primary hyperaldosteronism is rare in children. Evaluation for pheochromocytoma is guided either by a suggestive clinical history or a family history of multiple endocrine neoplasia. Abdominal tumors cause hypertension either through endocrine mechanisms (catecholamines in neuroblastoma or renin in Wilms' tumor) or from compression of renal vasculature. Other causes of hypertension are readily apparent from the clinical situation in which one meets the patient (i.e. traction-induced hypertension in those undergoing leg-lengthening procedures).

6. EVALUATION OF HYPERTENSION IN CHILDREN

Evaluation of hypertension begins with a complete medical history; symptomatic hypertension is most likely of recent onset (see Box 15.1). Hypertension can result in headaches in children, although the vast majority of headaches occur in normotensive patients. Infants are rarely screened for elevated blood pressure so they may present with a variety of symptoms before the diagnosis is established, such as unexplained congestive heart failure, seizures, irritability, abdominal masses or growth failure. Perinatal events may result in hypertension if asphyxia or acute renal failure occurred in the neonatal period or if an umbilical artery catheter was required. A history of urinary tract infection or an abnormal voiding pattern is relevant to a diagnosis of reflux nephropathy or obstructive uropathy. Growth history, sexual development, recent changes in weight, medication use (prescribed or illicit) or a history suggestive of systemic disease will direct the evaluation.

A family history of hypertension is always relevant. It may offer clues to a genetic disorder

(as described above) and may speak to a predilection toward essential hypertension. Even the presence of many family members with essential hypertension should not dissuade one from considering relevant secondary causes of high BP (as described in the previous section). Early onset hypertension with renal failure in other family members may be the clue to a diagnosis of PKD or hereditary nephritis. A kindred with multiple endocrine tumors or a genetic disorder, such as GRA, AME or Liddle's syndrome, may only be apparent after extensive questioning and testing of many family members. Early onset of cardiovascular morbidity and mortality in other family members will mandate aggressive risk factor modification (antihypertensive and lipid-lowering), likely through pharmacologic as well as nonpharmacologic approaches.

The physical examination in hypertensive children is often normal. However, important clues may become apparent (see Table 15.5): obesity is common among adolescent and teenage hypertensives; cushingoid features, growth failure or rickets may point to a chronic diagnosis. If examination of the skin demonstrates café-au-lait spots, tubers or 'ash-leaf' spots, neurofibromas, vasculitis or malar rash the evaluation is redirected. Abdominal masses or palpable organomegaly can lead to a diagnosis of neoplasm, heart failure or polycystic kidney disease.

Table 15.5 Important features of physical examination in children with hypertension

General	Growth failure, thinness, obesity, moon facies, elfin facies, proptosis
Skin	Rashes, impetigo, café au lait spots, neurofibromas
Abdomen	Masses, hepatosplenomegaly
Extremities	Blood pressure or pulse disparity edema, rickets
Genitalia	Ambiguous, virilized, precocious, delayed

Laboratory evaluation of children with hypertension (Table 15.6) begins with an assessment of renal function by serum electrolytes, urea nitrogen and creatinine, as well as urinalysis and culture. Screening for thyroid disease is often appropriate. Proteinuria or hematuria found on urinalysis will direct the evaluation toward a primary renal process. Plasma renin measurement is used to assess mineralocorticoid disturbances. A suppressed value is indicative of a disorder of excess mineralocorticoid activity (as discussed above). This may lead to further measurements of serum aldosterone, cortisol, and deoxycortisone and urinary metabolites of cortisol and cortisone. An elevated peripheral renin level may be suggestive of renovascular disease, but is an insufficiently sensitive test for ruling it out. Urine and serum catecholamines are measured when there is suspicion of a pheochromocytoma. Cholesterol is measured as in index of overall cardiovascular risk.

Ultrasound is the appropriate initial study for determining renal size, structure and echogenicity; nuclear scintigraphy with ^{99m}Tc dimercaptosuccinic acid (DMSA) or ^{99m}Tc glucoheptanate is preferred for detecting renal scars from vesicoureteral reflux. Renal arteriography remains the gold standard for diagnosis of renovascular disease and children tolerate the procedure well when it is performed in centers with pediatric expertise. It is particularly appropriate since fibromuscular dysplasia is the most common vascular disease and clinically significant lesions may occur in small branching vessels within the kidney. Findings on ^{99m}Tc mercaptoacetyltriglycine (Mag_3) renogram may be suggestive of renal arterial disease, but there are limited data on the sensitivity of the test in children and small intrarenal lesions are not well demonstrated as collateral flow is often adequate to mask them. Magnetic resonance imaging of renovascular lesions has not been studied in children and may similarly suffer from an inability to demonstrate intrarenal lesions; it is likely to be most useful for disease involving the main renal artery or close branches.

Table 15.6 Laboratory studies often utilized in evaluating hypertensive children

Electrolytes, blood urea nitrogen, creatinine	Acute or chronic renal disease
Cholesterol	Overall cardiovascular risk
Calcium	Hypercalcemic disorders (i.e. William's Syndrome)
Complete blood count	Anemia of chronic renal disease
Urinalysis/urine culture	Renal and urologic pathology
Thyroid function studies	Hyperthyroidism
Plasma renin activity	Mineralocorticoid excess, renovascular disease
Plasma and urine steroids	Mineralocorticoid or glucocorticoid disturbance
Urine and plasma catecholamines	Pheochromocytoma

Echocardiography is performed to assess for left ventricular hypertrophy as electrocardiogram criteria are insufficiently sensitive to detect early hypertensive cardiomyopathy in children. Studies must be compared to age or height-adjusted norms for left ventricular wall thickness. The utility of ambulatory BP monitoring is increasingly recognized. It is the best determinant of the contribution of white coat hypertension to office BP measurement and is also used to determine the effectiveness of antihypertensive therapy. As noted above, increased blood pressure index and blood pressure load (as determined by ambulatory BP monitoring) are better predictors of target-organ damage from hypertension than are casual office measurements.

When no specific cause for high BP is found in an adolescent or teenager, one generally presumes that essential hypertension is present, particularly if there is obesity or a family history of elevated BP. In a younger child, particularly early in the first decade, even if the evaluation has concluded without a specific etiology, the possibility of an underlying cause to hypertension must remain an active consideration. Nonetheless, essential hypertension represents the most common diagnostic category among pediatric hypertensives and its numbers are anticipated to increase following trends in pediatric obesity.

Among teenage essential hypertensives, a subgroup merits extra attention and this is children with coincident diabetes mellitus. The incidence of type 1 diabetes mellitus is stable while the incidence of type 2 diabetes mellitus among children is increasing dramatically in parallel with the rise in pediatric obesity.[29] Earlier age at onset is anticipated to result in earlier cardiovascular and renal complications, thus detection and treatment of diabetic hypertensives is a matter of great urgency. Urine microalbumin monitoring is appropriate for these patients to detect early diabetic renal disease. Some obese essential hypertensives will be found to have elevated insulin levels and evidence of early insulin resistance or even frank diabetes when tested before they become symptomatic.

7. THERAPY

The treatment of high blood pressure in children is directed either toward preventing immediate complications of malignant hypertension (when present) and the long-term modification of cardiovascular and cerebrovascular risks. Therapy of early onset hypertension can be expected to have significant lifelong benefit. However, long-term treatment trials are lacking and traditional end-points of death, myocardial infarction, and stroke are too distant to be studied in children. Thus, we are left with unanswered questions of what level of BP justifies initiation of pharmacotherapy to prevent later morbidity and mortality from cardiovascular, cerebrovascular and renal disease. Normal ranges for BP have been defined, but outcome measures for intervention to prevent progressive cardiovascular disease are only beginning to emerge. The most promising

measure is left ventricular hypertrophy, which may prove useful as a surrogate end-point for future trials.

At present, clinicians look first toward non-pharmacologic therapy in an attempt to modify risk factors for target organ damage. Changes in dietary and exercise habits are needed to combat the growing rate of childhood obesity and should be particularly directed at hypertensive children. Weight loss has been shown to lower BP and peripheral vascular resistance in such children.[30] Even modest changes can be expected to improve cardiovascular outcome. Lowering of serum cholesterol, either by dietary modification or lipid- lowering agents, should offer cumulative benefit to high-risk individuals. Most smokers begin as teenagers; this risk group should be educated to avoid tobacco. A young hypertensive can be seen as a marker for a family at risk for atherosclerosis; many obese, hypertensive children have obese, hypertensive parents. The recognition of this lethal pattern may motivate an entire family to make lifestyle changes for the sake of their children.

Virtually every antihypertensive agent developed for use in adults has been utilized in children. Choices in agents are largely based upon extrapolations from mechanisms of drug action and from indications in adults. Few agents have been tested for safety, efficacy or dose in children despite the obvious need for this. In an attempt to address this shortfall in our understanding of pediatric drug therapy, the US Congress included the Best Pharmaceuticals for Children Act as part of the FDA Modernization

Table 15.7 General guidelines for pharmacotherapy in the treatment of hypertension in children

Drug	*Dose*	
	Initial	*Maximum*
Hypertensive emergencies		
Sodium nitroprusside	0.5–1 μg/kg/min iv	8 μg/kg/min
Labetalol	0.2–1 mg/kg/dose iv	20 mg
Nicardipine	0.8–5 μg/kg/min iv	15 mg/h
Fenoldapam	0.2–2.5 μg/kg/min iv	
Hydralazine	0.1–2 mg/kg iv	20 mg
Nifedipine	0.1–25 mg/kg po	0.5 mg/kg
Enalaprilat	0.005–0.01 mg/kg/dose	1.25 mg
Chronic therapy		
Captopril	Neonates: 0.01–0.05 mg/kg/d	
	Infants: 0.15 mg/kg/d	6 mg/kg/d
	Children: 0.3–0.5 mg/kg/d	
	Adolescents: 12.5–25 mg	150 mg/d
Enalapril	0.1 mg/kg/d	0.5 mg/kg/d or 40 mg
Labetalol	1 mg/kg/d	
Atenolol	1 mg/kg/d	
Propranolol	1 mg/kg/d	8 mg/kg/d
Prazosin	0.05–0.1 mg/kg/d	0.5 mg/kg/d
Minoxidil	0.1–0.2 mg/kg/d	
Amlodipine	Children: 0.1–0.3 mg/kg/d	
	Adolescents: 0.1–0.2 mg/kg/d	
Furosemide	0.5–1 mg/kg/d	
Hydrochlorthiazide	1 mg/kg/d	

Act of 1997, which provided an incentive to manufacturers to study medications in children. Numerous studies of antihypertensive agents have been undertaken in response to this initiative and relevant information is expected to emerge.

General guidelines for pharmacotherapy are provided in Table 15.7. Most dosages shown are not the results of pharmacokinetic and pharmacodynamic testing; rather many are recommendations based upon anecdotal reports and experience gleaned from subspecialists. They do not reflect manufacturers recommendations or FDA-approved indications. Dosages are titrated to antihypertensive response. Often size-appropriate doses are smaller than available tablets or capsules and extemporaneously compounded solutions are needed to permit incremental dosing and to improve palatability for children who cannot swallow tablets.

Pharmacotherapy is clearly indicated in children with hypertension and underlying renal disease. Although the large prospective trials and metanalyses of the protective effects of angiotensin-converting enzyme inhibitors (ACEIs) on progressive renal insufficiency were performed in adults, most clinicians have adopted this approach in children as well. Therapy is usually adjusted to reach the 90th percentile for age- and height-adjusted BP, but a significant decrease in proteinuria is also used as an end-point in therapy. Angiotensin II receptor blockers (ARBs) have been used in children for similar indications, although there is less experience with them.

