THE YEAR IN HYPERTENSION, VOLUME 6

Hans Brunner
Editor

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EDITED BY

HANS BRUNNER

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Preface

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Hypertension is well recognized as one of the main causes of premature death; if it is not treated effectively, it causes multiple serious complications. Over the recent decades, hypertension has been the target of intense investigation and as a result considerable progress has been made in the understanding of the pathophysiology of blood pressure regulation and in the treatment of high blood pressure. Large sums of money have been spent in order to provide hard evidence from large groups of patients demonstrating an improved outcome due to blood pressure lowering therapy. This apparent success, however, has to be viewed with considerable scepticism, since the results in terms of improved general health of the population are much less impressive than one might expect. There are probably many reasons for this disappointing result which range from inadequate patient collaboration to a lack of perseverance of the treating physician, to a still less than complete understanding of the mechanisms involved in the pathogenesis of hypertension, to a decreasing interest in clinical investigation, all the way to a reduced interest in the hypertensive disease based on the false assumption that the problem has been solved with the means available today. It is indeed disturbing that still today in many developed countries the fraction of hypertensive patients who have their blood pressure normalized by adequate treatment is below 30 or even 20 per cent. As a consequence, many – far too many – hypertensive patients suffer enhanced morbidity and/or mortality which could readily be avoided with the means and knowledge available today. Hopefully, the present book with its chapters contributed by eminent experts in the field will enhance the interest of physicians in the clinical importance of hypertension in their daily practice.

Publicity is always given to the results of the large outcome studies since they provide what is commonly called **the** 'evidence' for 'evidence-based medicine'. Obviously, the practising physician has to keep up with the latest results of these mega-trials since they provide the framework on which up-to-date therapeutic strategies should be built. At the same time, it would seem important to keep in mind the limitations of these trials. Thus, the fact that they are almost exclusively financed by the pharmaceutical industry automatically implies that results have to become available within a time frame of only a few years while the patents of the drugs involved are still valid. As a result, mostly patients with a higher risk due to advanced age, associated disease, etc. are included. In contrast, there is very little 'evidence' available concerning younger patients with only slight blood pressure increases. Should they be treated aggressively? Can the further development of hypertension and its complications be

prevented? In this context, it would seem important to think about new strategies and new trial designs that may be able to provide long-term results in these less severe and younger hypertensive patients for whom the current approach provides little information. Of equal importance is the question of how the adherence to treatment by the patient, and the continued pursuit of blood pressure normalization by the treating physician, can be enhanced. Early discontinuation of therapy by the patient and inadequate perseverance by the physician are well-known and difficult-to-overcome obstacles on the way to a higher blood pressure normalization rate in hypertensive patients. This is potentially the aspect of hypertension management which could allow for the biggest gain in terms of decreases in morbidity and mortality involving a relatively small financial investment, but it necessitates commitment and time on the part of the physician which may not be adequately reimbursed by the insurance companies.

The kidney plays a central role in hypertension, firstly as a regulator of blood pressure via its excretory function and the secretion of renin and possibly other vasoactive substances, but at the same time it is one of the principal targets of the destructive force of an increased blood pressure. This double role of the kidney can easily result in a vicious circle, i.e. renal damage increases blood pressure and this in turn further enhances renal damage with rapid progression to terminal renal failure. Measurement of renal function, excretion, filtration, blood perfusion, renin secretion, etc. has therefore always been an important means to assess the severity of hypertension. In more recent years, it has also become evident that some treatment strategies can exert particular protective effects on the kidney and thereby prevent or at least retard the progression to renal failure. Three chapters are dedicated to bringing the reader up to date on the renal involvement in hypertension with special reference to the growing problem of diabetic nephropathy and the metabolic syndrome.

The heart being the target organ of hypertension has probably attracted the most attention over recent years. There is today little doubt that any increase in blood pressure is detrimental to the heart and that consequently blood pressure normalization is an absolute requirement for protecting the myocardium. Recent investigations have focused much more on differential cardioprotective effects of various antihypertensive therapies. An excellent chapter reviews the recent additional evidence emphasizing the importance of blocking the renin–angiotensin system in addition to reducing blood pressure. Important new information on interfering with other regulatory systems such as the sympathetic nervous system is also reviewed. Closely interconnected with the heart and also a primary target, the vascular tree has become the focus of intense investigation, *in vitro* and *in vivo*. Endothelial dysfunction and arterial stiffness are well-recognized alterations associated with the hypertensive diseases. Much more difficult to establish is the causality between these functional and morphological changes and hypertension. How much they are primary defects contributing to the pathogenesis of hypertension or rather secondary sequels of the disease process is still debated. The newest information on this aspect of hypertension is provided in a separate chapter.

A fascinating topic is the involvement of the sympathetic nervous system in the

pathogenesis of hypertension. This topic has been investigated and debated for decades, since the sympathetic nervous system appeared *a priori* as the primary suspect causing the blood pressure elevation in hypertensive patients. This view was strongly supported by the demonstration of the efficacy of the early antihypertensive agents all of which, with the exception of the diuretics, interfered either centrally or at the periphery with the sympathetic nervous system. Interestingly, it has turned out that the role of the sympathetic nervous system in the pathogenesis of hypertension is much more complex and difficult to understand than initially anticipated. An excellent chapter deals with new findings reported in this interesting area. In this context, it should be kept in mind that the sympathetic nervous system remains a proven target for potential new antihypertensive agents if the side effects that accompanied the older compounds can be reduced or completely eliminated.

It has long been recognized that hypertension runs in families and consequently the existence of some hereditary component to its pathogenesis has been generally accepted. However, this knowledge was of little use to the practising physician since there was no method to quantify the genetic contribution to the development of hypertension. The development of the new molecular and genetic methodologies and the elucidation of the human genome radically changed all this. Indeed, in an initial enthusiasm, some thought that the genetic background of hypertension will now become clear and easy to determine in every individual patient. Perhaps not surprisingly, it has turned out much more complicated to characterize the many genes and their precise role involved in raising the blood pressure. The illusion of a unique gene responsible for essential hypertension has clearly turned out to be wrong even though some very rare monogenetic forms of hypertension exist. Notwithstanding all the difficulties still present, one must nevertheless anticipate that in the future some important information that can be clinically applied to the management of hypertensive patients will result from the ongoing genetic research. For this reason, it seems important also for clinicians to keep up to date on ongoing research in the area. This is exactly the goal of the chapter reviewing the genetics of hypertension.

An exciting development is also that of new imaging techniques for an improved diagnostic work-up of hypertensive patients. This area has seen a tremendous development over recent decades that has resulted in diagnostic precision hitherto not thought to be possible with the simultaneous reduction or elimination of invasive procedures. There is obviously no end to this ongoing endeavour, and the information provided in a dedicated chapter should be of utmost interest to any clinician involved in the management of hypertensive patients.

Children and adolescents represent a very special population of hypertensive patients. Even if hypertension is much less frequent in this age group than in adults and specially elderly adults, it would seem particularly important to have a good understanding of the disease process in this age group and particularly to have clear work-up and treatment strategies. Unfortunately, for the same reasons already outlined above, there has been very little incentive to conduct well-controlled trials in paediatric patients. This shortcoming has been identified, and the FDA has intro-

duced some new rules that may hopefully change the situation. At the moment, physicians are often hesitant as to what to do with an adolescent who exhibits slight increases in blood pressure. *A priori*, one would think that a long-term investment in pharmacologic prevention should never be as rewarding as in a young person. On the other hand, it is true that the absolute short-term risk associated with zero treatment is rather low. To answer these important practical questions, an excellent chapter on the topic reviews the recent findings, and it is hoped that this chapter provides particularly helpful support for the practising physician in a difficult area.

Two more chapters should be of direct practical relevance since they review aspects in hypertension management known in recent years to have caused much emotional debate that has left the physician without any or with only partial answers to difficult questions. On the one hand, it is the question of whether and when hypertensive women should take hormone replacement therapy and, on the other, whether and when non-steroidal anti-inflammatory agents can be used in hypertensive patients. Whilst from a theoretical point of view it may be easy to answer both questions with a clear 'never', the decision has to be much more subtle when being confronted with the various complaints of a given patient. Both chapters provide comprehensive reviews of the newest research on these difficult topics and they should help the practising physician in his difficult therapeutic decisions.

The Year in Hypertension Volume 6 is an excellent collection of particularly important topics, published over the past year and discussed by eminent experts. It is a book to be kept close to hand for quick reference by the clinician who has to take daily decisions concerning the difficult long-term management of hypertensive patients.

Part I

Clinical management

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1

Recent hypertension trials

SVERRE KJELDSEN, STEVO JULIUS, OLE PEDERSEN, ÖYVIND STÖRSET

Introduction

A lively debate has been going on for several years about whether the mortality and morbidity benefits of treating hypertension with pharmacotherapy can be attributable exclusively to the reduction in risk from lowering blood pressure *per se,* or whether certain drugs confer additional cardiovascular benefits owing to effects not directly associated with their antihypertensive efficacy |**1,2**|. In particular, the claims that interfering with the renin–angiotensin system might be beneficial in patients at risk has been widely publicised and discussed. Studies such as CAPPP (Captopril Prevention Project), |**3**| HOPE (Heart Outcomes Prevention Evaluation) |**4**| and EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) |**5**| have claimed benefits for angiotensin-converting enzyme inhibitors not related to blood-pressure lowering, and the LIFE (Losartan Intervention For Endpoint reduction in hypertension) trial |**6**| reported greater beneficial effects on stroke from the angiotensin receptor blocker losartan than from the comparator substance, the β-blocker atenolol. However, not all trials claiming benefits were blood-pressure trials. Several compared active treatment with placebo, and in others it is unclear to what extent the effects were benefits from the inhibitor of the renin–angiotensin system rather than negative influences of the comparator substances. For example, in the LIFE trial losartan was associated with a lower risk of new-onset diabetes than atenolol, but as β-blockers are suspected to decrease insulin sensitivity the contributions of the respective drugs could not be established with certainty.

The one landmark hypertension trial reporting in 2004 was an ambitious large-scale attempt to tackle this question. The Valsartan Antihypertensive Long-term Use Evaluation Trial of Cardiovascular Events in Hypertension (VALUE) compared the effects of valsartan, an angiotensin receptor blocker, with those of amlodipine, a calcium channel blocker, in a population of over 15 000 hypertensive patients selected for high risk of cardiac events. The primary objective of the VALUE trial was, at the same level of achieved blood pressure, to compare the long-term effects on the incidence of cardiac morbidity and mortality of valsartan-based antihypertensive therapy with the effects of amlodipine-based therapy. The focus of VALUE was on cardioprotection, and all components of the primary end-point were cardiac events. Stroke,

which is widely agreed to be closely linked to blood pressure, was a secondary end-point. VALUE was an investigator-designed, prospective, multinational, multicentre, double-blind, randomized, active-controlled, parallel group trial |**7**|.

Amlodipine, the comparator in VALUE, is an effective antihypertensive agent with possible anti-ischaemic effects. In contrast to the effects of valsartan and other inhibitors of the renin–angiotensin system, amlodipine has been shown to increase sympathetic activity |**8,9**|. Further, in contrast to atenolol, amlodipine has a neutral effect on insulin resistance |**10**| and no effects on the development of type 2 diabetes. Such effects, which were possible confounders in LIFE, were unlikely in VALUE.

The study population consisted of patients 50 years or older, with treated (92% of patients) or untreated hypertension at baseline and predefined combinations of cardiovascular risk factors and cardiovascular disease. The qualifying risk factors were male gender, age greater than 50 years, verified diabetes mellitus, current smoking, high total cholesterol, left ventricular hypertrophy by electrocardiogram, proteinuria on dipstick and elevated serum creatinine (between 150 and 265 μmol/l; 1.7 and 3.0 mg/dl). The qualifying diseases were verified coronary disease, cerebrovascular disease or peripheral arterial occlusive disease, or left ventricular hypertrophy with strain pattern.

The primary end-point was time to first cardiac event (a composite of sudden cardiac death, fatal myocardial infarction, death during or following percutaneous coronary intervention or coronary artery bypass graft, death due to heart failure and death associated with recent myocardial infarction on autopsy, heart failure requiring hospital management, non-fatal myocardial infarction or emergency procedures to prevent myocardial infarction). Prespecified secondary end-points were fatal and non-fatal myocardial infarction, fatal and non-fatal heart failure and fatal and non-fatal stroke. Analyses of all-cause mortality and new-onset diabetes were also pre-specified.

The study was end-point-driven; 1450 patients with a primary event were required to provide 90% power to detect a 15% reduction in the primary end-point rate from 12.5 to 10.63% with 14 400 patients. All end-points and blood-pressure values were analysed using the intention-to-treat approach.

Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial

Julius S, Kjeldsen SE, Weber M, *et al.*; VALUE trial group. *Lancet* 2004; **363**: 2022–31

BACKGROUND. This article presents the main results from the VALUE trial, published simultaneously with an oral presentation of the trial at the 14th meeting of the European Society of Hypertension in Paris, France, in June 2004.

INTERPRETATION. A total of 15 245 randomized patients were included in the analysis. The majority of patients (92%) were receiving antihypertensive therapy at the time of

enrolment. The two treatment groups were similar in demographic characteristics, severity of hypertension, antihypertensive drug usage prior to enrolment, and prevalence of coexisting cardiovascular conditions. Only 90 patients (0.6%) were lost to follow-up. The mean duration of exposure to study medication was 3.6 years in both treatment groups. The study accumulated 63 631 patient-years of follow-up. The median daily doses were 151.7 mg of valsartan and 8.5 mg of amlodipine. The majority of patients in both groups were on combination treatment by the end of the trial. Fewer patients in the valsartan-based group (27.0%) than in the amlodipine group (35.3%) remained on monotherapy during the course of the study.

Blood-pressure control rates (defined as target blood-pressure levels below 140/90 mmHg) were 56% of patients in the valsartan group and 62% of patients in the amlodipine group. However, particularly during the first 6 months of the trial – the treatment-adjustment period – the degree of blood-pressure reduction was greater in the group receiving an amlodipine-based regimen (Fig. 1.1). Differences in systolic/diastolic blood pressure were 4.0/2.1 mmHg after 1 month and were reduced to 1.5/1.3 mmHg after 1 year ($P < 0.001$ between groups).

In spite of these differences in blood pressure, the primary outcome of composite cardiac end-points did not differ between the valsartan and amlodipine groups (Fig. 1.2). The primary composite end-point occurred in 810 patients in the valsartan arm (10.6%; 25.5 per 1000 patient-years) and in 789 in the amlodipine group (10.4%; 24.7 per 1000 patient-years) (hazard ratio 1.04; 95% confidence interval [CI] 0.94–1.15; $P = 0.49$). All-cause death occurred in 841 and 818 patients (hazard ratio 1.04; 95% CI 0.94–1.14; $P = 0.45$) in the valsartan and amlodipine groups, respectively. Of the secondary end-points, myocardial infarction occurred in 369 and 313 patients (hazard ratio 1.19; 95% CI 1.02–1.38; $P = 0.02$), although it should be noted that this was due to lower rates of non-fatal events with amlodipine (hazard ratio 1.22; 95% CI 1.04–1.44; $P = 0.02$) and that the rates of fatal events were not different between the treatment groups (hazard ratio 1.04; 95% CI 0.74–1.47; $P = 0.81$). Hospitalization because of heart failure occurred in 354 and 400 patients (hazard ratio 0.89; 95% CI 0.77–1.03; $P = 0.12$) and because of stroke in 322 and 281 patients (hazard ratio 1.15; 95% CI 0.98–1.35; $P = 0.08$). Notably, new-onset diabetes developed in 690 patients on valsartan-based and in 845 patients on amlodipine-based regimens (odds ratio 0.77; 95% CI 0.69–0.86; $P < 0.0001$).

The Kaplan–Meier curves for the primary end-point (Fig. 1.2) separated during the first 6 months, but thereafter started to converge and towards the end of the study the two curves overlapped. The Kaplan–Meier curves for myocardial infarction separated during the first 6 months and remained separated in favour of amlodipine throughout the trial. The curves for hospitalization for heart failure separated after 36 months with a trend in favour of valsartan-based regimens. For stroke (fatal and non-fatal), the Kaplan–Meier curves separated early in favour of amlodipine-based regimens, with later parallel slopes. The curves for total mortality separated early but converged later in the trial.

The early differences in blood pressure appeared to have influenced the overall outcomes. During the treatment-adjustment period (the first 6 months of the trial), odds ratios tended to favour amlodipine-based treatment for all end-points. This corresponded to the time of greatest differences in blood pressure between treatments. As blood-pressure differences diminished during the following months, odds ratios became smaller. For the end-point of heart-failure hospitalization, there was a trend in favour of valsartan during the last 4 years.

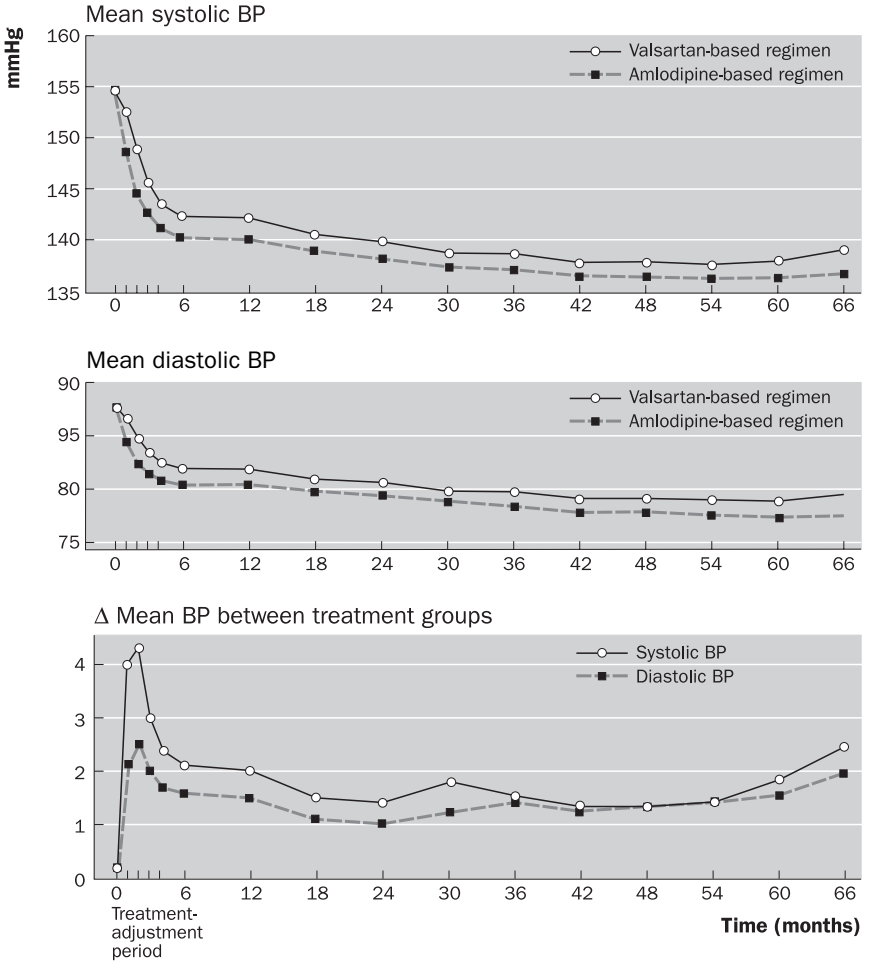

Fig. 1.1 Systolic and diastolic blood pressure and differences (valsartan–amlodipine) in blood pressure between the treatment groups during the treatment-adjustment period and follow-up. Source: Julius *et al*. (2004).

Tolerability was good in both groups, but the most common adverse event, oedema, including peripheral oedema, was twice as common in amlodipine-treated patients as in valsartan-treated patients. Hypokalaemia was more frequent in the amlodipine group. Although of low frequency, dizziness, headache and diarrhoea were more frequently reported in patients on valsartan-based regimens. Discontinuation rates from adverse events were significantly lower with valsartan-based treatment (13.4% compared with 14.5% for amlodipine; $P = 0.045$). Potassium decreased in patients randomized to

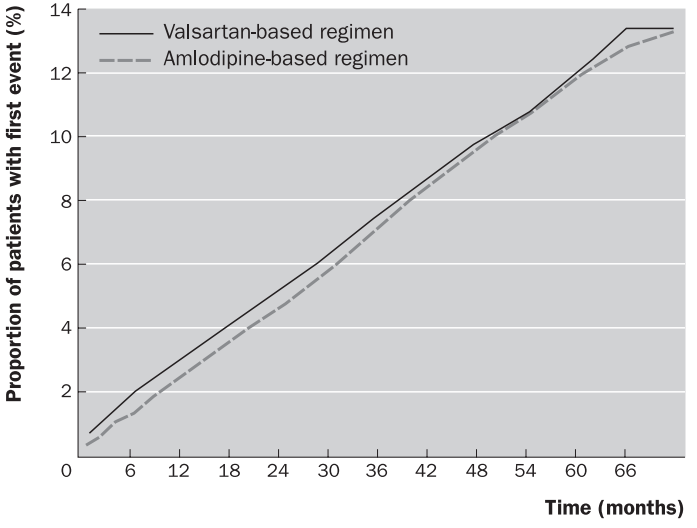

Fig. 1.2 Kaplan–Meier curves for primary composite end-point. Source: Julius *et al*. (2004).

amlodipine and remained stable in the valsartan group. Serum creatinine increased with time in both treatment groups but the increase was larger in the valsartan-based treatment group.