Children with hypertension and diabetes mellitus represent a particular high-risk group in which clinical judgement mandates BP lowering, despite the lack of long-term prospective trials. These children are seen to be at significant risk of renal disease and cardiovascular disease. ACEIs and ARBs would be the first choice because of their recognized beneficial effect on the progression of early diabetic nephropathy.

Diuretics are not usually first-line agents in children with high BP, but they are often adjunctive therapy in those with renal insufficiency. Some teenagers with essential hypertension can be successfully managed with only a thiazide diuretic: the minimal cost of these agents, their long-term safety record and the anticipated duration of therapy (decades) make a compelling argument for their use. Spironolactone is appropriate for children with apparent mineralocorticoid excess (AME); pediatric data on eplerenone are not yet available. Triamterene and amiloride are used in hypertension due to Liddle's syndrome.

Calcium channel blockers have been used in children for rapid onset management of hypertension in hospitalized children (i.e. nifedipine and isradipine) as well as for chronic therapy (e.g. amlodipine and felodipine). They are generally considered safe and have not been shown to have the same risks of cardiovascular mortality found in adults.[31] They offer no specific benefit aside from the fact that can be used for interim therapy while an evaluation is undertaken since they do not interfere with measurements of hormones and catecholamines.

Beta-blockers have been used successfully in children with hypertension. Liquid formulations of propranolol are available and there is a great deal of experience with this agent even in newborns. Longer-acting agents (e.g. bisoprolol and metoprolol) have been tested as well.

There is experience with the use of direct acting vasodilators in hypertensive children of all ages. Hydralazine has been used orally and intravenously for hypertension in infants and children for emergency management and chronic therapy. Minoxidil is used in infants and children with difficult to control BP, typically in the setting of renal failure. Hirsutism is common.

Peripheral alpha-blockers are used in severely hypertensive children requiring multiple medications. They are rarely used alone. Central acting alpha agonists (clonidine and α-methyldopa) have a high incidence of sleepiness in children and are generally avoided.

Emergency or malignant hypertension is treated with the same agents as those used in adults. Parenteral therapy with nitroprusside, nicardipine, labetalol, enalaprilat, and fenoldapam have all been used in the pediatric intensive care setting and the choice of agents is determined by the presumed underlying etiology of

the hypertension, the presence of target organ damage and the clinician's familiarity with each of the agents. As indicated in Table 15.4, the range of BP which causes symptoms or complications, such as seizure and intracranial bleeding, is considerably lower in infants and children than in adults. Often, the duration of hypertension and the risk of complications cannot be determined during a single office visit or emergency room evaluation with a hypertensive child; hospital admission for observation and urgent or emergency therapy may be the most appropriate course of action.

8. CONCLUSION

Many pressing questions in pediatric hypertension remain unanswered. We have not fully defined the rising prevalence of hypertension among children through wide epidemiologic studies. Only small-scale studies of target-organ damage in young hypertensives have been performed. Thus, we have not yet drawn the definitive link between childhood hypertension, early onset risk factors, and adult cardiovascular, cerebrovascular, and renal diseases. These results will have important public health implications. Therapeutic strategies to prevent or treat target-organ damage have yet to be developed and tested in children. The appropriate choice of pharmacologic agents for different ages and etiologies of hypertension remains more a matter of art than science. Fortunately, research continues in all areas of pediatric hypertension. New etiologies of high blood pressure continue to be elucidated and children with hypertension appear to be the ideal patients for expanding our understanding of blood pressure regulation.

REFERENCES

1. Lauer RM, Clarke WR. Childhood risk factors for high adult blood Pressure: The Muscatine Study. Pediatrics 1989; **84**:633–641.
2. Bao W, Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: The Bogalusa Heart Study. Am J Hypertens 1995; **8**:657–665.
3. Lauer RM, Burns TL, Clarke WR. Epidemiology of blood pressure in childhood. In: Hofman A, Grobbee DE, Schalekamp MADH (eds), Early Pathogenesis of Primary Hypertension. Amsterdam: Elsevier Science Publishers BV 1987, 13–24.
4. Sinaiko AR. Current concepts: Hypertension in children. N Engl J Med 1996; **335**:1968–1973.
5. Sinaiko AR, Donahue RP, Jacobs DR, Prineas RJ. Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin and lipids in young adults. Circulation 1999; **99**:1471–1476.
6. Soergel, M, Kirschstein M, Busch C et al. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: A multicenter trial including 1141 subjects. J Pediatr 1997; **130**:178–184.
7. Sorof JM, Cardwell G, Franco K, Portman RJ. Ambulatory blood pressure and left ventricular mass index in hypertensive children. Hypertension 2002; **39**:903–908.
8. Daniels S, Loggie JMH, Khoury P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. Circulation 1998; **97**:1907–1911.
9. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA 2002; **288**:1728–1732.
10. Freedman DS, Srinivasan SR, Valedz RA, Williamson DF, Berenson GS. Secular increases in relative weight and adiposity among children over two decades: The Bogalusa heart study. Pediatrics 1997; **99**:420–426.
11. Szklo M, Epidemiologic patterns of blood pressure in children. Epidemiologic Reviews 1979; **1**:143–169.
12. Blumenthal S, Epps RP, Heavenrich R et al. Report of the task force on blood pressure control in children. Pediatrics 1977; **59**:797–820.
13. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A Working Group Report from the National High Blood Pressure Education Program. Pediatrics 1996; **98**:649–658.
14. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med 1997; **337**:869–873.
15. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to

cardiovascular risk factors among children and adolescents: The Bogalusa heart study. Pediatrics 1999; **103**:1175–1182.
16. Sorof JM, Portman RJ. White coat hypertension in children with elevated casual blood pressure. J Pediatr 2000; **137**:493–497.
17. Sorof JM, Poffenbarger T, Franco K, Portman R. Evaluation of white coat hypertension in children: importance of the definitions of normal ambulatory blood pressure and the severity of casual hypertension. Am J Hypertens 2001; **14**:855–860.
18. Recommendations for Preventive Pediatric Health Care (RE9939). Pediatrics 2000; **105**: 645–646.
19. Lauer RM, Clarke WR, Beaglehole R. Level, trend and variability of blood pressure during childhood: the Muscatine study. Circulation 1984; **69**:242–249.
20. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med 1992; **327**:1350–1355.
21. Luepker RV, Jacobs DR, Prineas RJ, Sinaiko AR. Secular trends of blood pressure and body size in a multi-ethnic adolescent population: 1986 to 1996. J Pediatr 1999; **134**:668–674.
22. Hiner LB, Falkner B, Renovascular hypertension in children. Pediatr Clin North Am 1993; **40**:123–140.
23. Feinleib M, Garrison RJ, Rabsitz R et al. The NHLBI twin study of cardiovascular disease risk factors: Methodology and summary of results. Am J Epidemiol 1977; **106**:284–295.
24. Wilson DK, Kliewer W, Plybon L, Sica DA. Socioeconomic status and blood pressure reactivity in healthy black adolescents. Hypertension 2000; **35**:496–500.
25. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001; **104**:545–556.
26. New MI, del Balso P, Crawford C, Speiser PW. The adrenal cortex. In: Kaplan SA (ed.), Clinical Pediatric Endocrinology. Philadelphia: WB Saunders 1990; 220–234.
27. Dluhy RG, Anderson B, Harlin B, Inglefinger J, Lifton R. Glucocorticoid-remediable aldosteronism is associated with severe hypertension in early childhood. J Pediatr 2001; **138**:715–720.
28. Dave-Sharma D, Wilson RC, Harbison MD et al. Examination of genotype and phenotype relationships in 14 patients with apparent mineralocorticoid excess. J Clin Endocrinol Metab 1998; **83**:2244–2254.
29. Kaufman FR. Type 2 diabetes in children and young adults: A 'new epidemic'. Clin Diabetes 2002; **20**:217–218.
30. Rocchini AP, Katch V, Schork A, Kelch RP. Insulin and blood pressure during weight loss in obese adolescents. Hypertension 1987; **10**:267–273.
31. Blaszak RT, Savage JA, Ellis EN. The use of short acting-nifedipine in pediatric patients with hypertension. J Pediatr 2001; **139**:34–37.

16

Blood pressure control in dialysis patients

Aldo J Peixoto

Introduction • Mechanisms of hypertension in end-stage renal disease (ESRD) • Assessment of blood pressure in dialysis patients • Management of hypertension in end-stage renal disease (ESRD) • Conclusions • References

1. INTRODUCTION

The relevance of hypertension (HTN) in the care of patients with chronic kidney disease is undisputable. Hypertension is recognized as a major risk factor for the progression of chronic kidney disease,[1] and 27% of prevalent dialysis patients in the United States have hypertension listed as the etiology of end-stage renal disease (ESRD).[2] Once on dialysis, 60–70% of patients remain hypertensive according to commonly used standards (Figure 16.1), and it is sobering to realize that as many as 11% of patients have blood pressure (BP) levels above 180/110 mmHg despite their frequent access to

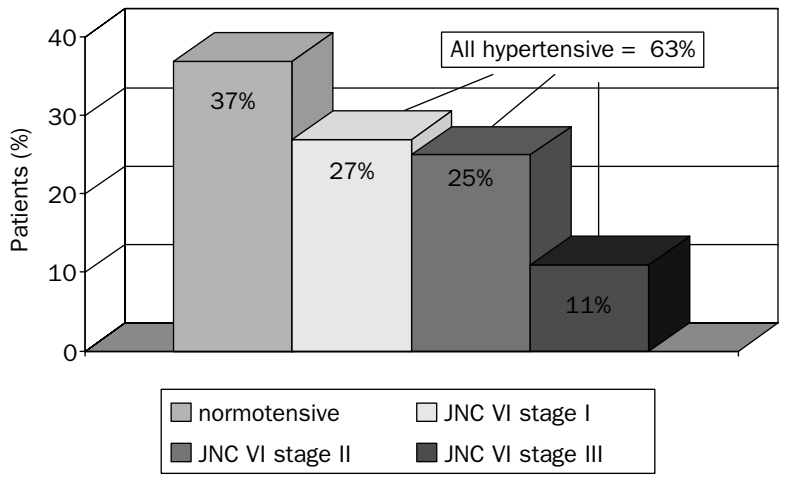

Fig. 16.1 Prevalence of hypertension according to degree of blood pressure (BP) control in a large, representative cohort of dialysis patients (hemodialysis and peritoneal dialysis combined). BP was measured pre-dialysis in hemodialysis patients, and on a routine visit in peritoneal dialysis patients. JNC VI stages:
I = 140–159/90–99 mmHg;
II = 160–179/100–109 mmHg;
III ≥ 180/100 mmHg. Based on data from Rahman et al, Am J Kidney Dis 2000[3] with permission from WB Saunders.

care.[3] In this chapter we will review the mechanisms and consequences of HTN in ESRD, the best methods to assess BP in dialysis patients, and options for the management of HTN in this selected patient population.

2. MECHANISMS OF HYPERTENSION IN END-STAGE RENAL DISEASE (ESRD)

The pathophysiology of hypertension (HTN) in ESRD is an intricate complex of factors (Table 16.1 summarizes the most relevant). Sodium and water retention is the most important mechanism of blood pressure (BP) elevation in ESRD. This is made clear by the observation that HTN is controlled in more than 90% of hemodialysis (HD) and peritoneal dialysis (PD) patients who effectively adhere to a low salt diet and in whom dry weight is aggressively pursued – and achieved – through ultrafiltration.[4,5] Volume overload leads to increased cardiac output, sodium excess contributes to increased vascular tone, and hypertension develops when systemic vascular resistance fails to decrease in response to salt and water excess.[6] Because uremia is a state of increased vascular tone (see below), this course of events is frequently observed.

Table 16.1 Relevant factors involved in the pathogenesis of hypertension in dialysis patients

Sodium and water retention

Increased activity of vasoconstrictive systems
- Sympathetic nervous system
- Renin-angiotensin-aldosterone system (RAAS)
- Endothelin-1
- Ouabaine-like factor
- Vasopressin

Decreased activity of vasodilatory systems
- Nitric oxide
- Kinins

Increased intracellular calcium

Increased arterial stiffness

Sleep apnea

Hyperparathyroidism

Erythropoietin

Renovascular disease

However, there is a subgroup of patients in whom adequate control of extracellular volume is not enough to control BP, suggesting that other mechanisms are operative as well.[7] Katzarski et al. studied three groups of patients on hemodialysis, one receiving long HD (7–8 h/d, 3 d/wk), all of whom were normotensive, a second group of normotensive patients receiving conventional HD (4 h/d, 3 d/wk), and a third group of hypertensive patients on conventional HD.[7] These subjects had their extracellular volume determined by bioimpedance and these values were normalized to their post-dialysis body weight so that they could be expressed as percentages and compared among subjects. As depicted in Figure 16.2, there is a large variability in the degree of expansion of extracellular fluid in hemodialysis patients, regardless of HD modality or degree of BP control.

The sympathetic nervous system is activated in patients with kidney disease, contributing to HTN through vasoconstriction and increased cardiac contractility. Elegant work has revealed an important role of afferent sympathetic outflow from the diseased kidneys as the source of this hyperactivity, and it has been demonstrated that bilateral nephrectomy normalizes sympathetic function in patients with ESRD.[8] In addition, this sympathetic activation appears to have a systemic detrimental effect: a recent study has linked high norepinephrine levels with increased risk of cardiovascular events and death in hemodialysis patients.[9] The renin-angiotensin-aldosterone system (RAAS) is inappropriately activated for the degree of volume retention that is usually present.[10] This activation leads to vasoconstriction and extensive cardiovascular remodeling. Other abnormalities found in renal failure can result in a state of increased vascular tone due to a combination of increased substances favoring vaso-

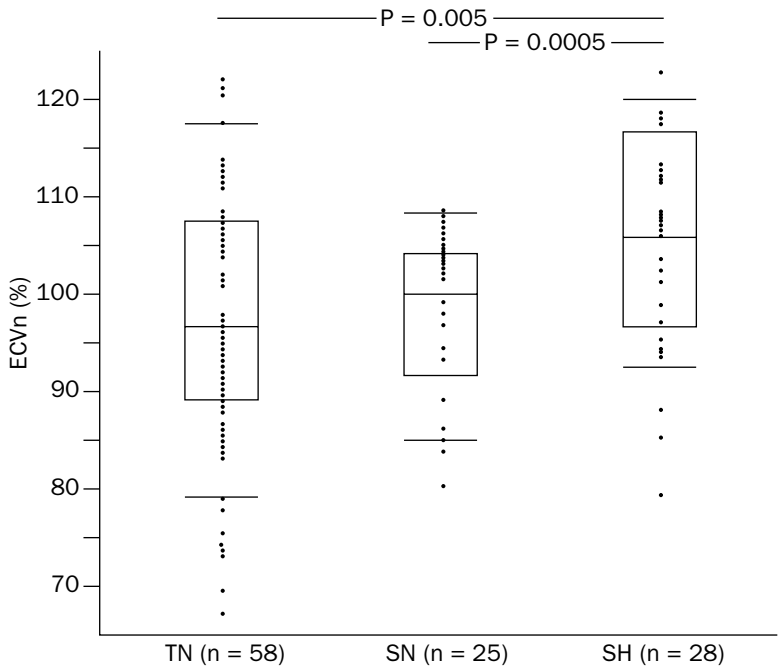

Fig. 16.2 Variability in the relationship between extracellular volume and blood pressure control in hemodialysis (HD) patients. Groups: TN, normotensive patients on long HD; SN, normotensive patients on conventional HD; SH, hypertensive patients on conventional HD; ECVn, normalized extracellular volume (as a percentage of post-dialysis weight). See text for details. From Katzarski et al, Nephrol Dial Transplant 1999[7] with permission from Oxford University Press.

constriction (ouabaine-like factor, endothelin-1, vasopressin, parathyroid hormone) and a decrease in vasodilatory pathways (especially nitric oxide, whose production is decreased by accumulated asymmetric dimethylarginine, kinins).[10–12] As discussed, it is the interaction between increased vascular tone and volume overload that ultimately sets the stage for increased BP in ESRD.

Arterial stiffness has received much attention as a pathophysiologic factor in the HTN of ESRD. Patients with chronic kidney disease develop progressive stiffening of the large arteries due to progressive medial calcification.[13] Arterial stiffness leads to more rapid conduction of the incident pulse wave, thus resulting in a faster return of the pulse wave to the central circulation (heart) leading to augmentation of aortic systolic pressure, as well as a more pronounced diastolic decay. This leads to increased left ventricular load and hypertrophy, and impaired coronary perfusion during diastole. These physiologic changes are noted clinically as predominantly systolic HTN with elevated pulse pressure, and recent data demonstrate that pulse pressure and, particularly impaired arterial compliance are potent predictors of mortality in dialysis patients.[14–16]

Sleep apnea (or sleep-disordered breathing) is present in 50–75% of dialysis patients, where it presents in a combination of obstructive and central components, with a predominance of the former.[17,18] Akin to observations in the general population, sleep apnea has been linked to high BP in dialysis patients, through mechanisms that are still unclear, although sympathetic activation is likely to be at its center.[18] Sleep apnea is associated with increased left ventricular hypertrophy and has been linked to an increased risk of cardiovascular events in hemodialysis patients.[19,20] It can be largely corrected by longer daily dialysis, an observation that may have clinical and prognostic implications.[17]

The use of erythropoietin (EPO), which revolutionized the management of anemia in ESRD, is associated with increased BP in 20–30% of patients,[10] a process that is not acute, requiring several days to weeks to develop.[21] HTN is often observed in patients who receive high doses of EPO and have a brisk erythropoietic response. However, rise in red blood cell mass is not the only factor responsible for this relationship.

Other factors include EPO-induced increases in cytosolic calcium, increased endothelin-1 release, acquired resistance to vasodilatory actions of nitric oxide, and vascular remodeling due to EPO-induced endothelial and vascular smooth muscle cell growth.[21]

Hyperparathyroidism is a common complication of ESRD and has been linked to HTN in renal failure, presumably due to an increase in intracellular calcium.[22] Results of parathyroidectomy to correct hypertension have been discordant,[10] but there is evidence that vitamin D analogues correct the increased cytosolic calcium and result in BP reductions.[22] and recent work suggests that this may be related to an inhibitory interaction of 1,25-$(OH)_2$-vitamin D_3 and renin/angiotensin II.[23]

Renovascular disease may be present in a sizable minority of patients reaching ESRD, especially older patients with vascular disease in other vascular beds,[24] and this may be an operative mechanism of HTN in dialysis patients. There are anecdotal reports of improvement of BP control after renal revascularization in patients with renal artery stenosis and ESRD, and this possibility should always be considered in patients with difficult to control BP after achievement of volume control.

3. ASSESSMENT OF BLOOD PRESSURE IN DIALYSIS PATIENTS

3.1 Defining hypertension in end-stage renal disease (ESRD)

Levels of normality for blood pressure are generally derived from observational studies that identify patterns of risk of morbidity and mortality, and possible 'thresholds' for this increased risk, and from intervention studies in which interventions (including drug treatment) are tested at different levels of BP with the intent of limiting morbidity. It is this approach that has generated current practice standards for the diagnosis and treatment of essential hypertension (HTN).

However, the situation in ESRD is quite different from essential HTN. Observational studies have resulted in conflicting information with respect to cardiovascular morbidity and mortality, and no interventional studies have been adequately completed to date. Thus, it is not surprising that no agreement exists for the management of HTN in ESRD. However, we can abstract from the available data to make some reasonable decisions in patient care.

First, we need to understand the current data on the impact of HTN on cardiovascular disease and mortality in ESRD. The analysis of several databases has demonstrated a U-shaped curve between BP and mortality, that is, mortality is highest at the extremes of BP, high and low, but most prominently among patients with low BP (systolic BP $<$ 90–120 mmHg, diastolic BP $<$ 75–90 mmHg).[16,25–27] Figure 16.3 outlines the findings of one such study, in which the risk of death progressively decreased as BP increased, only to increase again at post-dialysis SBPs $>$ 180 mmHg.[26] This observation seems counterintuitive to our general knowledge as applied to essential HTN, especially because previous prospective work in dialysis patients had revealed an increased risk of *de novo* coronary disease (39%) and *de novo* heart failure (44%) for every 10 mmHg increase in mean arterial pressure.[28] There are several possible explanations for this 'paradox'. It is possible that other clinical factors that are strong predictors of mortality in dialysis patients, such as malnutrition, inflammation, infections, and underlying atherosclerosis, overshadow the predictive value of HTN.[29] It is also possible that the phenomenon of reverse causation is operative. This means that other ominous factors that predispose to death also lead to lower BP, predominantly the presence of congestive heart failure. Indeed, a recent study of 11 142 dialysis patients has shown that the U-effect is no longer observed once adjustments for cardiovascular comorbidity are made.[30] One other argument is that follow-up may not have been long enough in the available studies. In support to this contention is a study of 405 hemodialysis patients who had survived at least two years on dialysis.[31] Mortality thereafter was stratified according to its timing, as either 'early' (during the third or fourth year of ESRD) or 'late' (after the fifth year). Similar to

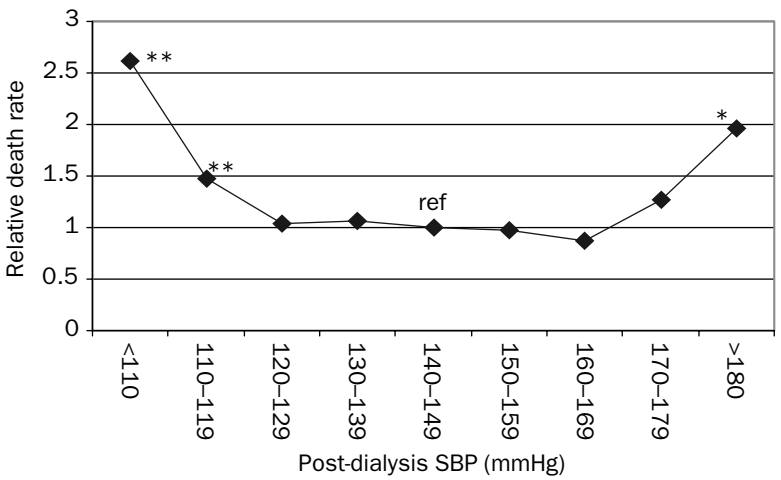

Fig. 16.3 Relationship between post-dialysis systolic blood pressure (SBP) and cardiac/cerebrovascular mortality in hemodialysis patients. Reference systolic BP interval for comparisons is 140–149 mmHg. *$p< 0.05$, **$p< 0.01$. From Zager et al, Kidney Int 1998[26] with permission from Blackwell Science.

previous studies, the relationship between BP and 'early' mortality had a 'U'-shape, but only high BP was associated with an increased risk of 'late' death.[31] These data suggest that it may take many years of survival on dialysis for HTN to display its detrimental effects on cardiovascular disease and mortality in these patients.

It becomes clear to the reader that it is difficult to establish limits of normality and therapeutic targets for BP in ESRD. A National Kidney Foundation taskforce suggested that BP should be treated to levels <140/90 mmHg in patients on peritoneal dialysis (PD) or hemodialysis (HD).[32] We agree that in light of such controversial data, this is a reasonable approach.