Comment

In the VALUE trial, the main outcome of cardiac disease did not differ between the valsartan and amlodipine groups, despite unequal blood-pressure reductions, particularly early in the study. Such differences are not uncommon in double-blinded clinical trials and have confounded the analyses of studies such as ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) |**11**| and HOPE |**12**|. In the VALUE trial, the differences might explain differences between the groups in cause-specific outcomes on secondary end-points.

VALUE was a clinical trial designed to test a specific hypothesis and the treatment regimen given does not correspond to what would be used in clinical practice. A large proportion of the high-risk patients in the VALUE trial were on multiple antihypertensive therapies and, knowing the outcome of the VALUE trial, we can state that such patients should not be taken off their previous drugs and rolled over immediately onto low-dose monotherapy, whether with amlodipine or valsartan.

Thus, although the results of the VALUE trial emphasize the importance of prompt blood-pressure control in high-risk patients, this conclusion refers to already-treated, high-risk patients of the kind enrolled in this trial. These conditions will often require combination therapy from the outset |**13,14**|. Firm conclusions as to the best therapy

for previously untreated patients, or for patients at lower cardiovascular risk, cannot be drawn from the main VALUE outcomes. Furthermore, although the doses of amlodipine corresponded to those given in clinical practice, the doses of valsartan in the VALUE trial were lower than that which is currently considered optimal in high-risk patients |**15**|. Valsartan doses of 160–320 mg are now recommended in the USA and are associated with more complete blockade of the renin–angiotensin system.

Nevertheless, blood-pressure control rates in the VALUE trial were among the highest reported for an outcome trial: 56% of patients in the valsartan group and 62% of patients in the amlodipine group reached target blood-pressure levels below 140/90 mmHg. These numbers should be viewed in the light of the fact that although 92% of patients were treated for hypertension at baseline, and many received more than one drug, only 22% had their blood pressure controlled at that time.

The rates of non-fatal myocardial infarction were lower with amlodipine-based therapy than with valsartan-based therapy, but rates of fatal myocardial infarction were identical in both treatment groups. A possible explanation for this is that treatment with amlodipine, which has anti-anginal properties, may have led to masking of anginal episodes and consequent under-reporting of silent, non-fatal myocardial infarctions.

The trend towards reduced heart failure with valsartan is consistent with what has been observed in other studies with renin–angiotensin system-inhibiting agents. The Kaplan–Meier curves started to separate after 3 years, which is very similar to the curves for heart failure with lisinopril compared with amlodipine in the ALLHAT trial |**11**|. The VALUE findings are more robust than those of ALLHAT, as all endpoints were adjudicated.

The reduction in new-onset diabetes with valsartan in the VALUE trial supports and extends earlier findings from angiotensin receptor blocker trials, such as LIFE |**6**| and SCOPE (Study on Cognition and Prognosis in the Elderly) |**16**|. It is notable that the VALUE trial is the first demonstration of benefits in the prevention of diabetes with an angiotensin receptor blocker compared with a metabolically neutral antihypertensive agent, and the results support an active beneficial effect of valsartan rather than a negative effect of the comparator agent. Although many patients in both groups received hydrochlorothiazide, the protective effects of valsartan appear to have been greater than any possible adverse effects of the diuretic.

At first sight, the rates of adverse events in the VALUE trial seem somewhat higher than those reported previously for these drugs. This is explained by the high-risk status of the hypertensive population and the widespread use of antihypertensive therapies additive to the primary treatments in both patients groups. The overall tolerability of the valsartan-based treatment regimen was greater than that of the amlodipine-based regimen, based on discontinuation rates from adverse events. Since antihypertensive treatments are given for life, tolerability profiles and the possibility of high patient persistence rates over the long term are important considerations for therapies, together with blood-pressure control and cardiovascular protection.

Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial

Weber MA, Julius S, Kjeldsen SE, *et al. Lancet* 2004; **363**: 2049–51

BACKGROUND. This companion paper to the main VALUE publication presents an attempt to explore further the correlation between early blood-pressure response and outcomes in the trial population.

INTERPRETATION. Three analyses were carried out:

1. Since the VALUE trial was designed to achieve control of blood pressure by 6 months, it was assessed whether reaching this goal affected outcomes for each of the drug groups. The hazard ratios for subsequent clinical events in patients whose blood pressure was controlled (systolic <140 mmHg by 6 months) were compared with those for patients who were not controlled, within each group. In both groups, control of blood pressure was a powerful determinant of end-points. The differences between the treatment groups were negligible and the data could be pooled to show the overall role of control of blood pressure in optimizing outcomes in these patients. The hazard ratio for the primary composite end-point for patients controlled at month 6 compared with non-controlled patients was 0.75 (95% confidence interval 0.67–0.83) (Table 1.1).
2. A second analysis focused on the differences in event rates between patients with systolic blood pressure higher than 160 mmHg by 1 or 6 months of treatment in the two treatment groups. Event rates in these uncontrolled patients in the valsartan and amlodipine groups were, respectively: at 1 month, 12.1% of 2456 and 12.3% of 1725 for the combined cardiac end-points; 5.4 and 5.0% for stroke; and 12.7 and 13.7% for death; at 6 months, 11.7% of 951 and 11.5% of 601 for the combined cardiac end-points; 5.9% of 953 and 7.0% of 603 for stroke; and 12.4% of 964 and 15.5% of 606 for death. Event rates during the remainder of the study for patients in this hypertensive stratum were similar in the valsartan and amlodipine arms.
3. The hypothesis of the VALUE trial was based on patients being controlled after 6 months of initial treatment adjustment. In an attempt to test the hypothesis in a controlled population, a technique of serial median matching was applied to the data set at 6 months. The method selected the most median patient (based on systolic blood

Table 1.1 Hazard ratios for events in controlled compared with non-controlled patients

End-point	Hazard ratio (95% confidence interval)
Fatal and non-fatal cardiac events	0.75 (0.67–0.83)
Fatal and non-fatal stroke	0.55 (0.46–0.64)
All-cause death	0.79 (0.71–0.88)
Myocardial infarction	0.86 (0.73–1.01)
Hospitalizations for heart failure	0.64 (0.55–0.74)

Source: Weber *et al*. (2004).

pressure) within the valsartan group and paired this patient with one from the amlodipine group matched for systolic blood pressure (within 2 mmHg), age, sex and the presence or absence of previous coronary disease, stroke and diabetes. The process was repeated until all eligible patients were included. In this way, 5006 comprehensively matched valsartan/amlodipine cohort pairs (a total of 10 012 patients) were created, with a mean systolic blood pressure of 139.9 mmHg in each treatment group. When the primary and secondary outcomes in this population were analysed (Fig. 1.3), there was a non-significant trend ($P = 0.11$) favouring valsartan for the composite primary end-point, whereas the secondary end-points myocardial infarction and stroke, and all-cause death were neutral. However, for heart-failure hospitalizations the outcome significantly favoured the group receiving valsartan-based therapy.

Comment

The early blood-pressure differences between treatment groups in the VALUE trial made the overall results difficult to interpret. This paper represents further data on the importance of blood-pressure control in the trial, together with an attempt to test the original study hypothesis in a controlled population. The analysis of risk of events in patients controlled versus uncontrolled at month 6 showed clearly that, regardless of drug type, event rates were very similar in these patients. Thus, achieved blood pressure rather than drug type was the main determinant of event rates in the high-risk population in the VALUE trial. This conclusion was reinforced by the analyses of the differences in event rates between patients with systolic blood pressure higher

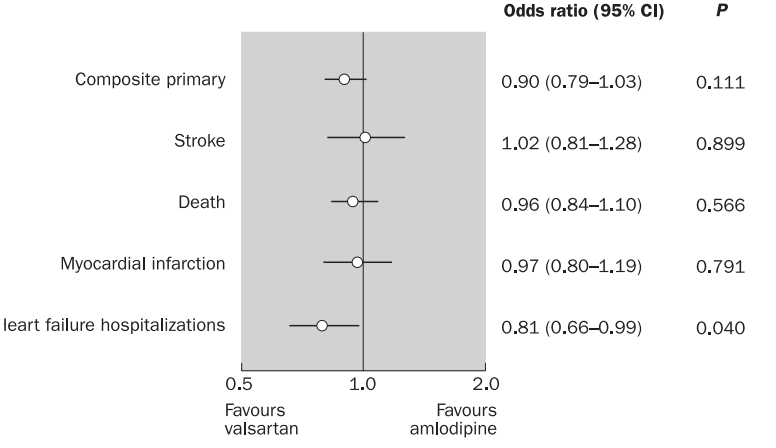

Fig. 1.3 Hazard ratios for major study end-points in patients on valsartan- or amlodipine-based therapies for events occurring after a baseline translocated to the 6-month point of the trial and after treatment adjustment designed to achieve blood-pressure control. Data are shown for 5006 treatment cohort pairs matched by systolic blood pressure, age, sex and the presence or absence of prior coronary disease, stroke and diabetes. Source: Weber *et al*. (2004).

than 160 mmHg by 1 or 6 months of treatment in the two treatment groups. Event rates in these uncontrolled patients were similarly high in the valsartan and amlodipine groups, both at 1 month and at 6 months. These findings provide evidence to validate the target recommendation (140/90 mmHg) and the aggressive initiation of therapy recently emphasized in hypertension guidelines from both Europe and the USA for this high-risk population.

The technique of serial median matching represents a novel way of dealing with blood-pressure differences between treatment groups. The technique is not perfect: in the VALUE trial it was a *post hoc* analysis and the population was selected for blood-pressure control. Still, in a large-scale trial such as VALUE, the population available for the matched-pair analysis is substantial (in excess of 10 000 patients or more than two-thirds of the VALUE population) and the results are very intriguing. The analysis indicated that, if blood pressure is controlled, valsartan-based therapy is associated with a reduced risk of hospitalization for heart failure, and is otherwise closely similar to amlodipine for other cardiovascular end-points.

As this is the first time such a method has been applied to a large population, it needs validation from other trials. Thus, the method should be considered in plans for new studies, and perhaps even tested in previously reported studies with substantial blood-pressure inequalities.

Conclusion

The overall outcome of the VALUE trial was neutral and the trial did not provide a definitive answer to the question of benefits from blood-pressure lowering drugs beyond the antihypertensive effects. However, the trial provided a wealth of information that is only beginning to be analysed and interpreted. The VALUE trial established beyond doubt that treatment with angiotensin receptor blockers, or at least valsartan, has the potential actively to reduce new-onset diabetes. Further, in high-risk patients, controlling blood pressure is of overarching importance in reducing the risk of cardiovascular events. Once blood pressure is controlled, inhibition of the renin–angiotensin system appears to have beneficial effects on the risk of developing heart failure. More trials would be needed to clarify whether the risk of non-fatal myocardial infarction is reduced solely by effects on blood pressure, and what lies behind the differences between treatment groups in the VALUE trial.

The VALUE trial further supported the treatment of high-risk patients with combination therapies. It is clear that the initial therapies in the study algorithm were too timid for these patients and that no patients receiving multiple therapies should be rolled over to low-dose monotherapy on any drug. The combination of valsartan and hydrochlorothiazide has long been used successfully and, although the VALUE protocol did not allow it, adding amlodipine or a different calcium channel blocker to such a cocktail might well bring additional benefits in high-risk individuals.

The technique of serial median matching introduced by the VALUE investigators is an imaginative approach to dealing with blood-pressure differences between treatment

groups. If this technique is validated in other trials and perhaps applied to studies that have already been concluded, such as ALLHAT, it might become a valuable tool for future research and help to bring us closer to an understanding of blood-pressure-independent effects of therapies.

Future prospects

Outcome data from the blood pressure intervention part of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) were presented at the 54th Scientific Session of the American College of Cardiology on 8 March 2005 and full articles |**17,18**| came out in early September 2005. ASCOT has been a large randomized trial with more than 19 000 hypertensive patients in Scandinavia, UK and Ireland. Randomization was successful and the two treatment arms were very well balanced at the outset. After more than 100 000 patient-years, treatment with the combination of the calcium channel blocker amlodipine plus the angiotensin-converting enzyme inhibitor perindopril was associated with highly significantly reductions in total mortality, all cardiovascular events, all coronary events, strokes and new-onset diabetes than those after treatment with atenolol combined with bendroflumethiazide. Though the importance of somewhat lower blood pressure throughout the trial in the amlodipine–perindopril arm is discussed |**18**|, it seems obvious that combination of the calcium channel blocker with an inhibitor of the renin–angiotensin system (in the case of the ASCOT study the angiotensin-converting enzyme inhibitor perindopril) appears to be a powerful treatment in the prevention of cardiovascular complications and new-onset diabetes in patients with hypertension.

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2

New strategies for future clinical trials in hypertension

TREFOR MORGAN

Introduction

In the last 5 years, billions of dollars (or euros) have been spent on clinical trials of drugs to be used in hypertension. Despite this large expenditure, the major problems that face us in the management of hypertension have not been resolved |**1,2**|. Our aim is surely to determine how to manage a person with hypertension so that we return the prognosis to that of a normal person. Treatment does improve prognosis (morbidity and mortality) |**3,4**| but treated hypertensive patients still have a higher mortality from cerebral and cardiovascular disease. The problem is that a high proportion of the money spent on clinical trials is to satisfy regulatory requirements or to promote the sale of a new drug rather than to address important problems. To achieve these aims successfully, studies are performed in selected groups of patients and comparisons are made with other drugs which are likely to be inferior.

Efficacy of drugs in lowering blood pressure

The most recent major drug class to be studied is angiotensin type 1 receptor blockers (ARBs). Data from placebo-controlled studies or studies comparing the effect of a drug with that of another drug claim a response rate of up to 80 or 90% and achievement of control in up to 50% or more patients |**5–10**|. This statement is true for the group selected. The studies are usually performed on patients who have been treated previously. Most patients entered in these studies will usually have had their blood pressure controlled on one or two drugs. There is evidence that people who respond well to one drug show a higher response rate to other drugs. In addition, in many patients an angiotensin-converting enzyme inhibitor (ACEI) will have been stopped, and as in general these patients also respond to an ARB the response rate is artificially high. Likewise, when comparison is made with another drug it is critical that there should be no bias in the medication stopped. Most studies do not state what drugs have been stopped.

Studies by Morgan *et al.* |**11**| and Deary *et al.* |**12**| in patients not previously treated for hypertension show a much lower response rate to all classes of drugs. Monotherapy, even when the best drug is selected by sequential monotherapy, achieves

control in fewer than 30% of people. In these two studies there was an important dichotomy in response to the different classes of drugs (Table 2.1). The study by Morgan *et al*. |**11**| performed in patients older than 65 years with systolic hypertension showed that response rates decreased in the following descending order: dihydropyridine calcium blockers, thiazide diuretics, ACEI and β-blockers (Table 2.1). In the study by Deary *et al*. |**12**| in people younger than 55 years, the response pattern in descending order was: ACEI, β-blockers, calcium blockers and diuretics. Thus, results in efficacy studies in which comparisons are with placebo or other drugs will depend upon the agent stopped and the age group chosen, and this is rarely taken into account.

Outcome studies

To successfully launch and market a drug, it is important to show that prognosis is improved compared with placebo and, more recently, compared with other drugs. These studies are usually performed in older patients, frequently with end-organ damage as this increases the event rate and allows a conclusion to be reached with fewer patients in a shorter time, thereby reducing expense. The conclusions reached in these studies are frequently taken to apply to all patients with hypertension. This is clearly an unjustified conclusion if older and younger patients respond differently to various drug classes |**11,12**|. To justify the use of new expensive drugs, pharmaceutical companies wish to demonstrate that therapy based on their drug as the initial treatment is more effective than initial therapy based on a thiazide diuretic or a β-blocker. They then claim that the drug has effects beyond blood pressure lowering. However, the drug with which it is compared may have harmful effects and all the improvement may be due to lowering of blood pressure. In this regard, three studies are of interest: the ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) |**13**|, ANBP2 (Australian National Blood Pressure Study 2) |**14**| and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) |**15**|. It is frequently stated that these studies are in conflict. ALLHAT is claimed to show the benefit of initial diuretic-based therapy, the other two of ACEI-based therapy (Table 2.2). All

Table 2.1 Fall in blood pressure (mmHg) with the different drug classes in people not previously treated for high blood pressure

Drugs used	Elderly patients |11| >65 years		Younger patients |12| <55 years	
	Systolic*	Diastolic*	Systolic†	Diastolic†
Calcium blockers	16	6.2	17	9
Diuretics	14	4.2	2	4
ACEI	8	3.3	24	17
β-blockers	7	4.0	20	21

*Placebo-corrected; †24 hour ambulatory blood pressure measurement
Source: Morgan *et al*. (2001) |**11**| and Deary *et al*. (2002) |**12**|.

Table 2.2 Comparison of results in patients treated with therapy based on a thiazide diuretic or an ACEI

	ALLHAT [13]	ANBP2 [14]	ASCOT [15]
Difference in systolic blood pressure (mmHg)*	2.1	0.0	0.0
Primary end-point†	0.99	0.89‡	0.85‡
Cardiovascular events†	1.05	0.88‡	0.85‡
Strokes†	1.15‡	1.02	0.75‡
New diabetes	0.7‡	0.67‡	0.77‡
Cardiac failure	1.19‡	0.85	NA

*Thiazide–ACEI; †odds ratio ACEI/thiazide; ‡$P < 0.05$.
Source: ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group [**13**], Wing *et al*. (2003) [**14**] and Server *et al*. (2005) [**15**].

three studies were performed in older patients, who respond better to a diuretic. All three studies show the same result if it is accepted that blood pressure lowering is the critical determinant of outcome. In ALLHAT the blood pressure achieved was lower in the diuretic-based group (Table 2.2). This would mean that prognosis should be better in the diuretic-based group, but the primary outcome was the same. Thus, there was an advantage of ACEI equivalent to a difference of 2.1 mmHg in systolic blood pressure. The interpretation is that diuretics had an adverse effect or that ACEI and calcium-blocking drugs had an effect over and above blood pressure lowering. In ANBP2 and ASCOT the fall in blood pressure in the two groups was the same but the primary outcome in the ACEI-based therapy was better (Table 2.2). This has been interpreted as showing that ACEI have an effect over and above blood pressure lowering, but it may be that diuretics and/or β-blockers have an adverse effect on outcome. In addition to the overall outcome, the frequency of new diabetic patients in the three studies was lower in the ACEI-based therapy, suggesting that ACEI-based therapy is to be preferred. The question of what should be the initial therapy is largely irrelevant. Most patients will require at least two drugs to control blood pressure. If an ACEI or an ARB is used initially and does not control blood pressure, a low-dose diuretic is the most sensible drug to be added. If a diuretic is used and blood pressure is not controlled, the logical drug to add is an ACEI or an ARB. Thus, most people would end up on a similar combination. The only group who may be at risk from the initial choice are those people who achieve blood pressure control with initial monotherapy. To my knowledge, this analysis was not performed in any of the three studies.

Unresolved problems in hypertension

Detection and control

The major unresolved problem is how to ensure that blood pressure is detected and controlled in all people. It is important to have drugs that have very few side effects and no increase in morbidity and mortality as this allows drugs to be used for a longer time and lower levels of blood pressure to be treated. However, in most countries –

even those with good medical services – 30% or more of patients have undetected hypertension |**1,2**|. Thirty per cent of patients known to have hypertension are not treated; 30% are not adequately controlled and only about 30% have effective control. A study which showed how to detect blood pressure, how to be certain that therapy was started and maintained and blood pressure controlled would be of far more importance than studies that show that one drug is slightly superior to another. The design of such a study is difficult, as is the choice of the intervention to be used. Treatment must be carried out, and ethically it may be remiss not to follow up people who do not continue treatment. Thus, the very nature of what is being attempted may be negated. A study could be based on blood pressure lowering with any drug or drugs. The effect of patient education by various techniques; the effect of patient involvement by blood pressure monitoring; the effect of intensive follow-up by trained nurses or technicians—all these need to be studied. Such studies have been performed on a short-term basis (1–2 years) |**16,17**| but the aim of these studies was usually to determine if therapy with one drug class was maintained longer than with another. This is of importance but is trivial compared with the question of whether blood pressure can be controlled in the long term in most people in the community and whether this translates into a positive morbidity and mortality outcome.

What blood pressure should be treated?