3.2 Methods to assess blood pressure in dialysis patients

Standard methods can be used to assess BP in PD subjects, who are usually seen monthly in the ambulatory setting.[33] BP should be measured in the seated and standing positions to rule out the presence of orthostatic hypotension.

In HD patients, however, BP levels can be significantly affected by the dialysis session (ultrafiltration) and the variable amounts of interdialytic weight gain. The use of ambulatory blood pressure monitoring (ABPM) has been useful in addressing this issue. ABPM studies have revealed that patients who respond to hemodialysis often return to baseline levels within less than 24 hours.[34] Accordingly, an average of the interdialytic period is a more accurate way to evaluate BP control in HD patients, and ABPM has been shown to be a more reproducible method in these patients.[35] Using ABPM to evaluate the ability of pre- and post-dialysis BP to estimate interdialytic BP, Agarwal and Lewis demonstrated that pre-dialysis readings are marked by an overestimation of interdialytic pressure, whereas post-dialysis values provide a closer approximation.[36] However, both pre- and post-dialysis BPs were marked wide variability (agreement) with interdialytic BP, outlining the limitations of both readings (Figure 16.4). These data reinforce the importance of closer monitoring of BP during the entire interdialytic period, which can be performed with ABPM or with home BP monitoring.[37] Unfortunately, ABPM is not widely available, and many patients prefer not to monitor their BP at home, so peridialysis readings are often the only option for the practicing nephrologist. In view of the available literature, the following recommendations should be considered:

1. Do not react to a single BP measurement. Instead, follow trends over a period of several dialysis sessions and use the average BPs for decision making. These averages have better reproducibility.[35]

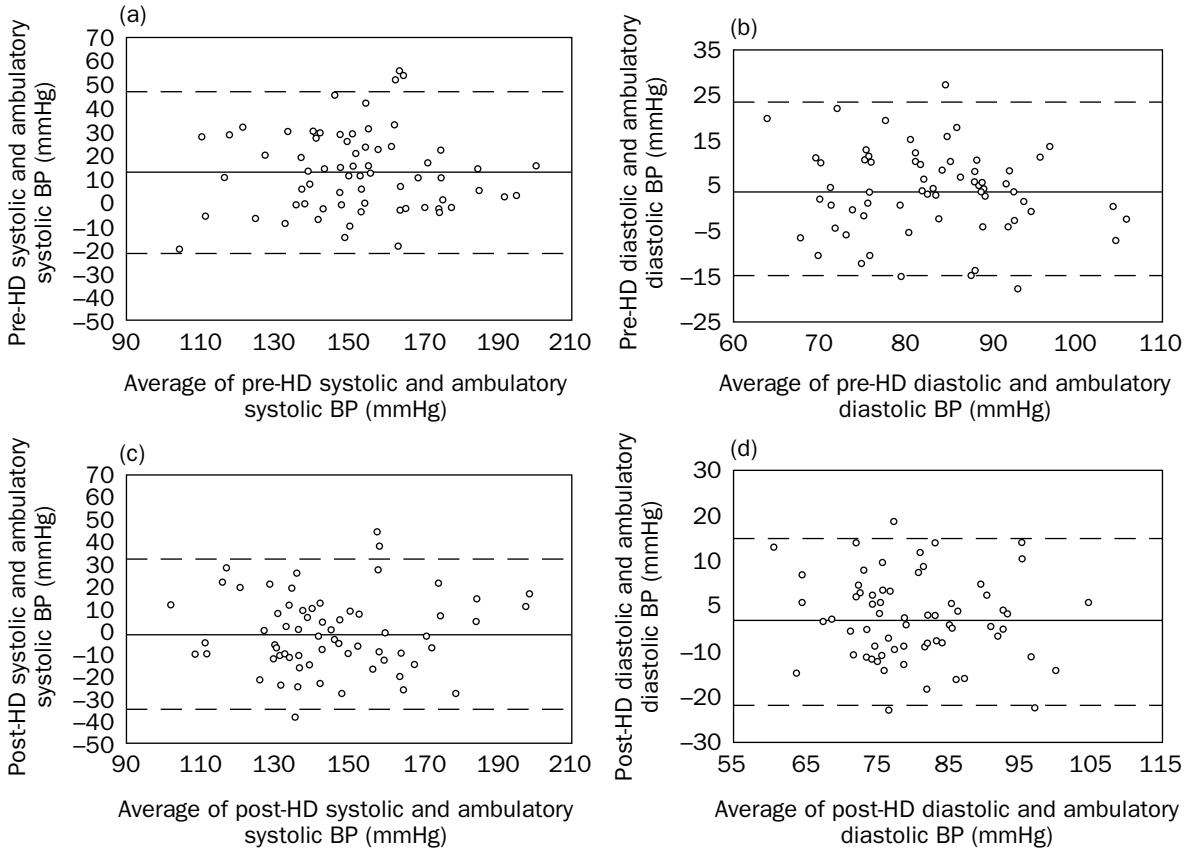

Fig. 16.4 Agreement between peridialysis BP measurements and interdialytic BP in hemodialysis (HD) patients. Plots show the difference between each method on the *y*-axis and the average of each pair of measurements on the *x*-axis. Ideally, the difference between each two methods should be zero, and the scatter (limits of agreement) should be 'tight'. (a and b) Pre-dialysis systolic (a) and diastolic (b) overestimate interdialytic BP by 13.5/3.8 mmHg (solid lines). (c and d) Post-dialysis BPs show no over-or underestimation of interdialytic BP. However, the limits of agreement (1.96 SD) are very wide for all peridialysis values (dashed lines). From Agarwal and Lewis, Kidney Int 2001[36] with permission from Blackwell Science.

2. Both pre-and post-dialysis BP have similar diagnostic value, but in view of the tendency of pre-dialysis BPs to overestimate BP, the thresholds used to define HTN are different. As shown in Table 16.2, a 75% likelihood of HTN is present if BP is >155/96 mmHg pre-dialysis or >140/88 mmHg post-dialysis.[36]
3. Management decisions should be made always with reference to measurements taken at the same time (pre- or post-dialysis). An important caveat is that patients with large intradialytic drops in BP should be managed based on pre-dialysis levels, whereas those with an intradialytic rise in BP should be managed preferably based on post-dialysis readings.[38]

ABPM studies in ESRD have also revealed an abnormal pattern of blood pressure throughout the day. Approximately 80% of patients on dialysis (HD or PD) lack the normal fall of BP during sleep and are thus exposed to a greater BP load. This pattern (called non-dipping) is associated with worse cardiovascular outcomes in essential hypertension, and has been linked to increased left ventricular dilatation in a prospective study in HD patients.[39] However, the available data do not provide enough

Table 16.2 Thresholds of peridialysis blood pressure levels to define hypertension in dialysis patients

	Diagnosis of HTN	*Likelihood of HTN*		
BP (mmHg)	*AUC on ROC curve*	*50%*	*75%*	*90%*
Pre-SBP	0.811	140	155	171
Pre-DBP	0.835	90	96	102
Post-SBP	0.802	125	140	155
Post-DBP	0.841	82	88	95

Note: Hypertension (HTN) was defined as 44 h interdialytic BP > 135/85 mmHg. AUC on ROC curve, area under the curve on the receiver-operator characteristic curve, a marker of diagnostic accuracy. SBP, systolic blood pressure; DBP, diastolic blood pressure. From Agarwal and Lewis, Kidney Int 2001[36] with permission from Blackwell Science.

insight on the true relevance of this finding in ESRD, and further studies are needed before any recommendation is made to define a patient's circadian BP profile for risk stratification or for treatment decisions.[38]

4. MANAGEMENT OF HYPERTENSION IN END-STAGE RENAL DISEASE (ESRD)

4.1 Lifestyle modifications

Patients on dialysis should be counseled about certain lifestyle changes that may improve blood pressure control. Of greatest importance is dietary advice to limit sodium intake to less than 100 mmol/day (2300 mg/d) and to limit interdialytic weight gain to the lowest possible value, but certainly no larger than 2.5 kg. Such goals are often difficult to achieve and demand a close relationship between patient, physician, and renal dietitian. Alcohol should be strongly discouraged and restricted to a maximum of 1–2 drinks/day. An exercise program may be effective in lowering BP in selected patients with ESRD,[40] although this intervention is often limited by the ailing, older composition of this patient group. A search should be made for hypertensogenic drugs, illicit or not, such as cocaine, amphetamines, and sympathomimetic substances (including nasal decongestants, nutritional supplements containing ephedra, and over-the-counter preparations to improve sexual performance containing yohimbine). Last, addressing other issues related to cardiovascular care, such as smoking, lipid control, and diabetic control, is important to limit cardiovascular disease burden in this population.

4.2 Volume control

Sodium and water retention is the most important mechanism of BP elevation in ESRD. Accordingly, salt restriction and effective ultrafiltration during dialysis should be the cornerstones of BP management in these patients. In a summary of their experience with 712 HD patients, Charra et al. described a 13 mmHg fall in mean arterial pressure over the course of 6 months as a result of salt restriction and ultrafiltration to clinical 'dry weight', with further BP reductions up to 12 months after initiation of dialysis (the so called 'lag phenomenon').[4] The definition of 'dry weight' is an important one in this context: whereas classic definitions refer to the lowest post-dialysis weight at which there is no evidence of volume overload and no symptoms related to hypovolemia (hypotension, cramps, nausea, and vomiting), hypertensive patients may benefit from a HTN-specific definition. In this regard, Charra et al. have proposed that 'dry weight is that body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis without antihypertensive medication'.[41] Using this approach, ultrafiltration is progressively adjusted to a lower weight on a weekly basis until the patient reaches normotension, which in their experience occurs in 95% of cases. Newer techniques are now being used to improve the definition of dry weight and include bioimpedance, inferior vena cava ultrasound, and blood volume monitoring, although their impact on hypertension control has not yet been well defined.[42]

This probing for dry weight often requires a longer duration of dialysis that allows for

slower ultrafiltration rates that can be tolerated by the patient. However, current hemodialysis practices (short dialysis sessions thrice weekly) seldom allow this to happen, even though it is well established that patients receiving more frequent HD have better BP control than patients on conventional HD. This observation applies to long HD thrice weekly,[4,43] daily nocturnal HD,[44] and interestingly, to short daily HD,[45] all of which result in better control of the extracellular volume, excellent BP control, and significantly decreased use of antihypertensive medications.

A final comment that is of interest to the issue of dialysis duration is that even though achievement of extracellular volume control (ECV) control is a key factor, not all patients with controlled BP have an effectively controlled ECV.[7] With this in mind, Luik et al. tested the BP-lowering effects of an increase in dialysis duration from 4 to 6 hours thrice weekly without change in dry weight in comparison with a push to lower dry weight with or without increasing dialysis duration.[46] In this pilot study the authors did not find any significant difference between the group that remained at the same weight but received longer HD and the groups in which ultrafiltration was increased to forcefully lower the dry weight. These interesting data show that there is more to longer dialysis than just better control of extracellular volume. What these factors may be (dialytic losses of vasoconstrictor factors or of inhibitors of vasodilation leading to a state of improved vascular tone) remains strictly speculative.