Systolic blood pressure, diastolic blood pressure, mean pressure and pulse pressure all correlate with morbidity and mortality |**18,19**|. Blood pressure varies at different times of the day, with the lowest blood pressure during sleep and the highest on awakening in the morning |**20,21**|. Brachial artery systolic blood pressure may not accurately reflect the central aortic systolic blood pressure, which is the major determinant of the work load of the heart |**22**|. There is evidence from animal and clinical studies that sleep blood pressure may be a more important determinant of outcome. Thus, in rats sleep blood pressure was the most important determinant of cardiac hypertrophy |**23**|. People who do not have a fall in blood pressure when asleep have a worse outcome than those who have a fall |**24,25**|, In ANBP2 the sleep blood pressure both before and during therapy was a better predictor of outcome than either the clinic or the daytime blood pressure |**26**|. In observational studies, patients in whom sleep blood pressure was controlled had less complications than those in whom sleep blood pressure was not controlled |**27**|. If sleep blood pressure is the more important variable, should we give medication in the evening? Three studies indirectly suggest this might be a preferred option. The HOPE (Heart Outcomes Prevention Evaluation) study |**28**| and the PROGRESS (Perindopril [Aceon®] Protection against Recurrent Stroke Study) study |**29**| both used ACEI to treat patients at high risk of cardiovascular disease. The fall in blood pressure achieved with both drugs was similar, but the reduction of 25% in cardiovascular events in the HOPE study was much greater than in the people on monotherapy in the PROGRESS study (Table 2.3). Ramipril was given in the evening, and in a HOPE substudy |**30**| the reduction in sleep systolic blood pressure was 16 mmHg, with a similar reduction in daytime blood pressure to that seen in the main study (Table 2.3). In the PROGRESS study perindopril was

Table 2.3 Comparison of outcome in three studies in high-risk patients treated with ACEI at different times of the day

Drug	HOPE [28] Ramipril	PROGRESS* [29]		EUROPA [31] Perindopril
		Perindopril	Perindopril + indapamide	
Dose (mg)	10	4	4 + 2.5	8
Administration time	p.m.	a.m.	a.m.	a.m.
Fall in daytime systolic blood pressure (mmHg)	3	5	12	5
Fall in sleep systolic blood pressure (mmHg)†	16	NA	NA	NA
Reduction in:				
Cardiovascular events	25‡	4	40‡	20‡
Stroke	33‡	5	43‡	2

*PROGRESS monotherapy arm and combined arm separately; †HOPE substudy [30]; ‡$P < 0.05$. NA, not available.
Source: Yusuf *et al*. (2000) [28], Progress Collaborative Group (2001) [29] and Fox *et al*. (2003) [31].

given in the morning, and it is unlikely that the fall in sleep blood pressure would have been as great. Thus, a difference in sleep blood pressure could explain the difference in results. When a diuretic (indapamide) was added in the PROGRESS study there was a greater fall in daytime blood pressure and also probably in sleep blood pressure, and the reduction in cardiovascular events was similar or even greater than in the HOPE study. The EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) study [31] was performed in a group of patients with cardiac disease but at lower risk than in the HOPE study. Perindopril 8 mg was given in the morning. This would be expected to have a full duration of effect on blood pressure lowering over 24 hours and would cause a significant fall in sleep blood pressure. The reduction in cardiovascular events with this higher dose of perindopril was similar to that achieved with ramipril at night.

Do results in the elderly apply to the young?

Most recent studies have been performed in elderly patients and the results may not apply to younger people. From results in older people, recommendations are now largely based on the principle of not treating patients until they reach a certain absolute risk profile [1]. It is expensive to treat people at low risk, but if not treated they develop end-organ damage, which impairs their eventual outcome [32,33]. Long-term prognostic studies should be performed in young people, and in such studies the strategy of treatment of all patients with an elevated blood pressure (>135/85 or >140/90) should be compared with a strategy of not treating patients until they reach a predetermined absolute risk rate. Such a study would be large and take a long time to be completed, but may be the only way to prove that early treatment can return prognosis to that of normotensive people

Non-pharmacological intervention

Most people would now accept that blood pressure can be reduced by non-pharmacological measures, such as weight reduction, sodium restriction, potassium supplementation, increased exercise and combinations of all of these. There is, however, no evidence about how this translates into alteration of the outcome. Such intervention studies would be extremely difficult to implement in the Western world but may be possible in developing countries. One issue that has not been addressed in major studies on hypertensive patients relates to the importance of potassium intake. Epidemiological evidence links a low or reduced potassium intake with an increased incidence of strokes and sudden death |**34,35**|. In an analysis of the data from the SHEP (Systolic Hypertension in the Elderly Program) study there was good evidence that if a person developed a low plasma potassium concentration the incidence of sudden death and strokes rose about three-fold |**36**|. Overall there was a beneficial effect of thiazide diuretics in the SHEP study |**37**|, but the improvement was negated to a degree by this effect. A study in hypertensive patients in which plasma potassium was maintained in the high normal range, either by potassium supplementation or potassium-retaining diuretics compared with usual treatment, would be of interest and possibly of major importance.

Important future studies

I propose that the following are important areas of study, though the design of such studies is difficult.

1. Detection of hypertension.
2. Implementation and maintenance of effective therapy for hypertension.
3. Outcome based on control of sleep blood pressure.
4. Application of results in the elderly to the young.
5. Treatment of all patients with any blood pressure elevation compared with the absolute risk approach.
6. Effect of increased potassium intake or retention on outcome.
7. Outcome studies of non-drug management.

All are important questions. Studies to resolve them will be complex. The studies would be large and many would be long-term. Information to resolve these questions may be obtained in part by a different strategy. It may be that application of a registration-based approach coupled to a country's death registry could resolve a number of these questions. This is particularly relevant to treatment studies in the young and the question of when to start treatment. Accumulation of information nationwide might be the only way to answer these questions.

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3

Long-term management of antihypertensive therapy in general practice

MICHEL BURNIER, SARA TADDEI, CAROLINE RHÉAUME

Introduction

If hypertension is well controlled, target organ damage can be prevented and, in the long term, the likelihood of coronary disease, heart failure, stroke and premature death can be reduced. The most recent data provided by the National Health and Nutrition Examination Survey (NHANES III) have painted an alarming picture, suggesting that too many people are dying unnecessarily because of poor blood pressure control |**1**|. The effect of instigating the National High Blood Pressure Education Program, which aims to increase awareness, prevention, treatment and control of hypertension, was initially very encouraging. More recent findings suggest that complacency may have developed and that there is now cause for concern regarding the management of hypertensive patients. In the period 1999–2000, blood pressure was adequately controlled (defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) in only about one-third of the population |**2**|. This alarming report is not unique to the USA. Indeed, reports from developed and developing countries in Europe, Asia and Africa show that hypertensive patients with well-controlled blood pressure represent only a small percentage of the hypertensive population, as shown in Table 3.1 |**3**|. Thus, there is clearly a worldwide need for further sustained efforts in the management of hypertension.

Numerous randomized trials have demonstrated that intensive lowering of blood pressure in hypertensive patients can be achieved if physicians follow given therapeutic algorithms and that such approaches are associated with a reduced incidence of cardiovascular events. However, there appears to be a major discrepancy between the results obtained in clinical trials and those achieved in clinical practice. The reasons why there is such a discrepancy are not entirely clear but several factors may play a role |**4,5**|. In the present review, we shall discuss a series of studies recently published which have addressed issues that may be of importance for improving the management of hypertensive patients in clinical practice, such as the evaluation of the cardiovascular risk, the place of home blood pressure measurements, and the

Table 3.1 Control of hypertension in different countries of the world

Country	Study period	Age range	Hypertensives: % controlled
United States	1999–2000	18–80	31
Canada	1986–1992	18–74	16
Spain	1990	35–64	5
England	1998	16–75	9.3
Germany	1994–1995	25–74	9.3
Greece	1997	18–90	27
Japan	1980	30–74	23.6/36.0*
China	2000–2001	35–74	8.1
Korea	1990	30–70	0.9
Taiwan	1993–1996	>19	2.0/5.0*
South Africa	1998	15–65	10/18*
Egypt	1991	25–95	8
Turkey	1995	>18	9.4
Mexico	1992–1993	25–74	2.3
Venezuela	1996	>20	4.5
Cuba	1998	>15	15.2
Jamaica	1996	25–74	24

Percentages are for the total population.
* Men/women.
Source: Kearney *et al*. (2004) |**3**|.

importance of night-time blood pressure. Finally, we shall discuss the role of drug adherence and try to understand the reasons given by general physicians for not intensifying drug therapy when target blood pressure is not achieved.

Evaluation of the cardiovascular risk as a guide to antihypertensive therapy

The absolute benefit of blood pressure reduction by treatment depends on the total burden of risk as well as on the severity of the hypertensive state. Thus, the knowledge of comorbid conditions and target organ damage may be useful to set target blood pressure levels and to establish the indications for specific drugs or additional preventive and therapeutic measures in the individual patient. Several national and international recommendations, such as the European Society of Hypertension–European Society of Cardiology guidelines, propose that the global cardiovascular risk of each patient should be assessed before initiating any therapy. For this assessment, physicians have to rely on the local know-how and possibilities. Studies by Cuspidi and colleagues have demonstrated that the more extensive the diagnostic work-up the higher the percentage of correctly identified patients at risk |**6**|. Thus, the routine search for left ventricular hypertrophy and carotid intima–media thickening

using ultrasound has proved to be a very sensitive tool, allowing the reallocation of up to 50% of patients to a higher cardiovascular risk class |**6**|. Unfortunately, the relatively high cost of these procedures often limits their large-scale use in clinical practice. Identifying simpler, low-cost indicators of the presence of target organ damage could therefore lead to an improvement in the cost-effectiveness of the stratification process. The paper by Viazzi and colleagues presented below further extends the observations of Cuspidi and colleagues |**6**| by introducing microalbuminuria into the algorithm.

Previous studies have demonstrated that ambulatory blood pressure monitoring correlates better with end-organ damage and cardiovascular complications than office blood pressure |**7,8**|. Whether this is also true for home blood pressure has not been ascertained. Indeed, only one study, conducted in Japan, has suggested that home blood pressure is indeed better than office blood pressure in predicting the cardiovascular risk of hypertensive patients |**9**|. We shall discuss below a new study demonstrating that home blood pressure monitoring may be an effective complementary approach to the investigation of the cardiovascular risk of hypertensive patients.

Recently, several studies have suggested that night-time blood pressure, more particularly the absence of a significant decrease in blood pressure during the night, increases the risk of developing cardiovascular complications such as stroke and left ventricular hypertrophy |**10,11**|. However, the dipping pattern of night-time blood pressure is not always reproducible. Hence, it is often difficult to interpret. A recent study has compared the incidence of cardiovascular target organ damage in patients with a reproducible or non-reproducible fall in blood pressure during the night. These data provide interesting new information on how to integrate the values of blood pressure during the night in our interpretation of 24-hour blood pressure monitoring.

Optimizing global risk evaluation in primary hypertension: the role of microalbuminuria and cardiovascular ultrasonography

Viazzi F, Parodi D, Leoncini G, *et al*. *J Hypertens* 2004; **22**: 907–13

Background. Microalbuminuria has recently been acknowledged as an early sign of target organ damage and included among the factors influencing the prognosis of patients with essential hypertension, even in the absence of diabetes. The usefulness of this low-cost and easily obtainable test has recently been questioned and its use is still too often neglected in clinical practice. In this context, in order to assess the relative role of microalbuminuria and cardiac and vascular ultrasonography in the process of risk stratification, the authors compared the sensitivity and cost of these three diagnostic procedures, both alone and in various combinations, in the search for hypertensive target organ damage.

Interpretation. This study shows that, in a cohort of untreated hypertensives (405 patients), the evaluation of global risk is strongly influenced by the test used to search

for target organ damage. These results confirm and extend previous reports suggesting that the minimum work-up recommended by guidelines for hypertension is a highly insensitive approach for detecting patients with target organ damage and that adding other investigations, such as microalbuminuria or cardiovascular ultrasound, allows a better characterization of the patients' risk as, shown in Fig. 3.1. Of the three tests examined in this study (microalbuminuria, cardiac and vascular ultrasound), ultrasonographic detection of cardiac hypertrophy and vascular damage had the highest sensitivity in identifying high-risk hypertensive patients (echocardiography, 65%; carotid ultrasound, 41%). However, patients with microalbuminuria were much more likely to show either one or both signs of target organ damage using echocardiography and carotid ultrasound. When each test was evaluated by itself or in combination based on its sensitivity and cost, the first finding was that performing all investigations with no discrimination would increase the cost of the work-up by 40%. The most rational way to use these procedures would be to start screening patients with microalbuminuria and to perform ultrasonographic investigations only in patients found to be at low or medium risk using the traditional work-up. Thus, in order to optimize the cost-effectiveness of these diagnostic procedures, a routine search for microalbuminuria should be performed before considering cardiac or vascular ultrasound.

Comment

Today, most national guidelines propose a series of laboratory and radiological investigations to evaluate the cardiovascular risk of hypertensive patients before deciding what therapeutic approach to start. However, none of these guidelines indi-

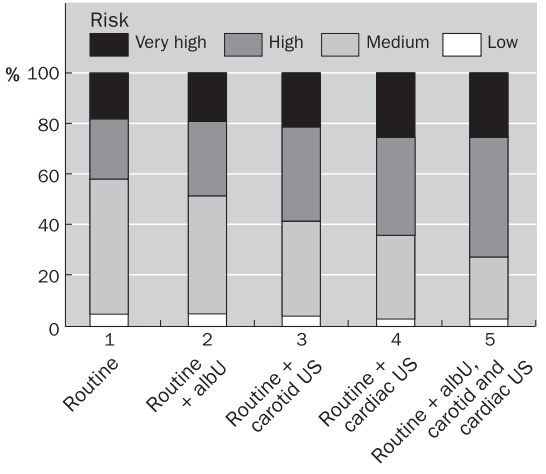

Fig. 3.1 Stratification of 405 patients on the basis of global level of cardiovascular risk following routine work-up and specific assessment of target organ damage.
Source: Viazzi *et al*. (2004).

cate how, when and in which sequence these investigations should be performed in order to be cost-effective. The study conducted by Viazzi and colleagues, like the one published previously by Cuspidi and colleagues |**6**|, is very important and useful for clinicians. As pointed out by the authors, routine evaluation of the risk profile can lead to underestimation of the risk and, therefore, to misclassifying a substantial number of patients if the work-up is incomplete. Ultrasonographic evaluation of cardiac and vascular structures is sensitive for detecting high-risk patients and may be very helpful in identifying such patients. However, the cost of these investigations is a major limitation. The finding that pre-screening of patients using the determination of microalbuminuria is the most cost-effective strategy for screening patients will probably be of major help to physicians. According to the authors, the proposed work-up would be that shown in Fig. 3.2.

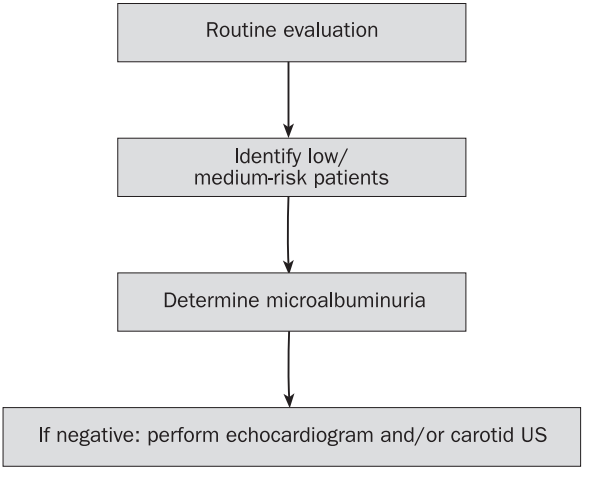

Fig. 3.2 Schematic representation of the algorithm proposed by the investigators to assess the cardiovascular risk of hypertensive patients. Source: Viazzi *et al.* (2004).

Cardiovascular prognosis of 'masked hypertension' detected by blood pressure self-measurement in elderly treated hypertensive patients

Bobrie G, Chatellier G, Genes N, *et al*. *JAMA* 2004; **291**: 1342–9

Background. The main reason for using office blood pressure measurements for the management of hypertensive patients is that these measurements correlate with the cardiovascular risk. Office blood pressure is also the reference blood pressure to monitor the effect of antihypertensive drugs in clinical practice and in clinical trials.

However, office blood pressure is known to have numerous limitations linked to the physician (observer bias, digit preference) as well as to the clinical situation during which blood pressure is taken (white-coat hypertension). Physicians' independent methods of blood pressure monitoring, such as ambulatory blood pressure (ABPM) and home blood pressure, are increasingly used, and ABPM, for example, has been shown to correlate better with target organ damage than office blood pressure. However, whether office blood pressure has a prognostic value remains unknown. To answer this question, the authors compared office and home blood pressure in a cohort of European elderly hypertensive patients followed by their general practitioners.

Interpretation. A total of 4939 patients treated for hypertension, older than 60 (mean age 67 years), were included in the study and were followed for a mean period of 3.2 years. The primary end-point was cardiovascular mortality and the secondary end-points were total mortality and the combination of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, hospitalization for angina or heart failure, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery. Home blood pressure was measured over 4-day periods. On these days, three consecutive measurements were taken in the morning (8 a.m.) and repeated in the evening (8 p.m.). A validated semi-automatic device equipped with a printer was provided to the patients. At the office, three measurements were taken with a mercury sphygmomanometer. Uncontrolled blood pressure was considered when office blood pressure was greater than 140/90 mmHg and for home blood pressure the limit was set at 135/85 mmHg. Patients were classified in four subgroups: (i) patients with a controlled blood pressure, i.e. office blood pressure less than 140/90 and blood pressure at home less than 135/85; (ii) patients uncontrolled with blood pressure above 140/90 at the office and below 135/85 at home; (iii) patients with white-coat hypertension, i.e. blood pressure greater than 140/90 in the presence of the physician and less than 135/85 at home; and (iv) patients with masked hypertension, i.e. those with an office blood pressure less than 140/90 and a home blood pressure greater than135/85 mmHg. The results show that for each 10 mmHg increase in home systolic blood pressure the risk of cardiovascular events increased by 17.2%. For a 5 mmHg increase in home diastolic blood pressure, the risk increased by 11.7%. For the same changes in blood pressure, there was no significant increase in cardiovascular risk according to office blood pressure measurements, suggesting that home blood pressure has a better predictive value than office blood pressure. Interestingly, the hazard ratio for cardiovascular events was comparable in patients with uncontrolled hypertension and in patients with a masked hypertension, i.e. an elevated blood pressure at home but not in the presence of the physician. The hazard ratio was slightly but not significantly increased in patients with white-coat hypertension (Fig. 3.3).

Comment

This study is the largest one to investigate the predictive value of home blood pressure monitoring in a population of elderly hypertensive patients in Europe. It clearly demonstrates that home blood pressure has a better prognostic value that office blood pressure. This important observation suggests that home blood pressure monitoring should be used more frequently in order to increase the accuracy of office

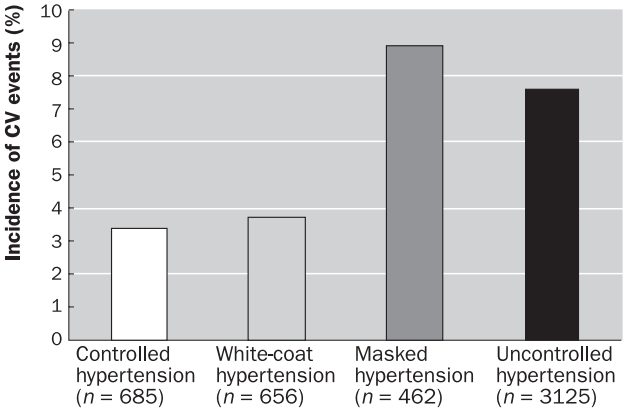

Fig. 3.3 Incidence of cardiovascular events in patients with controlled, uncontrolled, white-coat hypertension and masked hypertension. Source: Bobrie *et al*. (2004).

blood pressure monitoring. Another important observation made in this study is that home blood pressure makes it possible to identify two subsets of the hypertensive population which today are clearly overlooked. The first is represented by patients with white-coat hypertension, who appear to have a relatively good prognosis, although they might become true hypertensive patients with time, as suggested previously |**12**|. The second subset, which concerns 9% of the studied population in Bobrie's paper, has a less favourable prognosis and has been described as patients with 'masked' hypertension. This group of hypertensive patients is difficult to identify because diagnosis can only be made on the basis on ambulatory or home blood pressure. These patients are therefore mainly unrecognized. Yet their cardiovascular risk is comparable to that of patients with uncontrolled hypertension. So far, the mechanisms of masked hypertension are not known. Pickering and colleagues have suggested that this phenomenon is observed in 7–45% patients and that its frequency decreases with age |**13**|. Masked hypertension appears to occur more often in women and in people with several cardiovascular risk factors. In recent years, more and more data are being published on masked hypertension and we shall certainly learn more about it in the coming years.

Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure

Cuspidi C, Meani S, Salerno M, *et al*. *J Hypertens* 2004; **22**: 273–80

Background. The lack of a nocturnal fall in blood pressure has been related to an increase in target organ damage and cardiovascular events |10,11|. The clinical

significance of classifying patients as dippers and non-dippers on the basis of a single period of ABPM has been questioned. The aim of this study was to evaluate the relationship between nocturnal dipping status, defined on the basis of two periods of ABPM, and cardiac and extracardiac target organ damage in essential hypertension.

Interpretation. This study investigates the relationship between nocturnal blood pressure and target organ damage in untreated hypertensive patients with three different night-time blood pressure patterns (reproducible dipper, reproducible non-dipper, and variable dipper status) established on the basis of two periods of ABPM carried out within 4 weeks. Dipping is defined as a decrease in blood pressure of more than 10% during the night. The authors included 375 never-treated hypertensive patients of both genders. Despite similar clinic and 48-hour blood pressure values, hypertensive patients with a persistent non-dipper pattern showed a significantly greater extent of cardiac structural alterations compared with subjects with a reproducible dipping pattern, but not those with a variable nocturnal profile. A non-dipping pattern diagnosed on two concordant ABPM periods instead of a single monitoring therefore represents a clinical trait associated with more pronounced cardiac abnormalities, but not extracardiac abnormalities. In non-dipping middle-aged hypertensive patients, echocardiography appears to provide more accurate risk stratification than carotid ultrasonography or microalbuminuria.

Comment

This study further demonstrates that subjects with a persistently reduced nocturnal fall in blood pressure (<10% decrease during the night) have significant alterations in cardiac structure, as shown by significantly greater left ventricular hypertrophy, interventricular septum thickness and left atrium and aortic root diameters when compared with those exhibiting reproducible nocturnal dipping. Patients with a variable profile of nocturnal dipping had an intermediate cardiac phenotype. Moreover, extracardiac abnormalities were comparable in the three groups. Interestingly, the authors suggest that the greater extent of cardiac alterations in non-dippers is not related to a higher overall blood pressure load since the averages of 24-hour blood pressure were comparable between the groups. Other confounding clinical and demographic factors, such as age, body mass index and known duration of hypertension, did not seem to play a role either. Thus, the authors provide a very critical assessment of the relation between night-time blood pressure and the development of target organ damage, suggesting that it is not blood pressure during the night that plays a role in determining organ damage but rather the existing organ damage that determines the extent of the nocturnal fall in blood pressure. Thus, according to the authors, nocturnal blood pressure is mainly determined by cardiovascular organ damage rather than the reverse.

Long-term follow-up of antihypertensive therapy

One of the major problems of hypertension management is the long-term control of blood pressure and treatment persistence. Indeed, with time, an increasing percent-

age of patients interrupt their treatment, and long-term persistence with drug therapy is known to be relatively low in hypertension as well as in other chronic asymptomatic diseases |**14–16**|. Reasons why patients do not stay on therapy are multiple and may be linked to the patient's belief on the necessity to be treated, to the lack of efficacy or poor tolerability of the drugs prescribed as well as to a certain degree of 'therapeutic inertia' by physicians |**4**|. The long-term management of hypertensive patients raises numerous questions. What should we do when home blood pressure is apparently well controlled and office blood pressure is not? How is it possible to improve drug adherence so that patients remain on therapy? Why do physicians not intensify drug therapy when the target blood pressure is not achieved? These various questions have been asked in the three papers presented below.

Antihypertensive treatment based on blood pressure measurement at home or in the physician's office

Staessen JA, Den Hond E, Fagard R, Keary L, Vandenhoven G, O'Brien ET. *JAMA* 2004; **8**: 955–64

Background. Antihypertensive therapy is usually initiated and modified according to office blood pressure measurements. However, the determination of blood pressure in the office is influenced by the white-coat effect and observer bias, which tend to produce false increases in blood pressure. Today, home blood pressure measurement is increasingly used and is not limited by these confounding factors. Whether self-measurement of blood pressure offers advantages over office blood pressure in the management of hypertensive patients has not been demonstrated so far. The purpose of this study was to compare self-measurement of blood pressure and conventional office blood pressure measurement as guides for the initiation and adaptation of antihypertensive treatment and to evaluate the effect of the two approaches on left ventricular hypertrophy, symptoms and costs of treatment. A total of 347 patients with diastolic blood pressure greater than 95 mmHg participated in the study; one half of the patients was assigned to receive antihypertensive drug treatment based on office blood pressure measurements, and the other half was assigned to receive antihypertensive drug treatment based on self-measured blood pressure. At home, patients were asked to perform three consecutive measurements after 5 min of rest in the sitting position, twice daily, in the morning and in the evening. The average of all values taken during the 7 days preceding each follow-up visit was considered as home blood pressure. The office blood pressure was the average of three consecutive measurements after 5 min of rest in the sitting position, during the usual working hours. At the beginning and at 6 and 12 months, 24-hour ABPM was performed, but these data were not used to decide how to adapt the treatment. Patients were seen at 1 and 2 months and thereafter at 2-month intervals for 1 year; target blood pressure was defined as a diastolic value below 90 mmHg. At each visit, a physician who was blinded to randomization (he knew only the values of blood pressure at home or at the office) decided whether treatment should be modified.

Interpretation. After 1 year, patients followed using home blood pressure measurements received less intensive drug treatment and were more likely to stop therapy than those monitored using office blood pressure, as shown in Fig. 3.4. This observation suggests that, with self-measured blood pressure, more cases of the white-coat effect were diagnosed. The percentage of patients progressing to multiple therapy was comparable in the two groups. However, at 1 year the decrease in blood pressure as measured using ABPM was greater in office-monitored patients than in the home blood pressure group, suggesting that blood pressure control was not as good in the latter group. The cost was only slightly lower in the home blood pressure group and drug adherence was comparable in the two groups. Moreover, general well-being and left ventricular mass was similar in the two groups. From these data, the authors suggest that self-measured home blood pressure should be used in patients with borderline office hypertension without target organ damage in order to exclude white-coat hypertension, and in patients with normal blood pressure and unexplained target organ damage. In other situations, they recommended the use of both home and office blood pressure measurements to follow hypertensive patients. It is also important to teach patients how to take blood pressure and to use a schedule that recommends duplicate morning and evening home blood pressure measurements to be taken for 7 days; the measurements taken on the first day should be discarded.

Comment

This study addresses a very crucial and provocative clinical question: should we continue to follow our hypertensive patients on the basis of office blood pressure or should we give more credit to self-measured home blood pressure? This study clearly demonstrates that home blood pressure detects more patients with white-coat hypertension and therefore makes it possible to interrupt treatment in a substantial proportion of patients. However, there is a major caveat: for those patients who have true hypertension, follow-up based on home blood pressure values leads to poorer control of hypertension. Unfortunately, the study was too short (1 year) to evaluate correctly the clinical impact of this latter observation. In contrast to the general belief, self-measurement of blood pressure did not improve drug adherence over 1 year. Neither did it improve the feeling of well-being or left ventricular mass, although for this parameter the duration of the study may have been too short. Thus, self-measurement of blood pressure provides useful information complementary to office blood pressure and ambulatory blood pressure, but it does not seem ready to replace conventional office blood pressure. At this point, this report should not lead to the discontinuance of home blood pressure measurement as a management tool in hypertension until there are further data to support these observations.

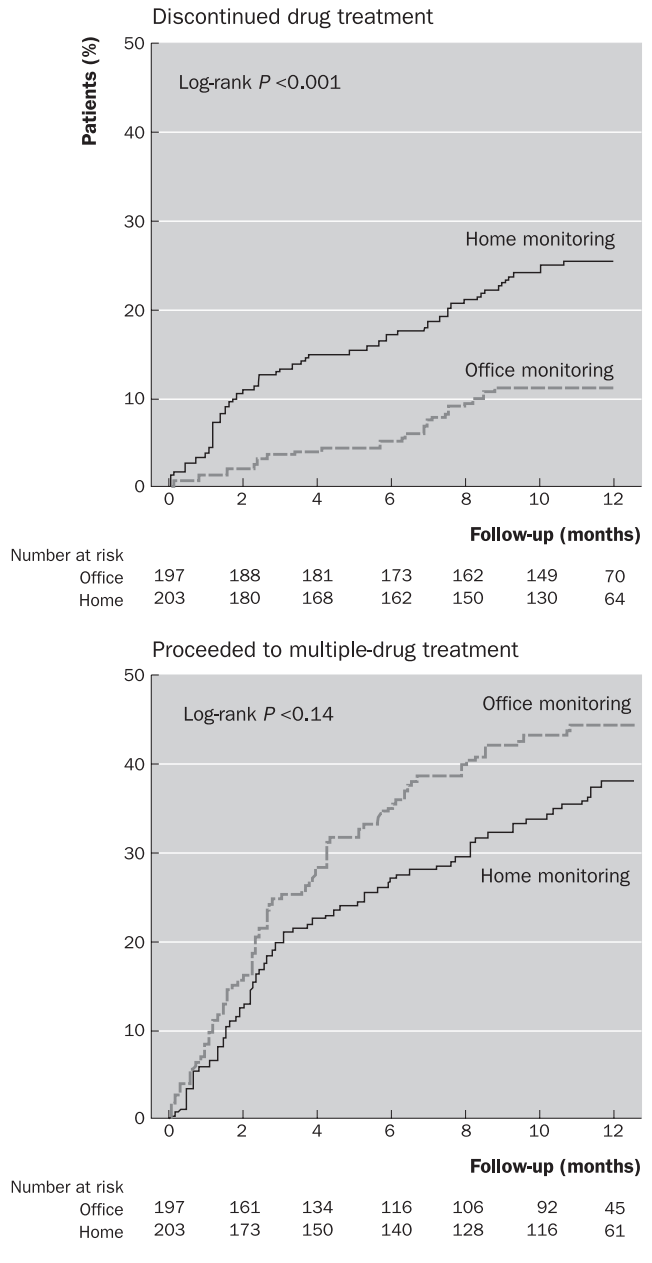

Fig. 3.4 Probability that during follow-up patients would permanently stop antihypertensive drug treatment (*top panel*) or proceed to multiple drug treatment (Kaplan–Meier estimates) (*bottom panel*). Source: Staessen *et al*. (2004).

Reasons for not intensifying antihypertensive treatment (RIAT): a primary care antihypertensive intervention study

Ferrari P, Hess L, Péchère-Bertschi A, Muggli F, Burnier M. *J Hypertens* 2004; **22**: 1221–9

BACKGROUND. The presence of cardiovascular risk factors, target organ damage or associated clinical conditions, such as stroke or myocardial infarction, should dictate the individual target blood pressure to be achieved as well as the treatment to be considered in hypertensive patients. Several surveys have demonstrated that the percentage of hypertensive patients with uncontrolled hypertension remains high despite a rising number of new antihypertensive drugs with different mechanisms of action and the clear demonstration that a much larger percentage of patients are controlled in clinical trials. Several reasons have been proposed to explain the discrepancy between the results obtained in clinical practice and those gathered in clinical trials. One potential reason is that general practitioners are defining target blood pressures different from those defined by current guidelines. Physicians may also have other reasons not to intensify the treatment when blood pressure is not well controlled, but these reasons are not always clearly expressed. In this study, the authors investigated the target blood pressure values defined by general practitioners in a large group of hypertensive patients with various comorbidities. In addition, physicians participating in this study were asked to justify why they were not intensifying antihypertensive therapy when blood pressure was not on target.

INTERPRETATION. The results of this study reveal several interesting points regarding the management of hypertensive patients by general practitioners. The first is that the average target blood pressure values proposed by the general practitioner are relatively low (138/84 mmHg) but they do not depend on the patient's cardiovascular risk or on the presence of comorbidities. The main factor determining the target value is actually the baseline blood pressure values, suggesting that general practitioners integrate the difficulty that they will encounter to lower blood pressure in some patients in the definition of the target blood pressure. In this large group of hypertensive patients ($n = 2621$), the target blood pressure was reached in 52% of patients according to the European Society of Hypertension–European Society of Cardiology guidelines and 69% according to the physician's opinion. Interestingly, when physicians considered the target as not reached, the treatment was not adapted in two-thirds of the cases (this figure represents 27% of the overall included population). The most frequent reasons provided by the general practitioners for not changing the treatment are presented in Fig. 3.5.

Comment

These data present several important issues regarding the management of hypertension in the real world. It is clear that this management differs in clinical practice and in clinical trials. Thus, general practitioners do not really define their blood pressure goals according to risk stratification, as suggested by several consensus guidelines. Nevertheless, the goals set by the general practitioner were relatively low and corresponded almost to the recommended values. However, when one considers

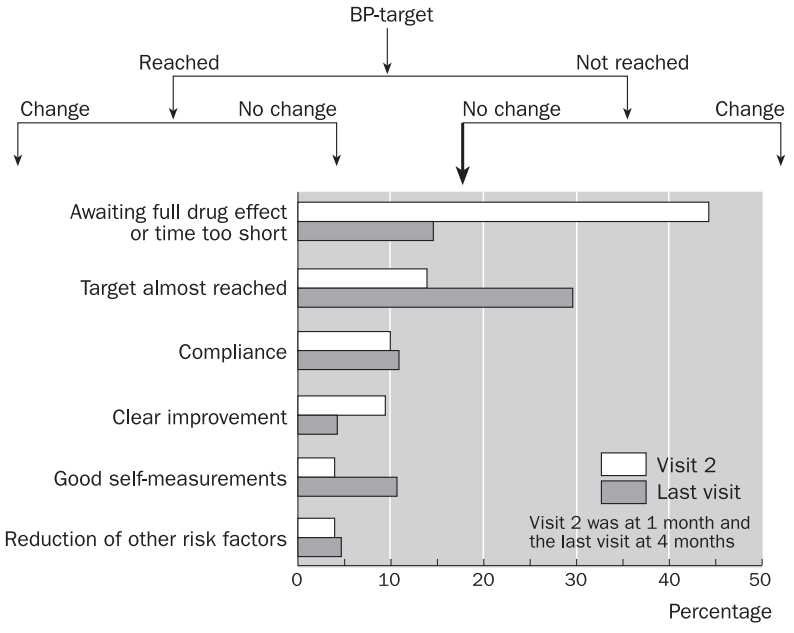

Fig. 3.5 Reasons given by general practitioners for not intensifying drug therapy when target blood pressure is not reached. Source: Ferrari *et al*. (2004).

the blood pressures achieved, it appears clearly that many general practitioners are reluctant to intensify the treatment in order to obtain the predefined blood pressure values. To justify this, general practitioners generally consider that they need more time and they are relatively satisfied by the target being almost reached. One has to admit that these factors are rarely taken into consideration in clinical recommendations and one does not know whether these beliefs do have a clinical impact. When considering the recent data of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, waiting for more than 4 months before reaching the target blood pressure may not necessarily be in the interest of the patient |**17**|.

How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials

Schroeder K, Fahey T, Ebrahim S. *Arch Intern Med* 2004; **164**: 722–32

Background. Lack of adherence to the prescribed medication is generally considered to be one of the major reasons why the control of high blood pressure is so bad despite the availability of effective antihypertensive drugs. Several

interventions have been proposed to improve drug adherence to antihypertensive medication, but so far meta-analysis of the efficacy of these interventions have never resulted in clear recommendations on how to improve drug adherence in clinical practice, i.e. outside a clinical study. However, in recent years the number of clinical studies addressing the issue of drug adherence in hypertension has increased considerably. The purpose of the present analysis was therefore to perform a new meta-analysis of these studies in order to determine the effectiveness of interventions to increase adherence to blood pressure-lowering medications.

INTERPRETATION. The authors performed a systematic review of all randomized controlled studies found in different databases until 2002. They included 38 studies evaluating 58 different approaches between 1975 and 2000. The studies were very heterogeneous and therefore could not be pooled together in a final analysis. Of all measures proposed to increase drug adherence, simplifying the dosing regimen appears to be most effective in seven out of nine trials. Motivational strategies were partly successful and resulted in a relative increase in drug compliance of about 23%. Complex interventions were less successful and need more evidence.

Comment

Whether poor adherence to drug therapy really contributes to the poor results of blood pressure control observed around the world is always a matter of debate. In some developing countries, low drug adherence certainly plays a major role because drugs are either not available for life-long treatments or not affordable. In developed countries, however, the reasons for not adhering are certainly different and the exact contribution of poor drug adherence to the quality of blood pressure control is more difficult to evaluate. Interestingly, one of the major limitations of the meta-analysis discussed above is that the majority of the studies did not report a blood pressure outcome. Thus, it is not possible to determine whether an improvement in drug adherence would lead to a further reduction in blood pressure. Logically, one would expect it, but this has not been formally demonstrated.

One of the major problems with drug adherence in everyday practice is that it is generally not measured. One of the reasons is that physicians have no easy-to-use and reliable tool to obtain objective data on the compliance of their patients. As long as such data are not available, the field of drug adherence will remain overlooked by general practitioners, although they do recognize that it is an important clinical issue |**18**|. In the meta-analysis presented above, simplifying the treatment remains the easiest and most effective approach that physicians can implement in their practice to improve drug adherence. Hopefully, in the field of hypertension, this can easily be done using the numerous fixed-dose drug combinations available on the market.

Conclusion

The long-term management of patients with hypertension remains a real challenge for physicians. Although every practitioner is convinced that a high blood pressure

must be lowered to prevent the development of cardiovascular complications such as stroke, congestive heart failure and kidney disease, only a minority of hypertensive patients actually have a normal blood pressure. One of the reasons why blood pressure is so poorly controlled may be the fact that physicians tend to underestimate the cardiovascular risk of their patients. Several recent studies presented in this paper show that this is indeed the case and that, by using a more complete work-up which includes the determination of microalbuminuria and a cardiac and vascular ultrasound, one can get a better assessment of the real risk of the patient. One important new message provided by recent literature is that home blood pressure is a valuable complement to office blood pressure. Indeed, home blood pressure correlates better with the individual risk than office blood pressure and offers the advantage of identifying subsets of hypertensive patients with a low (patients with white-coat hypertension) or an increased (patients with masked hypertension) cardiovascular risk, which would otherwise never be detected unless ambulatory blood pressure were monitored. Moreover, when introduced in the management of treated hypertensive patients, the use of home blood pressure often makes it possible to interrupt treatments which are perhaps not necessary.

Physicians should be encouraged to target a normal blood pressure for all patients. With the antihypertensive medications available today, a reasonable expectation would be that more than 60% of hypertensive patients have normal blood pressure. However, to achieve and, most importantly, to maintain this long-term objective, physicians should perhaps receive additional tools, which may not necessarily be new drugs. Thus, long-term persistence with antihypertensive medications is such an important problem that physicians should become able to monitor drug adherence and to establish a correct diagnosis of poor compliance. New approaches should also be developed to support patients by providing new management opportunities that involve other health professionals, such as nurses and pharmacists.

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Part II

Special groups and target organ damage

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4

Albuminuria as an important biochemical marker for optimal management of essential hypertension

ALBERT MIMRAN, PIERRE FESLER

Introduction

Definition of microalbuminuria

In the absence of urinary tract infection and acute illness, including myocardial infarction |**1**|, the term 'microalbuminuria' refers to patients with Albustix-negative testing and an albumin excretion rate (AER) higher than normal, usually 20 μg/min, as proposed by Mogensen |**2**| but lower than the 200 μg/min considered as the lowest level of macroalbuminuria (overt proteinuria). The sensitivity of the reference methods (radioimmunoassay or nephelometry) used for the estimation of urinary albumin is lower than 1 mg/l. Reactive strips or tablets with a sensitivity limit of more than 20–40 mg/l have become available for screening.

The AER can be quantified in a 24-hour urine collection with a coefficient of variation of approximately 30–35%, peaking at 60% in elderly subjects. Although 24-hour urine collections are frequently used, some groups have suggested the use of overnight timed urine collections or a 4-hour morning collection. Nevertheless, in order to facilitate compliance in large clinical trials, it was proposed to use one or preferably two or three first morning urine samples to estimate the albumin-to-creatinine ratio. In order to reduce the cost, it was shown that the measurement of albumin and creatinine in a single mixed sample of equal-sized aliquots obtained from each of the three first morning collections yielded accurate screening of albuminuria within a normo- to macroalbuminuric range |**3**|.

In recent years, it was shown that, in addition to immunoreactive albumin (detected by radioimmunoassay or immunoturbidimetry), there are non-immunoreactive albumin fragments. Using a newly developed assay based on high-performance liquid chromatography (HPLC), the detection of immunoreactive and non-immunoreactive albumin was made possible. Interestingly, it was ruled out that the

presence of non-immunoreactive albumin was the consequence of urine storage |**4**|. The precise nature of non-immunoreactive albumin (not recognized by antibodies raised against serum albumin) is not known, but it may result from changes in biochemical structure following passage through the glomerular barrier as well as tubular transit. Following intravenous injection of tritium-labelled albumin, no degradation of the molecule was detected in plasma, whereas less than 4% of the total radioactivity was recovered in urine as intact immunoreactive albumin. The capacity for albumin degradation into non-immunoreactive fragments during tubular transit seems to be increased with increasing proteinuria in man |**5**|.