Diuretics may be helpful in limiting salt and water overload, with the caveat that effective clinical response seems to be restricted to patients with some residual glomerular filtration rate (GFR) (preferably > 5 mL/min).[47] Anecdotally, it is worthwhile using high-dose furosemide (100–200 mg po twice daily) associated with metolazone (5–10 mg po twice daily) to try to maintain urine volume, thus limiting interdialytic weight gain, improving sodium balance, and resulting in less need for ultrafiltration during HD. Diuretics may be effective in PD patients as well.[5]

Current dialysis practice uniformly prescribes the use of higher dialysate sodium concentrations (at least 138–140 mmol/L, with the frequent use of sodium modeling to prevent hypotension, cramping, and osmotic disequilibrium). The prescription of sodium modelling leads to a net positive sodium balance during HD and results in increased thirst, interdialytic weight gain, and blood pressure,[48,49] and should be used only in patients who depend on them for comfortable dialysis, and not as a default prescription.

4.3 Dialysis modality: peritoneal vs hemodialysis

By virtue of its continuous nature, PD has been long assumed to be more effective to control volume status. However, available data show that BP control in PD is no different from HD series,[50] which may reflect limited compliance with salt restriction. No randomized trials have compared one modality against the other, and available crossover studies did not randomize the cross over. In the largest study available, 63 patients were switched from HD to PD for several clinical reasons.[51] In 19 of these patients there was an immediate weight loss of about 2% with PD which was accompanied by an 8% decline of mean arterial pressure compared with baseline. However, in the other 44 patients there was a net weight gain of about 4% and no significant change in BP levels. These data can be interpreted in the following way: PD is an effective modality to improve BP control, but will only do so when it results in better control of extracellular volume.

4.4 Drug therapy

Pharmacologic therapy is needed in the majority of patients on dialysis in the United States,[32] and should be used to achieve target BP levels after dry weight has been achieved (unless Charra's definition is used, in which case normotension, by definition, is sought solely through dry weight changes). There are no prospective, randomized studies evaluating outcomes related to antihypertensive drugs in

ESRD patients, thus, all decisions are made solely on the basis of clinical efficacy in BP-lowering and data from observational studies. Interestingly, the use of antihypertensive drugs has been associated with a decreased risk of death in two large series despite the lack of association between hypertension (HTN) and mortality in these studies (see above).[25,26]

When choosing the specific class of agents, we can take some observational data into account. Beta-blockers have been the drug class most consistently associated with improved survival in observational studies of dialysis patients.[30] These observations, coupled with the findings that high catecholamine levels are associated with increased mortality risk in hemodialysis,[9] and that carvedilol, significantly improved recurrent heart failure and overall survival in dialysis patients with dilated cardiomyopathy in a prospective, randomized trial,[52] make it very compelling that we consider beta-blockers as strong components of the antihypertensive regimen in ESRD. ACE inhibitors have been associated with improved survival of dialysis patients in both prospective,[53] and retrospective studies.[54] Because of the convincing data to support the use of ACE inhibitors in heart failure and coronary disease,[55] and in patients with high cardiovascular risk profiles,[56] it is tempting to extrapolate these data to ESRD patients, whose clinical features are marked by cardiac dysfunction and diffuse, progressive atherosclerosis. Calcium channel blocker use (of any type) has also been associated with improved survival in ESRD in a prospective cohort study.[57] From a surrogate marker perspective, angiotensin II receptor blockers (ARBs, losartan) have been reported to be the most effective class of drugs in reducing left ventricular hypertrophy (LVH) in ESRD when compared with calcium blockers (amlodipine) and angiotensin-converting enzyme inhibitors ACEIs (enalapril) .[58] In view of the prevalence of LVH in dialysis patients and the favorable results of ARBs on cardiovascular end-points in essential hypertension complicated by LVH,[59] it is also tempting to extrapolate the use of ARBs in this group. Unfortunately, limited data exist, thus decisions regarding drug class are still made largely based on personal preference and clinical efficacy to lower BP.

From a BP-lowering perspective, any category of drugs can be used alone or in combination. As in essential hypertension, it is useful to combine drugs that affect separate pathways related to hypertension (e.g. a blocker of the RAAS with a calcium channel blocker or a beta-blocker), avoiding early combinations of similar drugs (e.g. a beta-blocker with an alpha-blocker or clonidine). Clonidine is a very effective agent in patients with renal failure and is useful in patients with severe HTN, as is the potent vasodilator minoxidil.

It is important to pay attention to pharmacokinetic properties that are altered by uremia so that dosing changes are in place to avoid toxicity. On

Table 16.3 Interventions of value in the treatment of dialysis hypertension

Lifestyle modification
- Sodium restriction (<100 mmol/d)
- Limitation of interdialytic weight gain (<2.5 kg)
- Aerobic exercise
- Limitation of alcohol intake (<2 drinks/d)

Achievement of dry weight
- Aggressive ultrafiltration
- Diuretic use (if residual GFR >5 mL/min)
- Avoidance of high dialysate sodium concentration (including sodium modeling)

Longer hemodialysis duration

More frequent hemodialysis sessions (daily short, nocturnal)

Peritoneal dialysis

Pharmacologic therapy: any category of agents

Adjust EPO dose

Correct sleep apnea if present

Treat hyperparathyroidism (vitamin D analogues or parathyroidectomy)

GFR, glomerular filtration rate; EPO, erythropoietin.

the other hand, we may use these properties to our advantage, as well exemplified by atenolol and lisinopril, which have been effectively used for treatment under observed dosing three times a week following dialysis.[60,61] This dosing schedule showed adequate coverage throughout the interdialytic period and can be employed to improve compliance in selected patients.

Finally, it is important to address other mitigating factors that are often present in ESRD. These include the identification and treatment of sleep apnea with nasal positive pressure ventilation or intensification of dialysis; treatment of hyperparathyroidism; and adjustments in the dose of erythropoietin.

In patients in whom all of the above interventions have failed, less common causes of HTN should be investigated, especially renovascular disease (both atherosclerotic or fibromuscular dysplasia) and, in rare instances, pheochromocytoma, aldosterone-producing adenoma, cortisol-producing adenoma, perirenal hemorrhage ('Page kidney'), or coarctation of the aorta. In the past, bilateral nephrectomy was an effective strategy in many patients, but it is not clear that it has any role with the available pharmacologic options to block the RAAS and the adrenergic nervous system, the two major targets of bilateral nephrectomy.

Table 16.3 summarizes the interventions to be considered in the management of HTN in dialysis patients.

5. CONCLUSIONS

Hypertension is an important complication of end-stage renal disease. Because of its complex relationship to clinical outcomes, there is controversy about targets to be achieved in terms of blood pressure control, but a goal of $<140/90$ mmHg seems reasonable. Its management should focus on its major pathogenetic mechanism, volume overload, and on the effective use of the dialysis prescription as well as blood pressure medications. Drug choice is empirical given the absence of prospective randomized trials comparing different drug classes in this patient population.

REFERENCES

1. Ruilope LM. Renal protection by antihypertensive therapy. Curr Hypertens Rep 2002; **4**:324–328.
2. United States Renal Data System (USRDS) Incidence and prevalence. Am J Kidney Dis 2003; **41**:S41–S56.
3. Rahman M, Fu P, Sehgal AR, Smith MC. Interdialytic weight gain, compliance with dialysis regimen, and age are independent predictors of blood pressure in hemodialysis patients. Am J Kidney Dis 2000; **35**:257–265.
4. Charra B, Bergstrom J, Scribner BH. Blood pressure control in dialysis patients: importance of the lag phenomenon. Am J Kidney Dis 1998; **32**:720–724.
5. Lameire N, Van Biesen W. Importance of blood pressure and volume control in peritoneal dialysis patients. Perit Dial Int 2001; **21**:206–211.
6. Luik AJ, van Kuijk WH, Spek J et al. Effects of hypervolemia on interdialytic hemodynamics and blood pressure control in hemodialysis patients. Am J Kidney Dis 1997; **30**:466–474.
7. Katzarski KS, Charra B, Luik AJ et al. Fluid state and blood pressure control in patients treated with long and short haemodialysis. Nephrol Dial Transplant 1999; **14**:369–375.
8. Converse RL, Jr., Jacobsen TN, Toto RD et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med 1992; **327**:1912–1918.
9. Zoccali C, Mallamaci F, Parlongo S et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation 2002; **105**:1354–1359.
10. Horl MP, Horl WH. Hemodialysis-associated hypertension: pathophysiology and therapy. Am J Kidney Dis 2002; **39**:227–244.
11. D'Amico M, Locatelli F. Hypertension in dialysis: pathophysiology and treatment. J Nephrol 2002; **15**:438–445.
12. Smith MC, Rahman M, Dunn MJ. Hypertension associated with renal parenchymal disease. In: Schrier RW (ed.) Diseases of the Kidney and Urinary Tract, 7th edn, Philadelphia, Lippincott Williams & WIlkins, 2001, pp 1363–1397.
13. Blacher J, Safar ME, Pannier B et al. Prognostic significance of arterial stiffness measurements in end-stage renal disease patients. Curr Opin Nephrol Hypertens 2002; **11**:629–634.
14. Blacher J, Guerin AP, Pannier B et al. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999; **99**:2434–2439.

15. London GM, Blacher J, Pannier B et al. Arterial wave reflections and survival in end-stage renal failure. Hypertension 2001; **38**:434–438.
16. Klassen PS, Lowrie EG, Reddan DN et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. JAMA 2002; **287**:1548–1555.
17. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med 2001; **344**:102–107.
18. Zoccali C. Sleep apnoea and nocturnal hypoxaemia in dialysis patients: mere risk-indicators or causal factors for cardiovascular disease? Nephrol Dial Transplant 2000; **15**:1919–1921.
19. Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. J Am Soc Nephrol 2002; **13**:729–733.
20. Zoccali C, Benedetto FA, Tripepi G et al. Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients. Kidney Int 1998; **53**:1078–1084.
21. Vaziri ND. Mechanism of erythropoietin-induced hypertension. Am J Kidney Dis 1999; **33**:821–828.
22. Raine AE, Bedford L, Simpson AW et al. Hyperparathyroidism, platelet intracellular free calcium and hypertension in chronic renal failure. Kidney Int 1993; **43**:700–705.
23. Li YC, Kong J, Wei M et al. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002; **110**:229–238.
24. Textor SC, Wilcox CS. Renal artery stenosis: a common, treatable cause of renal failure? Annu Rev Med 2001; **52**:421–442.
25. Salem MM, Bower J. Hypertension in the hemodialysis population: any relation to one-year survival? Am J Kidney Dis 1996; **28**:737–740.
26. Zager PG, Nikolic J, Brown RH et al. 'U' curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. Kidney Int 1998; **54**:561–569.
27. Port FK, Hulbert-Shearon TE, Wolfe RA et al. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kidney Dis 1999; **33**:507–517.
28. Foley RN, Parfrey PS, Harnett JD et al. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. Kidney Int 1996; **49**:1379–1385.
29. Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome – the heart of the matter. Nephrol Dial Transplant 2002; **17**(suppl 1):28–31.
30. Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. Kidney Int 2002; **62**:1784–1790.
31. Mazzuchi N, Carbonell E, Fernandez-Cean J. Importance of blood pressure control in hemodialysis patient survival. Kidney Int 2000; **58**:2147–2154.
32. Mailloux LU, Levey AS. Hypertension in patients with chronic renal disease. Am J Kidney Dis 1998; **32**:S120–141.
33. Perloff D, Grim C, Flack J et al. Human blood pressure determination by sphygmomanometry. Circulation 1993; **88**:2460–2470.
34. Cheigh JS, Milite C, Sullivan JF, Rubin AL, Stenzel KH. Hypertension is not adequately controlled in hemodialysis patients. Am J Kidney Dis 1992; **19**:453–459.
35. Peixoto AJ, Santos SF, Mendes RB et al. Reproducibility of ambulatory blood pressure monitoring in hemodialysis patients. Am J Kidney Dis 2000; **36**:983–990.
36. Agarwal R, Lewis RR. Prediction of hypertension in chronic hemodialysis patients. Kidney Int 2001; **60**:1982–1989.
37. Agarwal R. Role of home blood pressure monitoring in hemodialysis patients. Am J Kidney Dis 1999; **33**:682–687.
38. Peixoto AJ, White WB. Ambulatory blood pressure monitoring in chronic renal disease: technical aspects and clinical relevance. Curr Opin Nephrol Hypertens 2002; **11**:507–516.
39. Covic A, Goldsmith DJ, Covic M. Reduced blood pressure diurnal variability as a risk factor for progressive left ventricular dilatation in hemodialysis patients. Am J Kidney Dis 2000; **35**:617–623.
40. Painter PL, Nelson-Worel JN, Hill MM et al. Effects of exercise training during hemodialysis. Nephron 1986; **43**:87–92.
41. Charra B, Laurent G, Chazot C et al. Clinical assessment of dry weight. Nephrol Dial Transplant 1996; **11**(suppl 2):16–19.
42. Jaeger JQ, Mehta RL. Assessment of dry weight in hemodialysis: an overview. J Am Soc Nephrol 1999; **10**:392–403.
43. McGregor DO, Buttimore AL, Nicholls MG, Lynn KL. Ambulatory blood pressure monitoring in patients receiving long, slow home haemodialysis. Nephrol Dial Transplant 1999; **14**:2676–2679.