As a consequence, estimation of albuminuria by radioimmunoassay or radioimmunoturbidimetry probably underestimates the level of albuminuria. Of 1312 subjects in the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort, which was artificially enriched in microalbuminuric subjects, 22% were classified as microalbuminuric (albuminuria >30 mg/24 h) and 3% as macroalbuminuric (albuminuria >300 mg/24 h) when albuminuria was estimated by immunonephelemetry. Measurement of albuminuria by HPLC showed that 34% classified as normoalbuminuric by nephelometry became microalbuminuric, whereas the prevalence of macroalbuminuria was unaffected. In fact, for an albuminuria level below 20 mg/l, the HPLC level was approximately 2.5-fold higher. The levels tended to be similar in subjects with radioimmunoassay-detected albuminuria higher than 200 mg/l. This suggests that the bias (HPLC minus nephelometry) markedly increases with decreasing albuminuria |**6**|.

Although the cut-off values of AER are little affected by gender, the albumin/creatinine ratio is markedly higher in women than in men, because of lower urinary excretion of creatinine in women. The recent Kidney Disease Outcomes Quality Initiative (K/DOQI) has proposed guidelines based on the screening of early kidney damage. Microalbuminuria was defined as albumin/creatinine ratio 17–250 mg/g (i.e. 1.9–28 mg/mmol) in men and 25–350 mg/g (i.e. 2.8–40 mg/mmol) in women. Two positive tests within the last 3 months are required for the diagnosis of microalbuminuria |**7**|. Critical analysis of longitudinal studies of patient survival according to baseline AER is now necessary in order to define new cut-off values for AER in the management of hypertensive patients.

Prevalence of microalbuminuria in essential hypertension

Reported figures concerning the prevalence of normal albuminuria in essential hypertension have yielded variable results because of the chosen cut-off value, patient selection and, more importantly, the duration of hypertension and/or the discontinuation of previous treatment associated with adequate or inadequate control of hypertension.

In a cohort of 787 patients aged 18–72 years, studied after discontinuation of antihypertensive treatment for at least 4 weeks, a prevalence of microalbuminuria ($\geq$30 mg/24 h) of 8% was observed |**8**|. A prevalence of microalbuminuria of 6% was found in a cohort of 1041 rather young patients aged 18–45 years with untreated mild hypertension (140–159/90–99 mmHg) |**9**|. Analysis of the population of the

Losartan Intervention For Endpoint reduction in hypertension (LIFE) study of 8029 subjects aged 55–80 years with stage II–III essential hypertension (sitting office blood pressure of 160–200/95–115 mmHg) and electrocardiographic left ventricular hypertrophy (LVH) and using a single cut-off value for AER in men and women (≥3.5 mg/mmol creatinine, corresponding to 30 mg/24 h) revealed a prevalence of microalbuminuria of 26%. Prior to inclusion, treatment was discontinued for 2–4 weeks; this may have reduced the prevalence of microalbuminuria |**10**|. Of interest, it was recently shown that 70% of patients with electrocardiographic LVH included in the LIFE study have echocardiographic LVH (left ventricular mass index, LVMI ≥104 g/m^2 in women and ≥116 g/m^2 in men) |**11**|.

In a subgroup of 480 never-treated individuals aged ≥40 years from our personal cohort of essential hypertensives, analysis of the prevalence of target organ damage (LVH defined as LVMI ≥110 g/m^2 in women and ≥125 g/m^2 in men and microalbuminuria defined as AER ≥30 mg/24 h) showed that 27% had LVH alone and 6% had microalbuminuria alone, whereas both abnormalities were present in 10% of patients and 57% were free of target organ damage. Overall, the presence of microalbuminuria was found in 16%, whereas LVH was found in 37% of the subgroup. In addition, 21% of patients with LVH were classified as microalbuminuric whereas 59% of patients with microalbuminuria had LVH, suggesting that microalbuminuria is a good predictor of the presence of LVH. Of interest, male patients were more frequently affected by the combination of LVH and microalbuminuria than women (15 vs 4% in the subgroup aged ≥40). The group of patients with both LVH and microalbuminuria had the highest arterial pressure level, more smokers and longer known duration of hypertension than patients with one isolated target organ damage. Importantly, urinary sodium excretion taken as an index of dietary sodium intake was markedly higher than in the other groups. AER as well as LVMI were of a similar magnitude when compared with groups with isolated microalbuminuria and LVH, respectively.

Factors influencing the relationship between arterial pressure and albuminuria

It is generally accepted that arterial pressure, mainly systolic arterial pressure (SAP) and to a lesser extent pulse pressure, is the major determinant of albuminuria. As shown in Fig. 4.1, the slope of the relationship between albuminuria and SAP is steeper in men than in women. It appears that albuminuria remains almost unaltered, with SAP within the normotensive (<140 mmHg) range. In contrast, the response of the left ventricle to SAP is linear within the whole range of SAP |**12**|. Some factors were shown to influence this relationship, such as oral contraception in non-menopausal women |**13**|, and impaired glucose tolerance or diabetes. In 2002, du Cailar *et al.* |**14**| assessed the influence of sodium intake (estimated by two consecutive determinations of 24-hour natriuresis) on the relationship between SAP and target organs (i.e. LVMI and AER) in a large cohort of 839 normotensive and never-treated hypertensive subjects aged 15–70 years. It was observed that increasing dietary sodium was associated with an increasingly steeper slope of the relationship SAP versus AER or LVMI. As shown in Table 4.1, the prevalence of LVH, microalbuminuria, or both

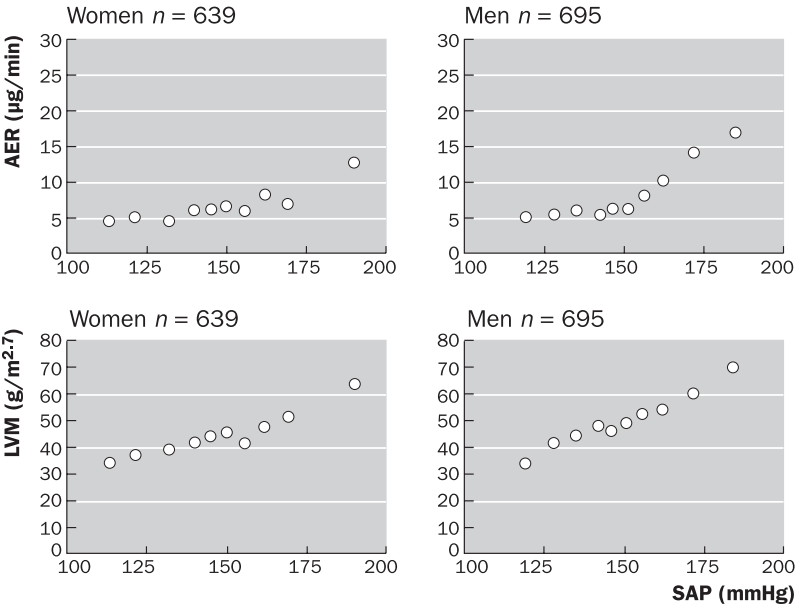

Fig. 4.1 Relationship between deciles of systolic arterial pressure (SAP) and median values of albuminuria (AER) and left ventricular mass (LVM) index. Note that the progression of LVM index with SAP is linear whereas the progression of AER remains relatively flat within the 'normal' range of SAP.

Table 4.1 Prevalence of left ventricular hypertrophy (LVH), microalbuminuria (MA) or both as a percentage of each quintile of urinary sodium excretion (UNaV)

	Quintiles				
	I	II	III	IV	V
UNaV range (mmol/24 h)	18–95	96–124	125–161	162–200	201–415
Presence of LVH (%)	26	29	38	33	49
Presence of MA (%)	5	15	17	17	30
Presence of LVH and MA (%)	3	5	8	8	18

Source: du Cailar *et al*. (2002) |**14**|.

progressively increases from the lowest to the highest quintiles of urinary sodium excretion. This was the first evidence in favour of a modulating influence of dietary sodium on blood pressure-associated target organ lesions.

In addition to SAP, obesity as well as insulin resistance and smoking were shown to be associated with a level of AER inappropriately high for the SAP status |**15**|. The influence of obesity and insulin resistance suggests that albuminuria may be linked to

the presence of the metabolic syndrome. It was reported that in patients with the metabolic syndrome (defined according to the Adult Treatment Panel III [ATP3] report, it has three or more of the following: waist circumference >88 cm in women or 102 cm in men, hypertriglyceridaemia >150 mg/dl, high-density lipoprotein cholesterol <50 mg/dl in women or 40 mg/dl in men, high blood pressure [SAP >130 mmHg, diastolic arterial pressure >85 mmHg] and fasting blood glucose >110 mg/dl), the prevalences of LVH and microalbuminuria were higher in patients with the metabolic syndrome than in those without it (30 vs 24% for LVH and 11 vs 8% for microalbuminuria) |**16**|. Similar prevalences of target organ damage were found in larger population studies; in fact, the prevalence of microalbuminuria increased with the number of components of the metabolic syndrome (from 3% in subjects without any abnormality to 9.8% in those with three abnormalities and 22.1% in subjects with five abnormalities) |**17**|.

C-reactive protein (CRP) is a sensitive marker of subclinical inflammation which has been shown to be a good predictor of cardiovascular outcome. In a cross-sectional study conducted in the very large Groningen cohort, Stuveling *et al.* |**18**| observed that increasing CRP values from 0.2 to 10 mg/l resulted in a remarkable steepening of the slope of albuminuria versus mean arterial pressure; however, the potentiating trend became significant for mean arterial pressures above 90 mmHg.

With regard to plasma homocysteine as a predictor of clinical disease, it was shown that this parameter was correlated with arterial stiffness assessed by pulse wave velocity in hypertensive subjects with a mean age of 58 years |**19**|. Nevertheless, the highest level of homocysteine was associated with the lowest level of glomerular filtration rate (GFR). Taking into account the fact that plasma homocysteine concentration is closely related to renal function |**20**|, the significance of plasma homocysteine should be considered with great caution.

In the future, the advent of reliable methods for the measurement of superoxide radicals might be a useful marker in the management and treatment of essential hypertension.

In some studies it was reported that the extent of the night dipping of blood pressure tended to be blunted in subjects with abnormal albuminuria |**21**|.

Albuminuria and treatment of hypertension

In the Treatment of Mild Hypertension Study (TOMHS) conducted in patients with mild hypertension (diastolic blood pressure 85–99 mmHg), it was reported that the use of enalapril over 12 months afforded a larger decrease in albuminuria despite a similar achieved blood pressure decrease when compared with acebutolol, amlodipine, chlortalidone and doxazosin |**22**|. In the population of the LIFE study, administration for 4.8 yrs of a losartan (an angiotensin II receptor antagonist)- or atenolol (a beta-blocker)-based treatment to a target blood pressure of 140/90 mmHg, was associated with a more marked decrease in AER with losartan (–33 vs –25% at 1 year of follow-up) |**23**|. As in most studies on the long-term effect of treatment on target organ damage, the number and characteristics of patients in whom no improvement in LVH or AER occurred were not disclosed. Efforts should be devoted to the issue

of resistance of target organ damage despite adequate control of blood pressure. In a study conducted in 187 normoalbuminuric patients aged less than 50 years with previously untreated hypertension and followed up for 2.7 years on various antihypertensive regimens, including angiotensin-converting enzyme (ACE) inhibitors, Redon *et al.* |**24**| observed progression from normo- to microalbuminuria (≥30 mg/24 h) in 11% of patients, and less frequently in ACE inhibitor-treated subjects. Moreover, a tendency to a higher body mass index, less reduction in blood pressure and increases in blood glucose and uric acid were found in 'albuminuria progressors'. Analysis of the influence of obesity, insulin resistance or the metabolic syndrome and, more importantly, sodium intake could be of great value in the search for causes of resistance of target organ damage despite satisfactory control of blood pressure.

Is albuminuria a predictor of subsequent renal disease?

Microalbuminuria was originally used to detect subjects at risk of the development of overt proteinuria and subsequently progressive renal insufficiency associated with insulin-dependent diabetes mellitus. In the early (incipient) stage of diabetic nephropathy, microalbuminuria was associated with glomerular hyperfiltration, suggestive of elevated intraglomerular pressure, in patients who subsequently progressed to macroalbuminuria |**2**|. The value of microalbuminuria as a predictor of the future development of nephropathy associated with type 2 diabetes mellitus is less than certain, probably because of the less uniform histological pattern of renal lesions resulting from the almost constant superimposition of essential hypertension and obesity-related renal abnormalities. Nevertheless, in the analysis of the Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, conducted in patients with clinical proteinuria (>0.03 g/mmol or >0.5 g/24 h), de Zeeuw *et al.* |**25**| observed that the risk of reaching the renal end-point of doubling of serum creatinine or end-stage renal disease within a follow-up period of 3.4 years was positively correlated with baseline and in-treatment (after 6 months of satisfactory control of hypertension) proteinuria. If we admit that proteinuria is a predictor of progressive renal disease, it is crucial to try to prevent the progression from micro- to macroalbuminuria and eventually from normo- to microalbuminuria. Both attempts have been successful after pharmacological blockade of the renin–angiotensin system, as demonstrated by the Irbesartan Reduction Microalbuminuria (IRMA) study with the angiotensin II antagonist irbesartan |**26**| and more recently the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) using the ACE inhibitor trandolapril |**27**| by comparison with placebo and the non-dihydropyridine calcium-channel blocker verapamil, respectively. As reported by Parving *et al.* (IRMA study) |**26**|, administration of irbesartan was associated with a reduction (from 14.9 with placebo to 9.7 and 5.2% with 150 and 300 mg daily of irbesartan, respectively) in the number of patients progressing from micro- to macroalbuminuria within a 2-year period. When the progression rate from normo- to microalbuminuria within a 3-year period was compared in patients given trandolapril, verapamil or both, the primary outcome

was achieved in 6, 11.9 and 5.7%, respectively. Despite a similar decrease in blood pressure, the ACE inhibitor was superior to verapamil in preventing the evolution to incipient nephropathy. It was interesting to note that blood pressure targets of 135/85 mmHg (IRMA) and 120/80 mmHg (BENEDICT) were chosen; however, the mean values of final blood pressure remained well above the objective. In both studies, analysis of the outcome according to the issue of whether the desired blood pressure target was reached would be of great interest.

In type 2 diabetes mellitus, low GFR (<60 ml/min per 1.73 m^2 using plasma clearance of the radioactive marker 99m-Tc-DTPA) was identified in 36% of a group of 301 patients. Microalbuminuria and clinical proteinuria were present in 35 and 26% of subjects with low GFR, whereas 39% presented with normoalbuminuria (<30 mg/day). Within a follow-up period of 3–10 years, GFR decreased to a similar extent whatever the status of baseline albuminuria |**28**|.

In population studies, no correlation between albuminuria and GFR has been detected. In the PREVEND, study conducted in non-diabetic residents of the city of Groningen (The Netherlands), it was observed that GFR, estimated by 24-hour creatinine clearance, tended to be elevated in subjects with high–normal AER (15–30 mg/day), whereas macroalbuminuria was independently associated with a slight reduction in creatinine clearance below values expected for age and sex |**29**|. In the study conducted in a sample of 1632 subjects aged 45–64 years from Gubbio, an Italian community, no relationship between increasing AER and the prevalence of 'low' creatinine clearance (<60 ml/min) was found |**30**|.

In the PREVEND cohort and within a follow-up period of 4 years, an incidence of *de novo* development of renal insufficiency (creatinine clearance <60 ml/min per 1.73 m^2) of 4.2% was observed. Although age, serum cholesterol and glucose were higher whereas baseline renal function was lower in this group of the population, multivariate analysis showed that baseline AER was a good predictor of the risk of developing impaired renal function |**31**|. In a group of 486 Aborigines (10.5% with type 2 diabetes mellitus at inclusion), Hoy *et al.* |**32**| reported a close correlation between baseline albuminuria (range <1.1 mg/mmol in 30% to >100 mg/mmol in 6.2% of the population) and the decline in GFR estimated by the Cockroft and Gault equation within a follow-up period of 1–6 years. The annual decrease in GFR, which was almost negligible in normoalbuminuric people, increased to 2.2 and 11.6 ml/min per year in micro- and macroalbuminuric subjects, respectively.

In patients with essential hypertension, no difference in GFR was detected between normo- and microalbuminuric individuals, and no alteration in intrarenal haemodynamics, including an increase in the filtration fraction that would be suggestive of an elevated intraglomerular pressure, was detected. Of interest, the renal vasodilatory response to acute administration of the ACE inhibitor captopril was significantly blunted in microalbuminuric subjects, despite a similar level of circulating renin. This suggested that microalbuminuria may be a marker of early functional or fixed intrarenal vascular dysfunction |**33**|. In a minority of patients, hyperfiltration relative to a theoretical age-related value may be observed and may be associated with a slightly higher level of albuminuria |**21**|. Whether microalbuminuria or hyperfiltration is a

precursor of further renal alterations, as already reported in type 1 diabetes, remains to be documented.

In cross-sectional studies, age is strongly and inversely correlated with GFR, and glomerular filtration falls progressively during ageing at a rate of approximately 0.5–1 ml/min per year. Several factors were identified as accelerators of the age-related decline in GFR. In a recent study conducted in 195 normotensive subjects and 645 patients with never-treated hypertension, it was observed that the existence of hypertension and (more precisely) concentric LVH was associated with a marked acceleration of the age-related decline in GFR |**34**|. Other cross-sectional studies have shown that the slope of the relationship of age with GFR is steeper in patients with impaired glucose tolerance or diabetes discovered during an oral glucose tolerance test |**35**|.

Although a recent longitudinal study confirmed that the decline in GFR found in hypertensive subjects left untreated for 6 years was greater than in a normotensive group (–1.22 vs 0.12 ml/min using 99m-Tc-DTPA urinary clearance) |**36**|, only a few studies have assessed the evolution of renal function during long-term antihypertensive treatment in individuals with normal renal function. In a retrospective study conducted in 141 patients (38% with microalbuminuria, defined as 30–300 mg/day), it was shown that, within the 7 years of follow-up, the decrease in 24-hour creatinine clearance amounted to 12.1 ml/min in microalbuminuria versus 7.7 ml/min in normoalbuminuric patients; no influence of the type of antihypertensive regimen (containing or not an ACE inhibitor) was observed |**37**|. Within a follow-up period of 14 years, a decrease in GFR, estimated by inulin clearance, of approximately 19 ml/min was found in a small group of 23 hypertensive subjects adequately controlled by antihypertensive therapy |**38**|. No relationship between baseline albuminuria and the yearly decline in GFR was reported in most studies |**36,38**|. Of interest, the most important determinant of the GFR progression was the baseline level of blood pressure.

Albuminuria and cardiovascular morbidity and mortality

In the last few years, several studies have pointed out the role of microalbuminuria as a predictor of cardiovascular morbidity |**39–41**| and mortality |**39,42–45**|. The main characteristics of some of these important prospective studies are shown in Table 4.2. It clearly appears that threshold values of microalbuminuria are consistently lower than the usually accepted cut-off points. In studies performed in people aged more than 40 years, the risk of increased cardiovascular mortality was significant above AER values of 1.28 mg/mmol |**39**| to 2 mg/mmol |**44**|, which correspond to 10–16 μg/min in timed urine collections. In contrast, in two studies conducted in populations aged 30–70 years |**40,41**| with ischaemic heart disease as the primary endpoint, the threshold of AER was 0.65 mg/mmol creatinine, roughly corresponding to 5–6 μg/min. The hypothesis that microalbuminuria may reflect generalized atherosclerosis was tested in the 5-year follow-up period of the Hoorn study |**44**|, conducted in subjects aged 50–75 years. It was observed that both microalbuminuria (albumin/creatinine >2 mg/mmol) and peripheral arterial disease (assessed by the ankle–brachial index) were associated with a four-fold increase in cardiovascular mortality

Table 4.2 Morbidity mortality studies and albuminuria

Study name	Age range (years)	Population characteristics	Follow-up duration (years)	Outcome	Cut-off value of albuminuria
LIFE |**39**|	55–80	EKG LVH	4.8	Cardiovascular death, first MI, stroke	>1.28 mg/mmol (10 μg/min)
Utrecht |**45**|	52–67	Post-menopausal	20	Cardiovascular death	>2.4 mg/mmol (18 μg/min)
MONICA |**40**|	30–70	Blood pressure <150/90 mmHg	10	CHD	>0.65 mg/mmol (5.1 μg/min)
HOORN |**44**|	50–75	Peripheral arterial disease	5	Cardiovascular death	>2 mg/mmol (16 μg/min)
Copenhagen |**41**|	30–70	Hypertension in 10–15%	5	CHD	>4.8 μg/min (0.64 mg/mmol)
HUNT |**42**|	>20	Non-diabetics	4.4	All-cause death	>0.76 mg/mmol (6 μg/min)
HUNT |**43**|	>20	Treated hypertension	4.3	All-cause death	>1.7 mg/mmol (13.3 μg/min)

EKG LVH, electrical left ventricular hypertrophy; MI, myocardial infarction; CHD, coronary heart disease.
Source: adapted from references |**39**| to |**45**|.

which was more marked in hypertensive than in normotensive people; however, it was concluded that microalbuminuria affected mortality through a mechanism different from extensive atherosclerosis.

Significance of excessive albuminuria

Although albuminuria results from exaggerated transglomerular passage of albumin blood driven by blood pressure rather than from decreased tubular reabsorption of albumin, it is now accepted as a marker of increased leakiness of systemic vessels. This hypothesis was documented by the association of microalbuminuria with an increased transcapillary escape rate of albumin |**46,47**|. It is widely claimed that albuminuria is a marker of endothelial dysfunction. When this parameter was assessed by the post-ischaemia dilatation of the brachial artery, blunting of the response to ischaemia was observed for AER >6.6 μg/min in normotensive individuals |**48**|. In another study, no correlation was found between AER and the vasodilatory response of the forearm circulation to the endothelium-dependent agent acetylcholine in subjects with essential hypertension |**49**|. All these vascular abnormalities, together with the important impact of mild impairment in renal function, which may act through endothelial impairment and/or mediators of inflammation, such as CRP, may require further studies.

In a recent study conducted in 1499 non-hypertensive (<140/90 mmHg) individuals (mean age of 55 years), it was reported that the albumin/creatinine ratio was a significant predictor of incident hypertension or progression of blood pressure to

a higher category, as defined by the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) |**50**|, within a mean follow-up period of 2.9 years. A 2-fold risk of developing hypertension and a 1.5-fold risk of blood pressure progression was associ-ated with albumin/creatinine values >0.58 mg/mmol in men and >1.36 mg/mol in women |**51**|.

Should we redefine the presently used threshold for microalbuminuria?

Most studies have defined microalbuminuria as AER ≥20 μg/min, corresponding roughly to an albumin/creatinine ratio of 2.5 and 3.5 mg/mmol creatinine in men and women respectively in a first morning urine sample |**2**|. Such 'normal' values were obtained in so-called normotensive insulin-dependent diabetic subjects with blood pressure <140/90 mmHg and without taking into account factors known to enhance the relationship between AER and blood pressure, such as smoking, cholesterol status and body mass index. In addition, the AER threshold value of 20 μg/min corresponded to the value associated with progression to overt diabetic nephropathy. We recently analysed AER values in an unselected population of 220 normotensive (<140/90 mmHg) subjects (mostly potential kidney donors). The AER values within the 75th and 95th percentiles were 8.2 and 16.4 μg/min, respectively (corresponding to 1 and 2.27 mg/mmol creatinine). When strict selection was performed (exclusion of smokers, body mass index >25 kg/m^2, cholesterol level >220 mg/dl) and, most importantly, blood pressure was within the optimal range (systolic pressure <120 mmHg and diastolic pressure <80 mmHg), the 75th and 95th percentiles were 5.7 and 9.8 μg/min (corresponding to albumin/creatinine ratios of 0.7 and 1.58 mg/ mmol) |**12**|.

The important question of whether reduction in AER during treatment translates into risk reduction has recently been approached in the LIFE study. Although baseline AER did not identify the treatment group with the largest benefit, the reduction in AER at years 1 and 2 of treatment to values below the median in-treatment level (albumin/creatinine ratio 0.67 mg/mmol) was associated with a significant reduction in severe risk |**23**|.

Taking these results together, and if the reduction in the risk of cardiovascular complications is our main concern, an albumin/creatinine ratio of less than 1.2 mg/ mmol (10 μg/min) may be proposed as the lower limit of microalbuminuria.

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5

Hypertension and the kidney

PETER HART, GEORGE BAKRIS

Introduction

Macroalbuminuria or proteinuria (≥300 mg albumin/g creatinine) in a morning spot urine is an established risk factor for the presence of cardiovascular disease and for progression of kidney disease. Recent pharmacological interventions with agents that lower blood pressure and reduce albuminuria in people with pre-existing kidney disease have resulted in attenuated progression of microalbuminuria (<300 mg albumin/g creatinine) to macroalbuminuria, a clear marker of the presence of kidney disease and of slowed decline in glomerular filtration rate (GFR). Current guidelines recommend that patients with kidney disease, either from diabetes or non-diabetic causes, be started on agents that block the renin–angiotensin–aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as part of a combination of medications to achieve blood pressure goals |**1,2**|. These agents are recommended since they attenuate the progression of micro- to macroalbuminuria and reduce the progression of kidney disease.

In almost all patients with kidney disease, an average of three to four drugs is frequently needed to reach the recommended goal blood pressure of <130/80 mmHg and to effectively lower albuminuria |**2**|. While RAAS blockers are effective in slowing kidney disease progression in patients with kidney disease and albuminuria, the timing of therapy initiation and the choice of which drug or drugs should be used to maximally reduce albuminuria and achieve the blood pressure goal in order to maximally slow kidney disease progression is not well defined in the literature.

We have reviewed eight key papers published in the last two years. These papers focus on changes in albuminuria as a therapeutic target in the context of both kidney and cardiovascular outcomes in people with kidney disease and highlight strategies to lower albuminuria in patients with hypertension and diabetic or non-diabetic renal disease.

Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for end-point reduction in hypertension study

Ibsen H, Olsen MH, Wachtell K, *et al*. *Hypertension* 2005; **45**: 198–202

Background. Albuminuria is a powerful predictor of cardiovascular risk. However, few studies have evaluated whether changes in albuminuria over time translate into changes in cardiovascular events. The purpose of this study was to examine whether changes in albuminuria during 4.8 years of antihypertensive treatment were related to changes in the risk of cardiovascular events in 8206 patients with hypertension and left ventricular hypertrophy in the Losartan Intervention for End-point reduction in hypertension (LIFE) trial. The urinary albumin/creatinine ratio (UACR) was measured at baseline and annually thereafter. Time-varying albuminuria was closely related to risk of the primary composite end-point (cardiovascular mortality, stroke and myocardial infarction). Thus, when UACR decreased during treatment, the risk was reduced accordingly (Fig. 5.1). When the population was divided according to a median baseline value of 1.21 mg/mmol (10.6 mg/g) and median year-1 UACR of 0.67 mg/mmol (5.9 mg/g), the risk increased stepwise and significantly for the primary composite end-point from patients with low baseline/low year-1 (5.5%), to low baseline/high year-1 (8.6%), to high baseline/low year-1 (9.4%) and to high baseline/high year-1 (13.5%) values. Similar significant stepwise increases in risk were seen for the components of the primary composite end-point (cardiovascular mortality, stroke and myocardial infarction). The observation that changes in UACR during antihypertensive treatment over time translated into changes in the risk of cardiovascular morbidity

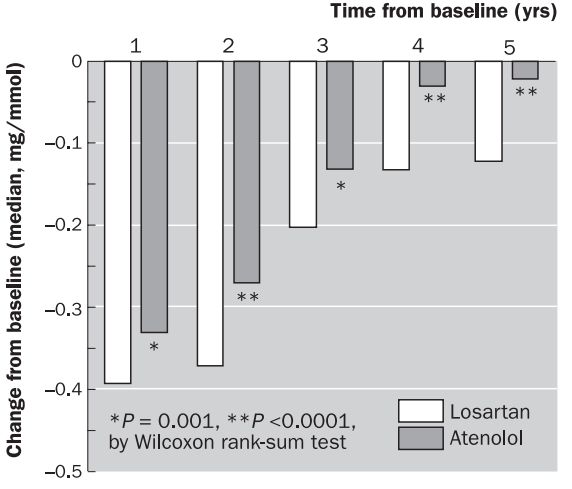

Fig. 5.1 Annual change from median baseline in albumin:creatinine ratio in the LIFE trial associated with number of primary end-point events. Source: Ibsen *et al*. (2005).

and mortality was not explained by the on-treatment level of blood pressure. The authors concluded that monitoring albuminuria should be an integral part of the management of hypertension. If albuminuria is not decreased on the patient's current antihypertensive and other treatment regimen, further intervention directed towards blood pressure control and other modifiable risks should be considered.

INTERPRETATION. This *post hoc* analysis of an older cohort (mean age 67 ± 7 years) with the presence of predominantly stage 2 nephropathy, based on the range of serum creatinine values, suggests that the level of albuminuria during antihypertensive therapy is closely related to cardiovascular events. It supports previous data indicating that, among patients with hypertension and left ventricular hypertrophy, the cardiovascular risk increases substantially as UACR increases from levels above 1.2 mg/mmol (10.6 mg/g). This level is much lower than the traditional definition of microalbuminuria, defined as 30–300 mg/g, implying that a cardiovascular risk that is higher than expected may already be present by the time microalbuminuria is detected. Additionally, it supports the notion that antihypertensive therapies that are associated not only with lowering of blood pressure but also with albuminuria produce better cardiovascular outcomes.

Comment

The magnitude of albuminuria is known to be a measure of increased vascular permeability, and an integral marker of structural and functional abnormalities in hypertension, such as endothelial dysfunction and loss of vascular integrity, the progression of which is associated with renal dysfunction |**3,4**|. The LIFE investigators and others have previously shown that baseline albuminuria is an independent predictor of the subsequent risk of cardiovascular complications in patients with hypertension |**5,6**|. These data support a notion that is espoused by many current guidelines: that physicians should assess the level of albuminuria in all patients with hypertension and the presence of either diabetes or kidney disease using a spot albumin:creatinine ratio test. Antihypertensive agents that lower blood pressure and reduce albuminuria are recommended to help achieve blood pressure goals and reduce cardiovascular risk. It should be assumed that using an agent that blocks the RAAS will automatically reduce albuminuria since salt intake can markedly blunt the effectiveness of these agents in reducing albuminuria. Thus, if these agents are used and albuminuria is not reduced, a 24-hour urine specimen should be checked along with urinary creatinine to ensure a sodium intake of less than 6 g per day.

The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African-American study of kidney disease and hypertension

Lea J, Greene T, Lipkowitz M, *et al*. *Arch Intern Med* 2005; **165**: 947–53

BACKGROUND. The magnitude of proteinuria is associated with a graded increase in the risk of progression to end-stage renal disease (ESRD) and cardiovascular

events. The purpose of this trial was to relate baseline levels and early changes in proteinuria and GFR to the long-term progression of hypertensive non-diabetic kidney disease. The trial had a randomized 3 × 2 factorial design and a total of 1094 African-Americans aged 18–70 years with hypertensive renal disease (GFR 20–65 ml/min per 1.73 m^2) were followed for a median of 3.8 years. Participants were randomly assigned to either of two mean arterial pressure goals (102–107 mmHg [usual] or <92 mmHg [lower]) and to initial treatment with a β-blocker (metoprolol), an ACE inhibitor (ramipril) or a dihydropyridine calcium channel blocker (amlodipine). Other agents were added to achieve the assigned blood-pressure goals. Both baseline proteinuria and GFR predicted the rate of GFR decline. For each 2-fold higher proteinuria level, an increase in the rate of GFR decline of 0.54 ± 0.05 ml/min per 1.73 m^2 per year was observed (P <0.001), and for each 10 ml/min per 1.73 m^2 lower baseline GFR there was an associated increase in mean GFR of 0.38 ± 0.08 ml/min per 1.73 m^2 per year (P <0.001). In multivariable regression analysis the effect of baseline proteinuria on decline in GFR persisted, unlike the effect of baseline GFR after adjusting for baseline proteinuria. The initial change in proteinuria from baseline to 6 months was a predictor of subsequent progression at 5 years, even with participants with a baseline proteinuria less than 300 mg/day (Fig. 5.2). The authors concluded that the change in the level of proteinuria is a predictor of progression of hypertensive kidney disease at a given level of GFR.

Interpretation. This *post hoc* analysis of a well-designed and adequately powered study demonstrates that both baseline levels and the initial change from baseline to

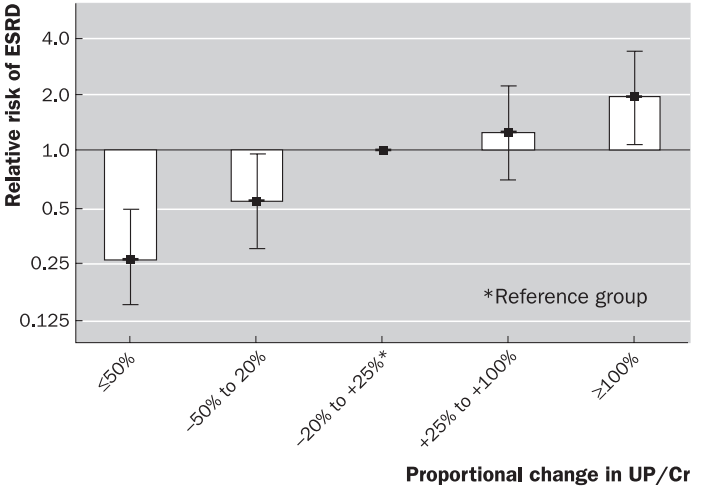

Fig. 5.2 Six-month change in proteinuria from baseline predicts outcome of kidney disease at five years. Comparator is no change in proteinuria ±20% from baseline. Note those with >50% reduction in proteinuria at 6 months had the slowest rate of progression to ESRD at 5 years. Source: Lea *et al*. (2005).

6 months in proteinuria predicts subsequent progression of hypertensive kidney disease to ESRD. This relationship was also observed in people with low levels of albuminuria (<300 mg/day). This association of early changes in proteinuria and subsequent renal outcomes in people who have lost 50% or more of their kidney function suggests that the effects of antihypertensive agents on proteinuria and blood pressure lowering should be considered when selecting antihypertensive agents to slow the progression of renal disease.

Comment

Over the past decade many clinical trials have reported a clear relationship between early reductions of 30–70% in proteinuria and slower rates of progression of kidney disease in people with stage 3 or greater nephropathy (estimated glomerular filtration rate [eGFR] <60 ml/min) |**7–11**|. This was especially magnified in the COOPERATE trial, reviewed later in this section, where the further reduction in proteinuria resulted in a lower ESRD rate, independent of blood pressure reduction. However, these benefits in terms of renal outcome (e.g. time to ESRD) are not clearly demonstrated in those with microalbuminuria, since most of these people have better preserved kidney function (GFR >60 ml/min). However, this study and more recent observational studies suggest that it is the level of proteinuria as well as the GFR that determines the subsequent course of progressive renal damage. Thus, in people with hypertensive renal disease with proteinuria including low levels of albuminuria, a strong consideration should be given to antihypertensive agents such as renin–angiotensin–aldosterone blockers, which have consistently been shown to reduce proteinuria and retard the progression of renal disease.

Proteinuria, a target for renoprotection in patients with Type 2 diabetic nephropathy: lessons from RENAAL

de Zeeuw D, Remuzzi G, Parving HH, *et al*. *Kidney Int* 2004; **65**: 2309–20

Background. Proteinuria or albuminuria is a well-known independent risk marker for progressive loss of renal function. There are effective therapeutic agents to reduce albuminuria, such as RAAS blockers, but these agents also lower blood pressure. Thus, it is difficult to distinguish between the antihypertensive and antiproteinuric effects of these agents in terms of renoprotection. The purpose of the trial was to determine whether albuminuria could not only serve as a marker of renal disease but also function as a monitor of the renoprotective efficacy of RAAS intervention by the angiotensin II antagonist losartan in patients with diabetic nephropathy. The data from the RENAAL (Reduction in End-points in Non-insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) study, a double-blind, randomized trial, were used to examine the effects of losartan on the renal outcome (i.e. the primary composite end-point of the doubling of serum creatinine, ESRD or death) in 1513 Type 2 diabetic patients with nephropathy. The study examined the effect of the degree of albuminuria at baseline, the initial antiproteinuric response to therapy and the degree of remaining (residual)

albuminuria on renal outcome (either the primary composite end-point or ESRD). Also evaluated was the contribution to renal protection of the antiproteinuric effect of losartan independently of changes in blood pressure. The results showed that baseline albuminuria is almost linearly related to renal outcome, and is the strongest predictor among all measured well-known baseline risk parameters. After adjusting for the baseline risk markers of age, gender, race, weight, smoking, sitting diastolic blood pressure, sitting systolic blood pressure, total cholesterol, serum creatinine, albuminuria, haemoglobin and haemoglobin A(1c), patients with high baseline albuminuria (≥3.0 g/g creatinine) showed a 5.2-fold (95% confidence interval [CI] 4.3–6.3) increased risk of reaching a renal end-point, and a 8.1-fold (95% CI 6.1–10.8) increased risk of progressing to ESRD, compared with the low-albuminuria group (<1.5 g/g). The changes in albuminuria in the first 6 months of therapy were linearly related to the degree of long-term renal protection: for every 50% reduction in albuminuria in the first 6 months there was a reduction in risk of 36% for renal end-point and 45% for ESRD during later follow-up. Albuminuria at month 6 (designated residual albuminuria) showed a linear relationship with renal outcome, almost identical to the relationship between baseline albuminuria and renal risk. Losartan reduced albuminuria by 28% (95% CI –25% to –36%), while placebo increased albuminuria by 4% (95% CI +8% to –1%) in the first 6 months of therapy. The specific renoprotective effect of the angiotensin II antagonist losartan in this study was thought to be due to an anti-albuminuric effect (approximately 100% for the renal end-point and 50% for the ESRD end-point). The authors concluded that albuminuria is the predominant renal risk marker in patients with Type 2 diabetic nephropathy on conventional treatment, and that the higher the albuminuria the greater the renal risk. Reduction in albuminuria was associated with a proportional effect on renal protection: the greater the reduction the greater the renal protection. The residual albuminuria on therapy (month 6) was as strong a marker of renal outcome as was baseline albuminuria. Thus, albuminuria should be considered a risk marker for progressive loss of renal function in Type 2 diabetes with nephropathy, as well as a target for therapy. Reduction of residual albuminuria to the lowest achievable level should be viewed as a goal for future renoprotective treatments.

INTERPRETATION. This *post hoc* analysis shows that, in people with nephropathy associated with Type 2 diabetes, albuminuria is a major marker of the subsequent progression of diabetic nephropathy. Reduction in albuminuria was associated with decrease in renal risk and predicted end-organ protection. Additionally, the study showed that the greater the reduction in albuminuria over the initial 6-month period and the lower the albuminuria level after 6 months of treatment, the lower the likelihood that a patient would experience doubling of creatinine or ESRD. This finding is similar to that described in the African American Study of Kidney Disease (AASK) trial, another study of patients with non-diabetic nephropathy. Patients who received the ARB losartan had a lower risk of a renal event compared with the placebo group, particularly those with high baseline albuminuria (>3.5 g/g). The mean reduction in the systolic blood pressure (baseline versus study end) in the losartan group was 12 mmHg compared with 9.2 mmHg in the placebo group. Although the authors suggested that the renoprotective effect of the ARB losartan was primarily due to its antiproteinuric effect, the losartan group had a mean systolic blood pressure approximately 3 mmHg lower than the placebo group, and this difference may have contributed to the renoprotection in the losartan group.

Comment

As in trials of non-diabetic kidney disease, e.g. AASK, AIPRI (Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency) and REIN (Ramipril Efficacy In Nephropathy), which demonstrate that RAAS blockers retard the progression of kidney disease by reducing not only blood pressure but also albuminuria levels, there are now data in diabetic nephropathy. This observation in diabetic nephropathy has previously been observed in relatively small studies and in a retrospective analysis of Type 1 diabetes. This study confirms the notion that albuminuria should become a target for therapy similar to blood pressure levels for renoprotection in Type 2 diabetes. However, the small but important difference in blood pressure levels in the losartan group compared with the placebo group does indicate that other factors may have coincided with the changes in albuminuria and could have influenced the outcome. It is also possible that the dose–response curves for blood pressure and albuminuria may be different |**12,13**|. Thus, there is a need for a randomized controlled trial that targets reduction in albuminuria as an index of risk renal outcomes with the goal of reducing albuminuria in concert with the reduction of blood pressure to the lowest achievable goal.