44. Pierratos A, Ouwendyk M, Francoeur R et al. Nocturnal hemodialysis: three-year experience. J Am Soc Nephrol 1998; **9**:859–868.
45. Fagugli RM, Reboldi G, Quintaliani G et al. Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. Am J Kidney Dis 2001; **38**:371–376.
46. Luik AJ, van der Sande FM, Weideman P et al. The influence of increasing dialysis treatment time and reducing dry weight on blood pressure control in hemodialysis patients: a prospective study. Am J Nephrol 2001; **21**:471–478.
47. Rastogi SP, Volans G, Elliott RW et al. High dose frusemide in the treatment of hypertension in chronic renal insufficiency and of terminal renal failure. Postgrad Med J 1971; **47**(suppl):45–53.
48. Flanigan MJ, Khairullah QT, Lim VS. Dialysate sodium delivery can alter chronic blood pressure management. Am J Kidney Dis 1997; **29**:383–391.
49. Song JH, Lee SW, Suh CK, Kim MJ. Time-averaged concentration of dialysate sodium relates with sodium load and interdialytic weight gain during sodium-profiling hemodialysis. Am J Kidney Dis 2002; **40**:291–301.
50. Rocco MV, Flanigan MJ, Beaver S et al. Report from the 1995 Core Indicators for Peritoneal Dialysis Study Group. Am J Kidney Dis 1997; **30**:165–173.
51. Saldanha LF, Weiler EW, Gonick HC. Effect of continuous ambulatory peritoneal dialysis on blood pressure control. Am J Kidney Dis 1993; **21**:184–188.
52. Cice G, Ferrara L, D'Andrea A et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy. A prospective, placebo-controlled trial. J Am Coll Cardiol 2003; **41**:1438–1444.
53. Guerin AP, Blacher J, Pannier B et al. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 2001; **103**:987–992.
54. Efrati S, Zaidenstein R, Dishy V. ACE inhibitors and survival of hemodialysis patients. Am J Kidney Dis 2002; **40**:1023–1029.
55. Schiffrin EL. Vascular and cardiac benefits of angiotensin receptor blockers. Am J Med 2002; **113**:409–418.
56. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; **342**:145–153.
57. Kestenbaum B, Gillen DL, Sherrard DJ et al. Calcium channel blocker use and mortality among patients with end-stage renal disease. Kidney Int 2002; **61**:2157–2164.
58. Shibasaki Y, Masaki H, Nishiue T et al. Angiotensin II type 1 receptor antagonist, losartan, causes regression of left ventricular hypertrophy in end-stage renal disease. Nephron 2002; **90**:256–261.
59. Lindholm LH, Ibsen H, Dahlof B et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; **359**:1004–1010.
60. Agarwal R, Lewis R, Davis JL, Becker B. Lisinopril therapy for hemodialysis hypertension: hemodynamic and endocrine responses. Am J Kidney Dis 2001; **38**:1245–1250.
61. Agarwal R. Supervised atenolol therapy in the management of hemodialysis hypertension. Kidney Int 1999; **55**:1528–1535.

Index

Entries have been kept to a minimum under 'hypertension' and readers are advised to seek more specific entries.
Page numbers in *italics* denote illustrations and tables.

Abbreviations
  ACEIs – angiotensin-converting enzyme inhibitors
  ARBs – angiotensin II receptor antagonists
Adult Treatment Panel III
  classification for dyslipidemia *117*
  coronary heart disease prevention guidelines *119*
African American hypertension treatment 165–74
  blood pressure goals 167, *170*
  blood pressure responsiveness, factors influencing 171
    kidney function and proteinuria 171
    salt sensitivity 171
  drug selection 171–2
    diuretics 172
    monotherapy or combination therapy 171
    renin-angiotensin-aldosterone system inhibitors 172
  epidemiological considerations 166–7
    factors influencing blood pressure control 166–7
    hypertension control rates 166
    systolic importance in complications 166
  glomerular filtration rate estimates 167, 169, *169*
  hospitalized patients with chronic hypertension 173–4
  hypertensive urgencies and emergencies 172–3
  renal disease incidence *44*
  therapeutic considerations 167–71, *168*
    antihypertensive therapy rationale 167
    hypertension asymptomatic myth 167
    lifestyle interventions 170–1
    rapidity of blood pressure lowering 169–70
African–American Study of Kidney (AASK) Disease Trial
  microalbuminuria in nondiabetics 26
  nephropathy management 95
  proteinuria associated GFR decline 85
  renal insufficiency link to cardiovascular disease 47, *48*
age
  blood pressure changes *58*
  hypertension prevalence differences *40*
  see also children; older people, hypertension
albumin, role in pathogenesis of vascular disease 28
albuminuria *see* microalbuminuria (MA); proteinuria
alcohol restrictions, blood pressure control in African Americans 170
aldosteronism, primary, in pregnant patients 62, 185
alpha-blocker therapy
  in childhood hypertension 210
  renal benefits in hypertensive patients 51
  renal failure management 132–3
ambulatory blood pressure monitoring (ABPM) 202
  in dialysis patients 217–18
amiloride, renal failure management 131
anemia in kidney disease 83–4
  left ventricular hypertrophy association 83, *83*
aneroid gauge 12–13, *13*
angiotensin-converting enzyme inhibitors (ACEIs) 95–6
  adverse effects 135
  in African Americans 172
  childhood hypertension 210
  diabetes management 158
    type 1 patients with proteinuria 158
    type 2 hypertensive patients 80
  dialysis patients 221
  dyslipidemia management 33
  hypertensive urgencies treatment 148
  mechanism of action *107*, 107–8
  microalbuminuria management 32–3
  nephropathy management 95
    diabetic 80, 96
    hypertensive patients 48, *48*, *49*

angiotensin-converting enzyme inhibitors (ACEIs) *continued*
pregnancy contraindications 189
postpartum avoidance 193–4
renal changes *109*, 109–10, *113*
renal failure management 135
elimination characteristics 135, *136*
safety 110–12
angiotensin II, proposed interactions with insulin *160*
angiotensin II receptor antagonists (ARBs) 96
in African Americans 172
in childhood hypertension 210
diabetes management 158–60
type 2 hypertensive patients 80, 159
in dialysis patients 221
mechanism of action 107–8, *108*
microalbuminuria management 32–3
nephropathy management 96
diabetic 96
renal benefits in hypertensive patients 48, *49*
renal changes *109*, 109–10
renal failure management 135–7
elimination characteristics *136*
mode of elimination *136*
safety 110–12
antihypertensive therapy
dose adjustment in renal failure 127–38, *130*
drug combinations *99*, 99–100
ethnic differences in responses 165–6
glomerular filtration rate affects 95–6, *111*
management
African Americans *see* African American hypertension treatment
childhood hypertension 208–11, *209*
diabetes type 2 patients 80
diabetics *100*, 101, 158–61, *159*
dialysis patients 220–2
elderly patients 45–51, *48*, *49*, *50*
hypertensive urgencies *146*, 146–50
microalbuminuria 32–3
pregnant patients 187–92, *190*, *191*
proteinuria 98
renal insufficiency *100*, 101
see also older people, hypertension
monotherapy 98–9
patient compliance recommendations 93, *94*
postpartum in breastfeeding mothers 192–4
renal changes *109*, 109–10, *113*
selection of drug therapy 95–8, 171
stepped-care approach 99
see also individual drugs
antiplatelet therapy, diabetes management 161
apparent mineralocorticoid excess (AME), hypertension cause 206
Appropriate Blood Pressure Control Study of Diabetes (ABCD), normotensive studies 78, *79*
arterial stiffness, in kidney disease 215
Asian (South and East) hypertension and kidney 175–81
hypertension prevalence 177–8
management implications 179
renal disease
etiology *178*, *179*
prevalence 178–9
aspirin, diabetes management 161
atenolol
diabetes management 160
postpartum antihypertensive therapy 193
atherosclerosis
affect on blood pressure measurements *7*
diabetic 155–6
genesis *27*
microalbuminuria role *27*, 27–8
atherosclerotic vascular disease, risks in target-organ systems 74, *75*

beta-blocking drugs 97
in childhood hypertension 210
diabetes management 160
in dialysis patients 221
pregnant patient management 188–9
renal benefits in older hypertensive patients 50–1
renal failure management 133
elimination characteristics *133*
bile acid resin, hypercholesterolemia management 121
blood pressure
adverse effects due to 167
control 106–7
diabetics 157–61
dialysis patients 75–6, 84, 213–24, *215*
ethnic differences in responses 165–6
hypertension prevalence in dialysis patients *213*
influencing factors 166–7
lifestyle interventions 170–1
diastolic *see* diastolic blood pressure (DBP)
disturbed circadian rhythm 61–2, *62*
effect on cardiovascular mortality 72, *73*
goals *see* blood pressure goals
height relationships in children 198
measurement *see* blood pressure measurement
obesity relationship in children 198, 201, 205–6
rapidity of lowering 169–70
systolic *see* systolic blood pressure (SBP)
tracking from child to adult 202–3, *203*
blood pressure goals 91–103
African Americans 167, *170*
barriers to achievements 92–5, *93*
patient 93–4
physician and health care system 94–5
technical 92–3
diabetics 91–2, 158
hypertension in diabetes or renal insufficiency *92*

pregnant patients 187–8
treatment approaches 95–101
see also antihypertensive therapy
blood pressure measurement 3–23
accuracy 3, 4
assessment 17–18, *18*
barrier to achieving BP target 92–3
improvements 9, *9*
ambulatory monitoring (ABPM) 202, 217–18
children 8, 19, 201–2
cuff and arm circumference *5*, *6*
dialysis patients 216–19, *218*
equipment 12–16, *13*
aneroid gauge 12–13, *13*
automated oscillometric devices 201–2
calibration 14, *14*
electronic devices 13–14
inspection 5, 18
mercury manometer 12, *13*
standards 14
stethoscope *15*, 15–16, 16
hearing ability of medical practitioner 5
history 10
Korotkoff sounds 7–8, *12*
elevation methods 15–16
orthostatic hypotension testing 17
pregnant patients 187–8
problems *8*
technique 10–12
arm position 6
arm selection 6, *7*, 17
auscultatory gap recording *12*, 17
bell position 7
cuff position and pulse detection 6, *7*, 16–17, *17*
cuff selection 5, *6*, 15, 201
environment 11
manometer deflation 7
maximum inflation level (MIL) detection 16–17
medical practitioner position 11, *11*
patient position 5, 11, *11*
patient preparation 11–12
poor, barrier to achieving target 92–3
recording blood pressure 17, *18*
training and practice review 4–9
accuracy improvements 9, *9*
brachial artery palpation 16, *16*
breastfeeding mothers, antihypertensive therapy 192–4
bumetanide, renal failure management 131–2