Preventing microalbuminuria in Type 2 diabetes

Ruggenenti P, Fassi A, Ilieva AP, *et al.*; Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. *N Engl J Med* 2004; **351**(19): 1941–51

Background. The multicentre, double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether ACE inhibitors and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, Type 2 diabetes mellitus and normal urinary albumin excretion. A total of 1204 subjects were randomly assigned to receive at least 3 years of treatment with trandolapril (at a dose of 2 mg per day) plus verapamil (sustained-release formulation, 180 mg per day), trandolapril alone (2 mg per day), verapamil alone (sustained-release formulation, 240 mg per day) or placebo. The target blood pressure was 120/80 mmHg. The primary end-point was the development of persistent microalbuminuria, defined as overnight albumin excretion at ≥20 μg/min at two consecutive visits. The primary outcome was reached in 5.7% of the subjects receiving trandolapril plus verapamil, 6.0% of the subjects receiving trandolapril alone, 11.9% of the subjects receiving verapamil alone and 10.0% of control subjects receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression), adjusted for predefined baseline characteristics, was 0.39 for the comparison between verapamil plus trandolapril and placebo ($P = 0.01$), 0.47 for the comparison between trandolapril and placebo ($P = 0.01$), and 0.83 for the comparison between verapamil and placebo ($P = 0.54$). Thus, trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of

2.6 and 2.1, respectively. The authors concluded that, in patients with normoalbuminuria who had diabetes and hypertension, the incidence of progression to microalbuminuria was decreased to similar extents by the use of trandolapril plus verapamil and that of trandolapril alone. The effect of verapamil alone was similar to that of placebo.

INTERPRETATION. Patients with diabetes and hypertension who develop microalbuminuria are at higher cardiovascular risk and those who progress to macroalbuminuria (>300 mg/g) have kidney disease. RAAS blockers, such as ACE inhibitors and ARBs, are very effective agents for reducing microalbuminuria in those with established kidney disease. Data on the use of non-dihydropyridine calcium channel blockers, such as verapamil, for microalbuminuria reduction are less consistent than with RAAS blockers. While there is an additive effect when verapamil is combined with an ACE inhibitor on proteinuria reduction, there is no evidence that this effect would occur with microalbuminuria since it is more a marker of inflammation and verapamil is not known to reduce vascular inflammation. Thus, the key question in this study was to determine whether ACE inhibitors combined with non-dihydropyridine calcium channel blockers can prevent the development of microalbuminuria in patients with Type 2 diabetes and hypertension. The data confirm previous studies, showing that an ACE inhibitor reduced the incidence of new-onset microalbuminuria and the addition of verapamil added nothing to this benefit. Moreover, verapamil alone failed to slow the development of microalbuminuria. This difference could not be explained by a difference in blood pressure.

Comment

Microalbuminuria is an inflammatory marker and mirrors high sensitivity C-reactive protein (hs-CRP) activity. While RAAS blockers have been shown to reduce this cardiovascular risk marker, no calcium channel blocker has been shown to have this effect independently of blood pressure reduction. Had this study achieved the blood pressure goal stated in the study design, i.e. 120/80 mmHg, an additional benefit would have theoretically been predicted based on animal data, but at the levels of blood pressure achieved, a reduced development of this marker would not have been predicted |**14,15**|. This study supports the concept already appreciated—that RAAS blockers reduce cardiovascular risk. Unfortunately, it adds little to our knowledge of the progression of kidney disease. The important data from this trial will come in the second half—the evaluation of those who develop microalbuminuria and progress to macroalbuminuria; this will be available in 2 years. These data will add to the established knowledge that ACE inhibitors and ARBs retard the development of macroalbuminuria in Type 2 diabetes |**16**|. Whether the results of this study will translate into a reduction in the number and severity of diabetic complications cannot be answered by this relatively short-term and underpowered study.

Angiotensin-receptor blockade versus converting-enzyme inhibition in Type 2 diabetes and nephropathy

Barnett AH, Bain SC, Bouter P, *et al*.; the DETAIL group. *N Engl J Med* 2004; **351**: 1952–61

BACKGROUND. Few studies have directly compared the renoprotective effects of angiotensin II-receptor blockers and ACE inhibitors in persons with Type 2 diabetes. In this prospective, multicentre, double-blind, 5-year study, 250 subjects with Type 2 diabetes and early nephropathy were randomly assigned to receive either the angiotensin II-receptor blocker telmisartan (80 mg daily, in 120 subjects) or the ACE inhibitor enalapril (20 mg daily, in 130 subjects). The primary end-point was the change in the GFR (determined by measuring the plasma clearance of iohexol) between the baseline value and the last available value during the 5-year treatment period. Secondary end-points included the annual changes in the GFR, serum creatinine level, urinary albumin excretion and blood pressure, the rates of ESRD and cardiovascular events, and the rate of death from all causes. After 5 years, the change in the GFR was –17.9 ml/min per 1.73 m^2 of body surface area, where the minus sign denotes a decrement, with telmisartan (in 103 subjects), compared with –14.9 ml/min per 1.73 m^2 with enalapril (in 113 subjects), giving a treatment difference of –3.0 ml/min per 1.73 m^2 (95% CI –7.6 to 1.6 ml/min per 1.73 m^2). The lower boundary of the confidence interval, in favour of enalapril, was greater than the predefined margin of –10.0 ml/min per 1.73 m^2, indicating that telmisartan was not inferior to enalapril. The effects of the two agents on the secondary end-points were not significantly different after 5 years. The authors concluded that telmisartan is not inferior to enalapril in providing long-term renoprotection in persons with Type 2 diabetes. These findings do not necessarily apply to persons with more advanced nephropathy, but they support the clinical equivalence of angiotensin II-receptor blockers and ACE inhibitors in persons with conditions that place them at high risk of cardiovascular events.

INTERPRETATION. This study was designed as a non-inferiority study to directly compare the ACE inhibitor enalapril with the ARB telmisartan, in order to determine if there was a substantive difference between the two classes with regard to preventing the progression of diabetic nephropathy in patients with Type 2 diabetes. The data indicate that the effects of enalapril and telmisartan on the progression of diabetic nephropathy do not differ. Moreover, the relationship between the changes in urinary albumin excretion, reported as the ratio of the final value to the baseline value, also did not differ between the telmisartan and enalapril groups.

Comment

There are very few trials that have directly compared the ACE inhibitors with ARBs to determine which of the RAAS blockers are more effective in (i) preventing microalbuminuria, (ii) reducing the rate of progression from microalbuminuria to macroalbuminuria and (iii) delaying the progression of nephropathy. These initial trials were relatively short-term studies and indicated that the ACE inhibitors and ARBs

reduced albuminuria to an equal degree |**17**|. This study adds little to the database of other large, long-term, event-driven, multicentre studies. The study was substantially underpowered—it was a non-inferiority study and had a very high dropout rate (about 33%) in each group. Thus, it does not answer the question of whether an ARB differs from an ACE inhibitor in terms of the progression of kidney disease in patients with Type 2 diabetes. It should, at best, serve as a pilot study to support the argument that ARBs do not differ in their renoprotective effects from ACE inhibitors in people with hypertension and Type 2 diabetes. On the basis of appropriately powered outcome trials in people with Type 2 diabetes, ARBs are considered first-line antihypertensive agents for renoprotection. This study, in spite of its major limitations, supports head-to-head animal studies that show no difference between the classes in renal morphology or function. Clearly, another head-to-head trial of ACE inhibitors versus ARBs is needed to clarify the specific indications of these agents in patients with Type 2 diabetes and hypertension.

Differential effects of calcium antagonist subclasses on markers of nephropathy progression

Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A. *Kidney Int* 2004; **65**: 1991–2002

Background. Numerous studies suggest that the dihydropyridine calcium antagonists (DCAs) and non-dihydropyridine calcium antagonists (NDCAs) have different antiproteinuric effects. Proteinuria reduction is a correlate of the progression of renal disease. In an earlier systematic review, calcium antagonists were shown to be effective antihypertensive drugs, but there was uncertainty about their renal benefits in patients with proteinuria and renal insufficiency. This systematic review was conducted to assess the differential effects of DCAs and NDCAs on proteinuria in hypertensive adults with proteinuria, with or without diabetes, and to determine whether these differential effects translate into altered progression of nephropathy. Studies included in the review had to be randomized clinical trials with at least 6 months of treatment, to include a DCA or NDCA treatment arm, to have one or more renal end-points, and to have been initiated after 1986. Summary data were extracted from 28 studies entered into two identical but separate databases, which were compared and evaluated by independent reviewers. The effects of each drug class on blood pressure ($n = 1338$) and proteinuria ($n = 510$) were assessed. After adjusting for sample size, study length and baseline value, there was no statistically significant difference in the ability of either class of calcium antagonist to decrease blood pressure. The mean change in proteinuria was +2% for DCAs and –30% for NDCAs (95% CI 10–54%; $P = 0.01$). Consistently greater reductions in proteinuria were associated with the use of NDCAs compared with DCAs, despite non-significant differences in blood pressure reduction or the presence of diabetes. The authors concluded that (i) the efficacies of the subclasses of calcium antagonists in lowering blood pressure were similar, and (ii) there was a greater reduction in proteinuria with NDCAs compared with DCAs in

the presence or absence of diabetes. Based on these findings, NDCAs alone or in combination with an ACE inhibitor or an ARB are suggested as preferred agents to lower blood pressure in hypertensive patients with nephropathy associated with proteinuria.

INTERPRETATION. This is an in-depth systematic review that updates current knowledge on the differential antiproteinuric effects of the subclasses of calcium channel blockers. The criteria for the review are valid and the results indicate that NDCAs significantly reduced proteinuria compared with DCAs in patients with diabetic or non-diabetic renal disease**.** Moreover, this differential reduction in proteinuria among persons with proteinuric nephropathy, either from diabetic or non-diabetic causes, results in a slowing of the progression of nephropathy. This is evidenced in two randomized trials, AASK and IDNT (Irbesartan Diabetic Nephropathy Trial).

Comment

Calcium antagonists are effective blood pressure lowering agents regardless of the subclass. However, the subclasses seem to differ with regard to their antiproteinuric effects as well as other renal outcomes in advanced nephropathy. These differences primarily relate to total obliteration of the kidney's autoregulatory ability by dihydropyridine calcium channel antagonists, and this relates to differences in the effects of the subclasses on calcium channels |**18**|. On the basis of these data and current guideline recommendations, the non-dihydropyridine calcium antagonists should be added to blockers of the RAAS in patients with proteinuric renal disease to help achieve blood pressure goals and further reduce proteinuria.

Antihypertensive efficacy of candesartan–lisinopril in combination vs up-titration of lisinopril: the AMAZE trials

Izzo JL Jr, Weinberg MS, Hainer JW, Kerkering J, Tou CK; AMAZE. *J Clin Hypertens (Greenwich)* 2004; **6**: 485–93

BACKGROUND. The AMAZE (a multicentre trial using Atacand [candesartan] and Zestril [lisinopril] vs Zestril alone) was a randomized, double-blind study to determine if addition of the ARB candesartan was more effective in lowering blood pressure than up-titration of the ACE inhibitor lisinopril. Two identical studies were carried out using hypertensive patients (n = 1096) who were uncontrolled on lisinopril 20 mg daily. These patients were randomized (1:1) to receive either 8 weeks of high-dose lisinopril (40 mg) or the addition of candesartan (16 mg) for 2 weeks followed by 32 mg for 6 weeks. Study 1 (n = 538) demonstrated decreases in trough sitting systolic and diastolic blood pressures at week 8 by 6.2 and 5.9 mmHg respectively for the lisinopril up-titration treatment group and by 11.6 and 8.3 mmHg respectively for the lisinopril plus candesartan treatment group (P <0.01 comparing both blood pressure reductions between the two treatment groups). Corresponding results for Study 2 (n = 558) were reductions of 8.7 and 6.2 mmHg and 9.5 and 7.4 mmHg for the two treatment groups. For Study 2, comparisons of systolic and diastolic blood

pressures between the two treatment groups were not significantly different ($P = 0.51$ and $P = 0.08$ respectively). *Post hoc* pooled analysis ($n = 1096$) demonstrated a slightly greater blood pressure reduction with lisinopril plus candesartan compared with lisinopril (3.1 and 1.7 mmHg). The 95% confidence limits for the difference in least squares mean change from baseline in systolic blood pressure between the two treatment groups were –4.8 to –1.5 and –2.8 to –0.7 mmHg for diastolic blood pressure. The blood pressure control rates (<140 and <90 mmHg) were 42.7 and 36.9% respectively. Both treatment regimens were well tolerated in all groups. The authors concluded that in hypertensive patients not controlled by lisinopril 20 mg once daily, addition of candesartan (32 mg once daily) or doubling the dose of lisinopril provided safe and additional reduction of blood pressure.

INTERPRETATION. This short-term study answers the long-standing question of whether the combination of an ACE inhibitor and an ARB in moderate doses lowers blood pressure to a greater extent than the maximum dosage of the ACE inhibitor alone. The results indicate that the two strategies lowered blood pressure levels to the same degree, without a significantly different side-effect profile. These results are in accord with previous observations in the literature.

Comment

Since the original Candesartan and Lisinopril Microalbuminuria (CALM) trial, low doses of an ACE inhibitor and an ARB have been thought to be efficacious for lowering not only blood pressure but also proteinuria |**19**|. On a theoretical basis, the combination of an ACE inhibitor with an ARB seems attractive because of the well-known minimum side-effect profile of the ARBs. This study supports the concept that moderate- to high-dose combinations of an ACE inhibitor + ARB offer no advantage over a high-dose ACE inhibitor alone for lowering blood pressure. Note that high-dose ACE inhibitors are equally well tolerated as combinations of moderate to high doses of an ACE inhibitor plus an ARB. These data, taken together with other studies, clearly support the role of an ACE inhibitor + ARB combination for use only in people with a high level of proteinuria (>1 g/day) for the reduction of proteinuria independently of blood pressure reduction, as was noted in the COOPERATE trial (see next article reviewed).

Effects of combination treatment with losartan and trandolapril on office and ambulatory blood pressures in non-diabetic renal disease: a COOPERATE-ABP substudy

Nakao N, Seno H, Kasuga H, Toriyama T, Kawahara H, Fukagawa M. *Am J Nephrol* 2004; **24**: 543–8

BACKGROUND. In the COOPERATE trial, combined treatment with the angiotensin-II receptor blocker losartan and the ACE inhibitor trandolapril significantly retarded progression of non-diabetic kidney disease compared with each agent used alone. This benefit could be attributable to the potent reduction in proteinuria, because the

three treatment groups showed the same reductions of office blood pressure (OBP). Ambulatory blood pressure (ABP) is reported to be better than OBP in predicting progression of kidney disease. Ninety-two patients enrolled in the COOPERATE trial underwent 24-hour ABP monitoring at randomization and at month 6, year 1, year 2 and year 3 on randomized treatment. OBP and ABP were similarly reduced among three groups at all measurement points and throughout the whole study period. No significant correlation between the change in 24-hour ABP and the change in proteinuria was seen. A Cox multivariable analysis showed that covariates affecting the renal outcomes (a doubling of serum creatinine level and/or end-stage renal failure) were the change in proteinuria (hazard ratio [HR] 0.49; 95% CI 0.34–0.78; $P = 0.01$) and treatments (HR 0.58; 95% CI 0.45–0.99; $P = 0.03$), but not 24-hour ABP (HR 0.98; 95% CI 0.89–2.01; $P = 0.17$). The authors concluded that the better renoprotective effect of the combination treatment is attributed to more complete renin–angiotensin system blockade operating through blood pressure-independent mechanisms.

INTERPRETATION. This is the first study to pay careful attention to dose of RAAS blockers and examine their antiproteinuric effects in non-diabetic kidney disease. The present nested cohort study, using 24-hour ambulatory monitoring, clearly demonstrates that the antiproteinuric effects cannot be solely attributed to blood pressure reduction (Fig. 5.3). These data, taken together with the results of the AMAZE study, clearly demonstrate that high

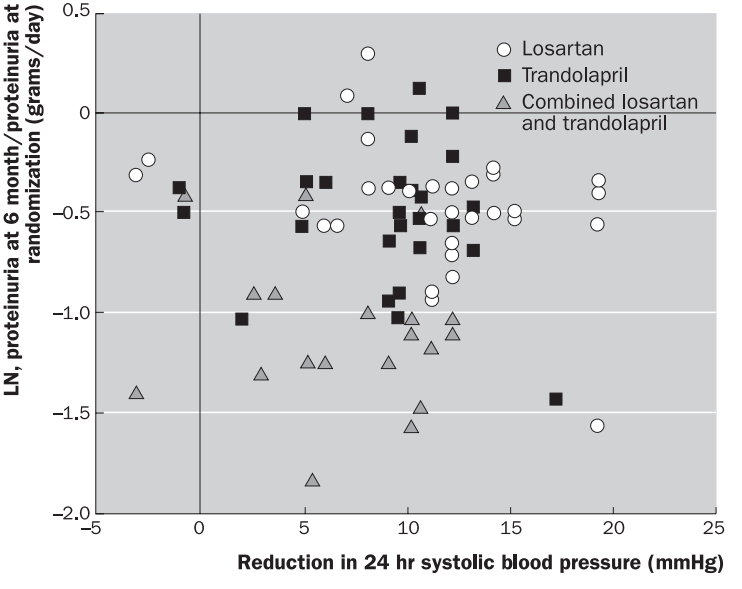

Fig. 5.3 Change in 24-hour ambulatory blood pressure monitoring (ABPM) at 6 months versus change in proteinuria. Note that the change in proteinuria in 6 months also predicted renal outcome at 5 years in the AASK trial (see Lea *et al*. (2005) reviewed in this chapter). Source: Nakao *et al*. (2004).

doses of ACE inhibitor + ARB combinations provide greater reductions of proteinuria than either agent alone. This additional 25 to 30% reduction in proteinuria could not be explained by further reduction in blood pressure, since blood pressure remained similar in the combination group compared to the groups where individual agents were used.

Comment

While this is a nested cohort within a large trial, statistically it is sound and generalizable to the larger trial. It also enables statements to be made regarding the interaction of agents that lower proteinuria in the context of blood pressure lowering. Taken together with other studies it sends a message that when proteinuria is present in kidney disease a good method of reducing it is to use higher doses of an ACE inhibitor/ ARB. This will translate into further slowing of nephropathy and not further lowering of blood pressure.

Conclusion

Macroalbuminuria (>300 mg/day) should be considered a risk factor for progressive loss of renal function as well as a target for therapy in patients with hypertension with or without diabetes. Physicians should (i) assess the level of albuminuria in these patients using a spot albumin:creatinine ratio determination (preferably a first morning void) and (ii) attempt to reduce proteinuria to the lowest achievable level, similar to treating to reach the blood pressure goal. Strong consideration should be given to antihypertensive agents such as renin–angiotensin–aldosterone blockers, which have consistently been shown to delay the onset of microalbuminuria, reduce macroalbuminuria and retard the progression of renal disease. Additional strategies to maximally reduce albuminuria may include combining ACE inhibitors with ARBs and/or non-dihydropyridine calcium channel antagonists.

Further studies are needed, especially head-to-head trials, to clarify the specific indication(s) of these agents in patients with hypertension and albuminuric renal disease.

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6

Diabetic renal and hypertensive disease

CARL ERIK MOGENSEN

Introduction

Several factors are important in determining the rate of progression of diabetic renal disease, always starting from microalbuminuria |**1**|, and elevated blood pressure seems to be a major factor in both Type 1 and Type 2 diabetes |**1–3**|. This was confirmed in a new analysis in the follow-up studies of proteinuric patients conducted by the Steno Diabetes Center |**2,3**|. Although the prognosis for diabetic nephropathy has improved in the last two decades, it is clear that proteinuric patients still have a poor prognosis. For Type 1 diabetes, this analysis |**2**| showed that elevated blood pressure, glycaemic control and albuminuria were major factors in the progression. Serum cholesterol level also seemed to play some role. The rate of progression in patients with albuminuria and Type 2 diabetes is quite similar |**3**|, although it should be noted that patients with Type 2 diabetes and proteinuria most often die from cardiovascular disease before progression to end-stage renal disease (ESRD), even more than patients with Type 1 diabetes and albuminuria.

Thus, there can be no doubt that high blood pressure is a major factor in the progression of diabetic nephropathy in the two types of diabetes |**1–3**|. Agents that block the renin–angiotensin system – angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) – now dominate antihypertensive treatment in these patients |**4**|. In the management of patients, not only renal prognosis, including decline in glomerular filtration rate (GFR), should be considered but other cardiovascular end-points as well. Obviously, cost–benefit considerations must also be taken into account as should whether so-called dual blockade may further improve the prognosis compared with single blockade of the renin–angiotensin system |**4**|. Another important question remains to be answered: is traditional antihypertensive treatment inferior to agents that block the renin–angiotensin system in inhibiting the progression of diabetic nephropathy? The emerging role of aldosterone antagonism should also be taken into consideration |**5**|. Furthermore, in a study of Type 2 diabetes, it was shown that the degree of diabetic retinopathy and anaemia was important. Anaemia was a significant risk factor, although not very strong, and this was also the case for cigarette smoking, emphasizing the multifactorial risk profile

|**1–3**|, including a low GFR. Therefore, it can be concluded that there is not a substantial difference between risk factors and progression promoters in the two types of diabetes. The same strategy for treatment seems warranted but early treatment is essential |**1,6**|.

Prevention of diabetes

ACE inhibitors and angiotensin receptor blockers?