calcium channel blockers (CCBs) 97
adverse effects 134–5
in childhood hypertension 210
diabetes management 160
diabetic nephropathy management 80, 97
in dialysis patients 221
dihydropyridine 97
cardiovascular effects 97
diabetic nephropathy management 97
hypertensive urgencies treatment 147
factors explaining differential effects on kidneys *97*
non-dihydropyridine 97
cardiovascular effects 97
postpartum antihypertensive therapy 193
pregnant patient management 189
renal benefits in hypertensive patients 50
renal failure management 133–5
elimination characteristics *134*
Canadian Normalization of Hemoglobin trial 83–4
captopril
diabetes management 160
oral, hypertensive urgencies treatment 148
cardiovascular disease (CVD)
epidemiology 72–4
left ventricular hypertrophy 84
microalbuminuria associated 25, 28–31, 31
predictors *43*
risk factors *74*
diabetes mellitus 78
in dialysis patients 216–17, *217*
hypertension 42, 75
in kidney disease patients 74–5, *75*, *118*
microalbuminuria 31–2, 74, 78–9, 85, 156, *156*
renal insufficiency 40–1, *42*, 47
thrombotic and inflammatory markers 84
risk reduction 71–90
anemia control 83–4
diabetics *78*, 78–81
glucose control vs blood pressure control *32*
homocysteine reduction 85–7, *86*, *87*
hypertension control 75–7
smoking cessation 82–3
systolic hypertension trials *47*
Caucasians, renal disease incidence *44*
Cerivastatin in Heart Outcomes in renal Disease: Understanding Survival (CHORUS) 120
children
blood pressure classification *19*
blood pressure levels for boys by percentiles of height *21–2*
heights for age percentiles *20*
hypertension *see* pediatric hypertension
overweight prevalence *201*
see also obesity in children
cholesterol, microalbuminuria associated changes 30
chronic kidney disease (CKD) *see* kidney disease, chronic
clonidine
hypertensive urgencies treatment 148
pregnant patient management 188
renal failure management 132–3

coarctation, affect on blood pressure measurements *7*
cold remedies, hypertensive cause 60
Collaborative Diabetic Nephropathy trial 112
coronary heart disease (CHD)
  in kidney disease patients
    assessment 120
    prevention guidelines 118–20, *119*
    risk factors *118*
  mortality due to blood pressure *73*
  see also cardiovascular disease (CVD)
coronary re-stenosis, decreased rated after homocysteine level reduction *85*, *87*
COX II inhibitors, hypertensive cause 60
creatinine
  antihypertensive therapy effects on serum levels 110–12, *112*
  renal function measure 128–9

Diabetes Control and Complications Trial (DCCT)
  dyslipidemia in type 1 diabetics 30
  glycemic control 157
diabetes mellitus 155–64
  blood pressure targets in hypertensive patients 91–2, *92*, 158
  childhood hypertension 208
  clinical trials 78, *79*
  hypertension treatment algorithm *100*, 101
  kidney disease 155
    cardiovascular disease risk reduction *78*, 78–81
    end-stage renal failure cause 78, 155
    mortality rates by severity of disease *74*
    treatment, ACEI vs ARB *48*
    treatment plan *81*, *121*, 156–62
  microalbuminuria 25, *34*
    cardiovascular disease predictor 31–2, 74, 78–9, 85, 156, *156*
    comorbid conditions 28–31
    hypertension 29
    nephropathy predictor 78–9, 156
    prevalence 26
    therapeutic intervention 32–3
  pathophysiology 155–6
    proposed interactions of insulin and angiotensin II *160*
  type 1
    hypertension management 158
    microalbuminuria pathophysiology 31
  type 2
    hypertension management 80, 159
    microalbuminuria pathophysiology 27–8, 31
    mortality rates 73–4
    proteinuria screening 85
  vascular and glomerular disease management 156–62, *157*
    antiplatelet therapy 161
    blood pressure control 157–61
    dietary protein restriction 161–2
    drug therapy 158–61, *159*
    glycemic control 157
    lipid control 161
    smoking cessation 161
dialysis patients
  anemia control 83–4
  blood pressure control 75–6, 84, 213–24
    variability in relationship with extracellular volume *215*
  blood pressure measurement 216–19, *218*
  dyslipidemia 81–2
  hypertension 75–6, 213
    blood pressure levels *219*
    management 219–22, *221*
    pathogenesis factors *214*
    prevalence *213*
  modality (peritoneal vs hemodialysis) choice 220
  mortality
    ethnic differences 179
    by systolic blood pressure and pulse pressure 76, *77*
  see also end-stage renal failure (ESRF)
diastolic blood pressure (DBP)
  cardiovascular disease predictor *43*, 72, *73*
  changes with age *58*
  mediator of therapeutic decisions 166
diet restrictions
  African Americans 170
  childhood hypertension 209
  diabetics 161–2
  see also salt restriction
diuretics 96–7
  African American hypertension treatment 172
  childhood hypertension 210
  diabetes management 160–1
  diabetic nephropathy management 80
  dialysis patients 220
  postpartum antihypertensive therapy contraindication 193
  pregnant patient management 189
  renal benefits in hypertensive patients 48, 50
  renal failure management 130–2
    loop diuretics 131
drug(s)
  accumulation 128
  antihypertensive *see* antihypertensive therapy
  clearance 128
  intolerance 59
dry weight 219–20
dyslipidemia
  classification *117*
  dialysis patients 81–2
  kidney disease patients 81–2, 117–25
    lipogenic drug usage limitations 123–4
    proteinuria reduction 123–4
    treatment 118–23, *121*, *122*

management 82
angiotensin-converting enzyme inhibitor (ACEIs) 33
of diabetic patients 161
microalbuminuria association 30–1
renal transplant recipients 124

Eastern Stroke and Coronary Heart Disease Collaborative Study 177
echocardiography, hypertension evaluation 208
eclampsia 185–6
elderly patients with hypertension *see* older people, hypertension
electrolyte abnormalities, secondary hypertension 61–2
enalaprilat, intravenous, hypertensive urgencies treatment 148
endothelial dysfunction
in diabetics 155–6
microalbuminuria association 27, 29–30
in preeclampsia 186
end-stage renal failure (ESRF) 155, 175
in Asians 178
blood pressure association with risk *44*
systolic blood pressure predictor 42–3, *44*, *73*
hypertension definition 216–17
impact on cardiovascular disease and mortality *217*
hypertension pathophysiology *214*, 214–16
arterial stiffness 215
erythropoietin use 215–16
hyperparathyroidism 216
renovascular disease 216
sleep apnea 215
sympathetic nervous system activation 214
management of hypertension *122*, 219–22, *221*
dialysis modality 220
drug therapy 220–2
lifestyle modifications 219
volume control 219–20
risk in diabetics 78, 155
see also kidney disease; renal failure
erythropoietin use, blood pressure increase in dialysis patients 215–16
essential hypertension 59
in children 205, 208
chronic in pregnant patients 184
ethnicity
antihypertensive therapy responses 165–6
hypertension prevalence differences *40*, 176–8
systolic blood pressure and renal disease *44*

fenoldopam mesylate, intravenous, hypertensive urgencies treatment 149–50
fibrates, hypertriglyceridemia treatment 123
folic acid, homocysteine reduction 85–7, *86*, *87*
furosemide, renal failure management 131–2

gender, hypertension prevalence differences *40*
genetic defects, in hypertension 206
gestational hypertension 187
glomerular disease, in diabetics 156, *157*
glomerular filtration rate (GFR)
antihypertensive therapy affects 95–6, *111*
estimation 128–9, 167, 169, *169*
systolic blood pressure affects 44, *45*
glomerular hypertension, role in producing structural renal damage *177*
glomerulosclerosis
avoidance 106
diabetic 155–6
see also kidney disease
glucocorticoid-remediable aldosteronism (GRA), hypertension cause 206
glycemic control, vascular disease reduction in diabetics 157
guanfacine, renal failure management 132–3

health care system, barrier to achieving blood pressure target 94
Heart Outcomes Prevention Evaluation (HOPE)
renal disease link to cardiovascular disease 72
renal insufficiency link to cardiovascular disease 40–1, *42*, 47
heights, blood pressure relationships in children 198
for age percentiles *20*
levels for boys by percentiles *21–2*, *199*
levels for girls by percentiles *200*
Hemolysis, Elevated Liver enzymes, Low Platelets (HELLP) 185–6
herbal preparations, hypertensive cause 60
homocysteine (HCY) in kidney disease, treatment of elevated levels 85–7, *86*, *87*
hospitalized patients, with chronic hypertension 173–4
hydralazine
hypertensive urgencies treatment 149
pregnant patient management 189
hyperaldosteronism
hypertension cause 65
primary
evaluation algorithm *65*
in pregnant patients 62, 185
hypercholesterolemia, treatment 120–2
hyperglycemia, in microalbuminuria 28
hyperinsulinemia, microalbuminuria association 29
hyperkalemia, drug-induced 110–12
risk factors *112*
hyperlipidemia *see* dyslipidemia
hyperparathyroidism, in kidney disease 216
hypertension
adverse effects related to blood pressure level 167

hypertension *continued*
asymptomatic, myth 167
atherosclerosis genesis role *27*
chronic, in hospitalized patients 173–4
distribution of subtypes by age *40*
drugs associated with onset *143*
drug therapy *see* antihypertensive therapy
essential *see* essential hypertension
gene defects 206
gestational (transient) 187
glomerular, role in producing structural renal damage *177*
historical aspects of risks 10
older people *see* older people, hypertension
prevalence
by age, gender and ethnicity *40*
Asians 177–8
in kidney disease stages *76*
renovascular *see* renovascular hypertension
resistant 58–9, *59*
secondary *see* secondary hypertension
stage 3 145–6
systolic *see* systolic hypertension
transient 187
uncomplicated 139
white coat 202
see also under individual conditions
Hypertension Detection and Follow-up Program (HDFP) 72, 75
hypertensive emergencies
African Americans 173
children 210–11
definition and examples *140*
diagnosis *144*
target-organ damage
diagnosis 144–5
signs and symptoms *141*
target-organ damage signs and symptoms *141*
Hypertensive Optimal Treatment (HOT) trial
cardiovascular disease (CVD) risk 72
diabetic patients 78
J-curve phenomenon 51
hypertensive urgencies 139–52
African Americans 173
definitions and examples 139–42, *140*
diagnosis *144*, 144–6
epidemiology and risk factors 142–4
outcomes 150
risk of lowering blood pressure 150
treatment *146*, 146–50
hypertriglyceridemia, treatment 122–3
hypokalemia 61

inflammatory markers, cardiovascular disease risk factor 84
insulin, proposed interactions with angiotensin II *160*
Irbesartan Diabetic Nephropathy Trial (IDNT) 79–80
nephropathy management 96
Irbesartan Microalbuminuria in Type 2 Diabetics (IRMA II)
nephropathy management 96
proteinuria in renal disease 79
ischemic heart disease (IHD), risk association with microalbuminuria *41*
isolated systolic hypertension (ISH) 45, 92

J-curve phenomenon 51

kidney disease
blood pressure targets in hypertensive patients *92*
cardiovascular disease risk factors 74–5, *75*, *118*
chronic (CKD)
anemia and left ventricular hypertrophy association *83*, 83–4
coronary risk equivalent 118, *118*
definition and stages *71*, 71–2
lipid disorders 117–25
management *121*
coronary heart disease *see under* coronary heart disease (CHD)
definition *71*, 71–2
diabetics *see under* diabetes mellitus
dyslipidemia *see under* dyslipidemia
homocysteine elevation treatment 85–7, *86*, *87*
hyperparathyroidism 216
hypertension association 39–41, 75, 176
treatment algorithm *100*, 101
incidence and systolic blood pressure *44*
left ventricular hypertrophy (LVH) and 76, 84
prevalence 178–9
of proteinuria and high blood pressure *76*
in stages *72*
proteinuria association *76*, 79–80, 156
renovascular hypertension 216
stages *71*
systolic blood pressure elevation in elderly *see under* older people, hypertension
see also renal failure
kidney function
antihypertensive therapy induced changes *109*, 109–10, *113*
determination 128–9
drug handling alterations 127–8
influence on blood pressure responsiveness 171
pulse pressure predictor 44, *44*
see also entries beginning with renal
kidney obstruction, hypertensive cause 60
Korotkoff (K) sounds 7–8, *12*
elevation methods 15–16

labetalol
hypertensive urgencies treatment 148–9
parental, pregnant patient management 189

left ventricular hypertrophy (LVH) 84
anemia association in kidney disease 83, *83*
cardiovascular disease (CVD) 84
in kidney disease 76, 84
lifestyle interventions in blood pressure control 170–1
dialysis patients 219
lipid control 117–25
in diabetics 161
see also dyslipidemia
lipogenic drug limitations in dyslipidemia 123–4
lipoproteins, cardiovascular disease associations 81–2
loop diuretics, renal failure management 131
losartan, blood pressure control in diabetics 159–60
Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) 96
type 2 diabetes mortality rates 73

magnesium sulfate, parental, preeclampsia management 192
mannitol, renal failure management 130–1
medical practitioners
barrier to achieving blood pressure target 94
hearing ability in blood pressure measuring 5
position during blood pressure measurement 11, *11*
mercury manometer 12, *13*
mesangial cell dysfunction, in diabetics 155–6
metabolic syndrome 27, 29
proteinuria 156
treatment 123
methyldopa
postpartum antihypertensive therapy 192–3
pregnant patient management 188
metoprolol, postpartum antihypertensive therapy 193
microalbuminuria (MA)
cardiovascular disease risk factor 31–2, 74, 78–9, 85, 156, *156*
clinical applications *31*, 31–2, 107
prognostic implications 25, 31–2
vascular risk assessment 31
clinical trials 26
comorbid conditions 28–31
definition 25, 26
diabetics *see under* diabetes mellitus
hypertension association 28–9, *34*
implications and measurements 25–37
ischemic heart disease (IHD) risk *41*
pathophysiology 27–31
associated processes *26*
atherosclerosis genesis *27*, 27–8
diabetic patients 27–8
endothelial dysfunction 27, 29–30
influencing factors *28*
prevalence 26
pulse pressure as predictor 44, *44*
screening 31
testing values for diagnosis *41*
therapeutic intervention 32–3
see also proteinuria
Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO-HOPE), nephropathy management 95
minoxidil, hypertensive urgencies treatment 149
Modification of Diet in Renal Disease (MDRD)
blood pressure control 44, *45*, 76, *77*
diabetic patients 161–2
Multiple Risk Factor Intervention Trial (MRFIT)
blood pressure prediction of renal failure 42–3, *44*
cardiovascular disease risks 72, *73*
myositis, dyslipidemia treatment adverse effect 82

nephropathy
algorithm for elderly patients 48, *50*
diabetic
management 48, 80, *81*, 96, 97
microalbuminuria prediction of development 78–9, 156
dyslipidemia 81–2
management 82
angiotensin-converting enzyme inhibitor 48, *49*, 95
angiotensin II receptor antagonists 96
hypertension control 76–7
nicardipine, intravenous, hypertensive urgencies treatment 149
nicotinic acid, hypercholesterolemia management 121–2
nifedipine capsules
hypertensive urgencies treatment 147
pregnant patient management 189–90
nitrate preparations, hypertensive urgencies treatment 149
nitroglycerine, hypertensive urgencies treatment 149
noncompliance 59–60
of patients 93, *94*
nonsteroidal antiinflammatory drugs (NSAIDs), hypertensive cause 60
Normalization of Hemoglobin study 83

obesity in children
blood pressure relationship 198, 201, 205–6
prevalence *201*
tracking into adulthood 202
obstructive sleep apnea
in dialysis patients 215
hypertension association 60
older people, hypertension 8
benefits of treatment 45–7
clinical trials 45–7

older people, hypertension *continued*
management 45–7, *46*
antihypertensive agent requirements *50*
antihypertensive selection 48, 50–1
renal failure-slowing strategies 47–8, *48*, *49*, *50*
proteinuria/albuminuria testing *41*
risk associations 42
cardiovascular disease 42, *43*
systolic pressure elevation in kidney disease patients 39–54
importance 42–5
isolated form 45
J-curve phenomenon 51

patient noncompliance, barrier to achieving blood pressure target 93, *94*
pediatric hypertension 8, 197–212
antihypertensive therapy 208–11, *209*
blood pressure measurement 8, 19, 201–2
causes 203–6, *205*
adolescents 205
infant/toddler 205
neonate 204–5
school-aged children 205
definitions 197–201
blood pressure classification *19*
blood pressure levels for boys by percentiles of height *21–2*, *199*
blood pressure levels for girls by percentiles of height *200*
systolic BP relationship to physical maturity markers *198*
diabetic patients 208
evaluation 206–8
family history 206–7
laboratory 207, *208*
physical 207, *207*
significant and severe levels *204*
symptoms *204*
tracking into adulthood 202–3, *203*
pheochromocytoma
hypertensive cause 60
in pregnant patients 185
physician, barrier to achieving blood pressure target 94
potassium-sparing diuretics, renal failure management 131
potassium wasting, inappropriate, evaluation algorithm *65*
preeclampsia 185
eclampsia 185–6
management 191–2, *193*
pathophysiology and prevention approaches 186
signs suggesting prompt delivery 191, *192*
superimposed 184, 187

pregnancy hypertensive disorders 183–96
blood pressure goals 187–8
blood pressure measurement 187–8
diagnosis and classification 183–7
chronic essential hypertension 184
gestational hypertension 187
preeclampsia-eclampsia 185–6
secondary hypertension 62–3, 184–5
superimposed preeclampsia 184, 187
management *193*
antihypertensive therapy 187–8
mild to moderate cases remote from delivery 188–9, *190*
oral antihypertensives *190*
preeclampsia 191–2
severe cases near to term 189–92, *191*
postpartum antihypertensive therapy 192–4
see also preeclampsia
proteinuria *42*
cardiovascular events and mortality risk factor 85, 156
influence on blood pressure responsiveness 171
kidney disease association 79–80, 156
prevalence in stages *76*
management 98
reduction in dyslipidemia 123–4
renal function loss mechanisms *110*
testing values *41*
see also microalbuminuria (MA)
pulse pressure 58
microalbuminuria and renal function predictor 44, *44*
mortality rates in dialysis patients *77*

radial artery palpation 16, *16*
Reduction of Endpoints in Non-insulin with the Angiotensin II Antagonist Losartan (RENAAL) study
nephropathy management 96
proteinuria in renal disease 80
type 2 diabetes mortality rates 73–4
renal artery disease, drug-induced 110
renal artery stenosis 62
management 95
medication discontinuation 95
renal autoregulation 106
renal clearance 127–8
renal damage
glomerular hypertension role *177*
progression to hypertension 175–6
renal disease *see* kidney disease
renal failure
acute, causes in India 178, *178*
chronic, causes in India 178, *179*
drug dose adjustments 127–38
criteria and influencing factors *130*
end-stage *see* end-stage renal failure (ESRF)

pharmacokinetics *129*, 129–30
strategies to slow progression in hypertension 47–8, *49*
renal function *see* kidney function
renal parenchyme disease 63, 176
blood pressure target 92
evaluation algorithm *63*
renal transplant recipients, specific therapy 124
renin-angiotensin-aldosterone system (RAAS) inhibitors 33, 105–7
African American hypertension treatment 172
mechanism of action 108
see also individual drugs
renovascular hypertension 63, *64*
evaluation algorithm *63*
in kidney disease 216
resistant hypertension 58–9
frequency of secondary causes *59*
rhabdomyolysis, dyslipidemia treatment adverse effect 82

salt restriction, for blood pressure control
in African Americans 170
in dialysis patients 219
salt sensitivity, influence on blood pressure responsiveness 171
secondary hypertension
causes 56–66, *57*
frequency in resistant hypertension *59*
historical features *57*, 57–60
hormonal 65, *65*
physical findings 60–1, *61*
in children 203
see also pediatric hypertension
clinical syndromes 62–3
definition 56
drug responses *59*
evaluation 55–68, *56*
algorithm for renal and renovascular hypertension *63*
indications 55–6, *56*
laboratory tests *66*
laboratory abnormalities 61–2
in pregnancy 62–3, 184–5
sleep apnea *see* obstructive sleep apnea
smoking cessation
African Americans 171
diabetics 161
smoking risks 82–3
in childhood hypertension 209
sodium nitroprusside, hypertensive urgencies treatment 149
spironolactone, renal failure management 131
statin therapy
in chronic kidney disease 120
hypercholesterolemia management 120–1
lipid control in diabetics 161
Study of Health Assessment and Risk in Ethnic groups (SHARE) 177
superimposed preeclampsia 184
sympathetic nervous system activation, in kidney disease 214
Syndrome X 27
see also metabolic syndrome
systolic blood pressure (SBP)
cardiovascular disease predictor *43*, 72, *73*
changes with age *58*
elevation in older patients *see under* older people, hypertension
end-stage renal failure predictor 42–3, *44*
glomerular filtration rate affects 44, *45*
mediator of blood pressure-related conditions 166
mortality rates in dialysis patients *77*
renal disease incidence in ethnic groups *44*
systolic hypertension
clinical trials 45–7
importance 42–5
isolated 45, 92
prevalence *46*
treatment 45–7
see also systolic blood pressure (SBP)
Systolic Hypertension in the Elderly Program (SHEP) 45–6
diuretic therapy 161
Systolic Hypertension in the Europe (Sys-Eur) 46

target-organ damage in hypertensive emergencies *see* hypertensive emergencies
thiazide 96–7
renal benefits in hypertensive patients 48, 50
renal failure management 131
thrombophilia 186
thrombotic markers, cardiovascular disease risk factor 84
torsemide, renal failure management 131–2
total body clearance (TBC) 127
tracking, high blood pressure 202–3, *203*
transforming growth factor-beta (TGF-beta), cardiovascular disease risk factor 84
transient hypertension 187
triamterene, renal failure management 131

ultrasound, hypertension evaluation 207
uncomplicated hypertension 139
United Kingdom Prospective Diabetes Study (UKPDS) 78
cardiovascular disease risk reduction *32*
glycemic control 157
type 2 diabetes mortality rates 73
United States Renal Data Service (USRDS), dialysis patient mortality 76

vascular injury and disease
  in diabetics 156, *157*
    management *see under* diabetes mellitus
  in microalbuminuria 27–8, 31
vasoconstrictive sympathetic agents, hypertensive cause 60

weight
  blood pressure relationship in children 198, 201, 205–6
  tracking from child to adult 202
weight loss
  blood pressure control in African Americans 170
  in childhood hypertension 209
white coat hypertension 202
Wisconsin Epidemiologic Study of Diabetic Retinopathy 72–3, *74*