In the treatment of hypertension in non-diabetic individuals, great care should be taken to select agents that do not confer an increased risk for the development of new diabetes. The aim should be to use agents that may at least be neutral or, even better, to some extent protective against the development of glucose intolerance. Hypertensive patients have a risk of developing diabetes of 1–2% per year |**7–10**|. It should also be noted that, apart from glucose intolerance, hyponatraemia and hypokalaemia may be a serious clinical problem, especially in elderly patients treated with thiazide diuretics.

A number of studies have shown that both ACE inhibitors and ARBs seem to confer an antidiabetic effect, at least when compared with diuretics and β-blockers. The recently published Valsartan Antihypertensive Long-term Use Evaluation Trial of Cardiovascular Events in Hypertension (VALUE) study |**11**| also showed that the ARB valsartan confers benefits in protecting against diabetes in comparison with the calcium channel blocker (CCB) amlodipine, with a highly significantly reduced risk of developing new Type 2 diabetes during 5 years of follow-up. A summary of evidence from clinical trials to date is provided in Table 6.1.

Table 6.1 Comparative incidence of new-onset diabetes with ACE inhibitors, ARBs, diuretics, β-blockers and calcium channel blockers in clinical trials

Study	Treatments	Duration (years)	New-onset diabetes (%)	*P*-value
CAPPP	ACE inhibitor versus β-blocker/diuretic	6.1	6.5 vs 7.3	<0.05
HOPE	ACE inhibitor versus placebo	4.5	3.6 vs 5.4	<0.001
LIFE	ARB versus β-blocker	4.8	6.0 vs 8.0	<0.001
SCOPE	ARB versus diuretic	3.7	4.9 vs 6.0	0.09
ALLHAT	ACE inhibitor versus calcium channel blocker versus diuretic	4.9	8.1 vs 9.8 vs 11.6	<0.05
ALPINE	ARB versus diuretic/β-blocker	1.0	0.5 vs 4.1	<0.05
CHARM	ARB versus conventional therapy	1.6	6 vs 7	<0.02
VALUE	ARB versus calcium channel blocker	5.5	13.1 vs 16.4	<0.0001

Source: Opie and Schall (2004) |**8**|; see also |**9,10**|.

Thus, a strong argument can already be made for the initial selection of these agents rather than diuretics or β-blockers alone, and now even CCBs |**11**|. This applies particularly to patients with cardiovascular disease and hypertension, and probably also to individuals with uncomplicated hypertension.

However, the issue is not completely settled. First of all, we may need a more definitive study, such as the ongoing Diabetes REduction Approaches with ramipril and rosiglitazone Medications (DREAM) study, which will assess the effects of ramipril and rosiglitazone in patients at high risk of developing diabetes. We also need more information on the mechanisms of action of antihypertensives, since details are not yet clearly understood.

Preventing microalbuminuria in diabetes

For the first time, normoalbuminuria patients with Type 2 diabetes were examined with an ACE inhibitor by Ravid and co-workers |**12**|. The ACE inhibitor prevented the development of microalbuminuria. Kvetny and colleagues showed the same for Type 1 diabetes using perindopril |**13**|. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) study was recently published |**14**|. Indeed, it is important to distinguish between normo- and microalbuminuria and renal insufficiency, as confirmed in the study by Adler and co-workers from the United Kingdom Prospective Diabetes Study (UKPDS) |**15**|. Clearly, patients with normoalbuminuria have the best prognosis and there is strong evidence to show that preventing progression is associated with a much better prognosis, which was also documented in the recent paper by Gaede and co-workers from the Steno Diabetes Center. They showed that remission to normoalbuminuria is associated with much better preservation of renal function in terms of GFR fall, which is stabilized |**16**|.

The most recent and comprehensive documentation regarding primary prevention, indicating that microalbuminuria can be prevented in Type 2 diabetes, comes from the BENEDICT study group in Bergamo |**14**|. This is the largest study so far conducted and, very interestingly, this study also compares an ACE inhibitor with a calcium channel blocker, verapamil.

This was a large study in Northern Italy, comprising 1204 patients randomly designated to 3 years of treatment with trandolapril alone, trandolapril + verapamil, verapamil alone, and placebo |**14**|. Interestingly, hypertension was defined as low as a blood pressure above 130/85 or ongoing antihypertensive treatment. The primary end-point was the development of persistent microalbuminuria with an overnight albumin excretion rate higher than 20 mg/min on two consecutive occasions.

The primary outcome was seen in 6% of the patients treated with the ACE inhibitor alone and in 10% of the patients receiving placebo, and there was a clearly significant difference ($P = 0.01$). Treatment with verapamil alone was not different from placebo. The authors also estimated the so-called acceleration factors, which were clearly in favour of the use of the ACE inhibitor. There were only minor differences in blood pressure between the treatment arms, but this may still have played a role in the

positive results with ACE inhibitor. There were few serious events in the two treatment groups. The conclusion was clear: in patients with Type 2 diabetes and hypertension (above 130/85), but with normoalbuminuria, treatment with an ACE inhibitor was clearly beneficial in preventing the development of microalbuminuria, which is the first sign of renal damage in these patients. Microalbuminuria is a major risk factor for vascular events and, obviously, also for advanced renal disease and death |**1,15**|.

In conclusion, there is now fairly good evidence from clinical trials that treatment with an ACE inhibitor should be started early in patients with Type 2 diabetes and normoalbuminuria. Treatment should be initiated when systolic blood pressure is more than 130 mmHg. Systolic blood pressure elevation is very common in patients with Type 2 diabetes and metabolic syndrome. This means that most Type 2 diabetes patients would qualify for this type of treatment. These patients also often show sodium retention and therefore a combination of ACE inhibitor with diuretic seems to be most effective in reducing microalbuminuria and blood pressure |**1**|. Now there seems to be a very good foundation for substantial improvement in the prognosis for patients with Type 2 diabetes |**1,14**| and early treatment of hypertension leads to better prognosis—as does, but perhaps to a lesser extent, improved euglycaemic control |**16**|. Clearly, treatment with statins is also important, as documented in many studies, among others the Steno 2 study |**16**|. Now we have apparently completed the paradigm shift: it is essential to normalize glycaemia, blood pressure and dyslipidaemia in all patients with Type 2 diabetes. Further studies are ongoing |**17**|. Genetic factors (as previously commonly believed in the USA) have not yet been documented to play any significant role |**18**|, but there is clearly much more available room for intensified clinical care in patients with Type 2 diabetes.

ACE inhibitors or angiotensin receptor blockers in early nephropathy

Furthermore, while it is evident that both classes of drugs inhibiting the renin–angiotensin system appear to be beneficial, an important question remains: is one class superior for the prevention of the development of cardiovascular and renal disease? This issue has now been addressed by the Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) trial |**19**|.

DETAIL was a much-needed, long-term study comparing an ACE inhibitor with an ARB in a diabetic population. The 5-year, prospective, multicentre, double-blind study directly compared the ACE inhibitor enalapril with the ARB telmisartan in patients with Type 2 diabetes, hypertension and evidence of early nephropathy, and in many cases microalbuminuria. DETAIL was also the first study of its kind to monitor the progression of kidney disease by directly measuring the GFR, now recognized as the best indicator of overall kidney function and ESRD.

The fall in GFR at 5 years – the main end-point – was the same in patients treated with either drug, with changes in GFR from baseline of around –17 ml/min per 1.73 m^2 in the telmisartan group and –15 ml/min per 1.73 m^2 in the enalapril group.

Analysis of the secondary end-point of the yearly change in GFR revealed an initial steep decline in GFR in both groups, of around –8 ml/min per 1.73 m^2, which then stabilized to around –2 ml/min per 1.73 m^2 beyond 3 years.

Blood pressure was lowered to a comparable degree in each treatment group, and cardiovascular mortality was much lower than would be expected at 5 years, with three and five cardiovascular-related deaths in the telmisartan and enalapril groups, respectively. Other adverse event rates were similar between the two groups, since ACE inhibitor-intolerant patients were excluded from the study. There were no cases of ESRD in either group.

Other, shorter studies have indicated that the ACE inhibitors and ARBs exert similar effects as far as albuminuria and blood pressure are concerned |**20–22**|. Furthermore, dual blockade using a drug of each class is a possible approach in patients who do not respond well to single blockade |**22,23**|, especially in microalbuminuric patients |**22**|.

Thus, with the latest results from DETAIL in mind, the clinician may choose either an ACE inhibitor or an ARB, or even the two in combination |**23**|. However, questions remain regarding the longer term in advanced nephropathy. The strong end-point studies, namely the Reduction in End-Points in Non-insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Study and the Irbesartan Diabetic Nephropathy Trial (IDNT) study, in patients with Type 2 diabetes and overt nephropathy, should be considered |**24,25**|. The results of these studies would favour the use of ARBs; as yet there are no similar studies comparing ACE inhibitors with ARBs to provide further information in this patient group. Indeed, compared with advanced disease, intervention in microalbuminuric patients may prove much more effective |**1,6,7,16,19–22**|.

The effect of ACE inhibitors and angiotensin receptor blockers on renal outcomes and mortality: studies in diabetic nephropathy

It would be of interest to compare ACE inhibitors with ARBs, because we know that ACE inhibitors are quite effective in Type 1 and Type 2 diabetes according to many studies |**24,25**| and an important review article on this issue was recently published in the *BMJ* |**26**|. It is an interesting meta-analysis conducted in a very systematic way.

The question put forward in this paper was relevant and clear: when considering all papers dealing with ACE inhibitors and ARBs on renal outcomes and all-cause mortality in patients with diabetic nephropathy, is there a difference? The data sources were solid: Medline, EM-base and the Cochrane Central Register for controlled clinical trials and contacts to investigators. Patients with all stages of disease were included, which may be a drawback.

The data extracted concerned mortality and renal outcomes, which were: (i) prevention of progression of micro- and macroalbuminuria as well as regression to

normoalbuminuria; (ii) doubling of serum creatinine concentration; and (iii) end-stage renal disease (ESRD). The final outcome in all studies was mortality.

All the relevant papers were identified on the date of submission, comprising about 7500 patients. A major interest in this area is ESRD and renal dysfunction.

Importantly, the two agents had similar effects on both renal outcomes, even when confounders were taken into consideration. Comparing ACE inhibitors directly with ARBs was difficult at that time, but results from a new study (DETAIL) are now available |**19**|.

The important point here is that ACE inhibitors had a significant effect on overall mortality, mainly driven by the MICRO-HOPE study |**1,26**|. The test for the overall effect on mortality had a *P*-value of 0.04. In contrast, the ARBs had no significant effect on mortality, with a *P*-value of 0.95 (but on ESRD). This is important because patients with renal disease may not die from ESRD (they undergo dialysis); the most common cause of death, especially in Type 2 diabetes, is cardiac mortality. A similar result is seen in a large Chinese study |**27**|.

Another impressive finding is that there was a very significant effect on regression from microalbuminuria to normoalbuminuria by ACE inhibitors – an effect that has been observed earlier for Type 1 diabetes |**6**|.

The authors |**26**| finally point out the need for more comparative trials. For instance, the ARB losartan was compared positively with a β-blocker in hypertensive diabetic (and non-diabetic) patients with left ventricular hypertrophy in the Losartan Intervention For End-point reduction in hypertension (LIFE) study |**28**|. In addition, the authors conclude that combination therapy – including the use of diuretics – is important. Combining ACE inhibitors with ARBs also seems interesting, especially in non-diabetic disease, as reported in the COOPERATE trials |**29**|. New studies are greatly needed in this area, and work is in progress |**30**|.

It is well known that ACE inhibitors have an effect on the accumulation of bradykinin |**4**|, which may be beneficial and relevant to the main results of the meta-analysis. Thus, the pendulum may now be swinging in favour of ACE inhibition, but generally there is a positive effect of blocking the renin–angiotensin system. Dual blockade is still being investigated, with positive results |**31,32**|.

No substantial arguments against the BENEDICT study and the DETAIL study have been presented |**33–39**|, but economic issues have also been discussed |**35**|.

Clinical significance of regression of albuminuria: a new paradigm shift involving ACE inhibitors, angiotensin receptor blockers and antihypertensive treatment

It is well known to all diabetologists that patients with proteinuria or albuminuria carry a poor prognosis. The same is the case for microalbuminuria, but to a lesser extent. Indeed, the higher the level of albuminuria, the greater the risk of renal pro-

gression and the risk of all complications, including early mortality. These results derive from studies of the so-called natural history of diabetic nephropathy, both in Type 1 and Type 2. The next question to ask is, of course, whether regression or remission of albuminuria is of clinical relevance. Is it really associated with better prognosis? Blocking the renin–angiotensin system as well as dual blockade should be considered |**1,22,23**|, along with several blood pressure-lowering agents.

This question was discussed in a recent article in *Kidney International* by Hovind and co-workers |**40,41**|, who analysed whether remission of nephrotic-range albuminuria is associated with a better prognosis. This, indeed, seems to be the case. It is now also clear from other studies that remission of albuminuria |**42–46**| signifies a good prognosis in microalbuminuric patients. The results from the LIFE study |**46**|, including diabetic patients, and the RENAAL study |**24**| clearly document that reduction of albuminuria and microalbuminuria indicate a good prognosis.

Thus, it is obvious that it is important to screen not only for microalbuminuria, but also to do a follow-up on the degree of albuminuria. Physicians should look for reduction by means of better blood pressure control, especially ACE inhibition or other blockade of the renin–angiotensin system.

This is indeed a second paradigm shift. The first paradigm shift was to screen for microalbuminuria, and the next is to follow up on the level of albuminuria.

It is not difficult to screen for microalbuminuria. In our unit we use the first morning urine sample measuring the albumin/creatinine ratio, a good parameter well associated with excretion rate, both short-term and over 24 h. These are good and reliable reference values |**1**|. It could be argued that the classification into normo-, macro- and microalbuminuria is somewhat artificial because albuminuria – like many other parameters (glycaemic control and blood pressure as well as cholesterol) – is a continuous variable. However, it is practical in the screening process to classify according to these entities. Early studies show that microalbuminuria is associated not only with progression to renal disease, but also with early mortality.

How can it be explained that reduction in albuminuria/microalbuminuria translates into better prognosis? Part of the explanation is reduction of blood pressure and treatment with agents that block the renin–angiotensin system, but this may not be the whole story. Reduction in albuminuria means that the pressure over the glomerular membrane is specifically reduced, and there is good evidence to indicate that pressure-induced damage is an important factor for the deterioration in renal function observed in diabetic patients with proteinuria. Patients with microalbuminuria usually have well-preserved renal function; thus, by reducing microalbuminuria by better treatment, both glycaemic and antihypertensive treatment translate into better preservation of GFR |**47**| and, in this situation, preservation of renal function before the decline in GFR. With proteinuria there is normally a decline in GFR, which is related to traditional risk factors, namely elevated blood pressure, microalbuminuria, and HbA1c—risk markers that are clearly modifiable.

It is quite clear that early antihypertensive treatment has improved the prognosis for diabetic patients dramatically, and that the prognosis may further improve with early screening for microalbuminuria and follow-up to monitor whether micro-

albuminuria is reduced. On the other hand, it may seem a paradox that we still have an increase in the number of patients developing end-stage renal failure due to diabetes. However, this is explained by the fact that many more patients develop Type 2 diabetes, and that these patients have a longer period of survival because of better cardiovascular management, but further studies are needed |**48**|.

The very good news is that the total number of patients with ESRD entering dialysis or transplantation is now declining in Denmark. Obviously, further observation is needed, but this is still a very promising sign, even if the patients are becoming older. However, in most parts of the world, especially in the USA, more than 50% of the patients with ESRD have diabetes as the background. It is interesting to note that screening for microalbuminuria is primarily used in Europe. However, this has already been proposed in guidelines from the American Diabetes Association for several years |**49**|. Regarding the wide range of cardiovascular diseases, ACE-inhibitors are to be preferred against ARBs at the present time, but further studies are needed |**50**|.

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7

Hypertension and the heart

ATHANASIOS MANOLIS, IRENE GAVRAS

Introduction

High blood pressure may progress and contribute to significant end-organ damage, such as left ventricular hypertrophy (LVH), myocardial infarction, systolic and diastolic dysfunction, and heart failure. Three major reasons justify interest in LVH in subjects with essential hypertension: (i) the high prevalence of hypertension (>30%) in the general population; (ii) the high prevalence of increased left ventricular mass in hypertensive subjects (30%); and (iii) the high risk of serious cardiovascular events, including myocardial infarction, heart failure, stroke and cardiovascular death in association with LVH, even in apparently healthy subjects |**1,2**|. The primary factors responsible for the development of LVH are pressure and volume overload, but a number of non-haemodynamic factors may also contribute, including a variety of humoral mechanisms and growth factors (e.g. catecholamines, angiotensin II, endothelins) that promote growth and proliferation of vascular and cardiac myocytes. LVH is a heterogeneous condition that has been characterized by the changes in individual myofibrils, which can increase their circumferential diameters (concentric hypertrophy), length (eccentric hypertrophy), or both. In untreated hypertension, progression from LVH to heart failure is associated with eccentric and concentric hypertrophy. The assessment of left ventricular mass and geometry may be useful in stratifying cardiovascular risk, and hypertensive patients with concentric hypertrophy have the greatest likelihood of experiencing cardiovascular events |**3**|. Impaired left ventricular systolic function is a common consequence of LVH, particularly in untreated patients. Diastolic dysfunction occurs in the absence of systolic dysfunction, but when systolic dysfunction already exists there is almost always some degree of impaired diastolic function as well. The precise explanation for the increased risk associated with LVH is not known, but a number of mechanisms contribute. LVH is associated with progressive impairment in coronary blood flow and flow reserve, as well as increased minimal coronary vascular resistance, fibrosis and endothelial dysfunction. All the above changes contribute to the development of coronary artery disease, cardiac arrhythmias, heart failure and sudden death |**4–6**|.

LVH can be diagnosed by chest X-ray, electrocardiography (ECG), echocardiography and magnetic resonance imaging. For routine evaluation, ECG remains the most useful and cost-effective method, but the most accurate and sensitive method

for detecting early LVH and assessing left ventricular function is the echocardiogram. It has been known for many years that the risk of major cardiovascular events is higher in patients with LVH than in hypertensive patients without LVH.

Novel targets of ANG II regulation in mouse heart identified by serial analysis of gene expression

Schwartz F, Duka A, Duka I, Cui J, Gavras H. *Am J Physiol Heart Circ Physiol* 2004; **287**: H1957–66

BACKGROUND. The relationship between angiotensin II excess and myocardial damage is well established. It was first reported in the early 1970s, when experimental studies and clinical surveys demonstrated that exogenous or endogenous angiotensin II excess was associated with myocardial necrosis and scarring in animals and with an increased incidence of heart attacks in hypertensive patients. Subsequent research has corroborated and amplified these findings and has clarified some of the cellular mechanisms involved in angiotensin II-induced cardiac hypertrophy, arrhythmogenicity and transition to heart failure. Finally, a number of large recent randomized controlled clinical outcome trials have proved that angiotensin II suppression by angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type 1 (AT_1) receptor blockers is cardioprotective. In the wake of the elucidation of the mouse genome, several investigators have embarked on genomic studies to elucidate some of the molecular pathways leading from activation of the AT_1 receptor to progression of ischaemic cardiomyopathy. The authors of this paper chose the serial analysis of the gene expression (SAGE) technique to assess global transcriptional changes in the heart of mice after a continuous 7-day infusion of angiotensin II. Unlike the microarray technique, which requires *a priori* knowledge of the genes being evaluated, the SAGE technique has identified patterns of gene expression indicative of cardiac remodelling, including characterized genes of known function, but also recently annotated genes of unknown function and putative genes not yet present in current databases.

INTERPRETATION. Excess angiotensin II triggers a number of molecular changes in cardiomyocytes. Changes in expression of genes previously described as being related to cardiac hypertrophy, fibrosis and remodelling seem to be the triggers that set in motion the cascade of events leading to ischaemic cardiomyopathy.

Comment

One finding of particular interest was the extreme upregulation of the *210008C07Rik* transcript, which turned out to be homologous to the recently annotated human cardiomyopathy associated 3 (*CMYA3*) gene. Of note, the upregulation of this gene was not due to elevation of blood pressure because it did not occur in the hearts of mice with salt-induced hypertension, and therefore it was attributable to the effect of angiotensin II on the heart, not to the influence of high blood pressure. The function and product(s) of this gene are still unknown, but evidently appear to be linked to

angiotensin II-induced ischaemic cardiomyopathy. Interestingly, this gene was prominently expressed in the heart and the vascular smooth muscle, but not in neural or renal tissues. Although it is too early to attempt the interpretation of these findings of genomic analysis in terms of practical applicability, one can envisage a future when interventions may be possible that will alter the expression of selected genes in order to influence a therapeutic outcome.

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease

Lopez-Sendon J, Swedberg K, McMurray J, *et al*.; Task Force on ACE-inhibitors of the European Society of Cardiology. *Eur Heart J* 2004; **25**: 1454–70

Background. The renin–angiotensin system plays a major role in cardiovascular disease, and during the past decade extensive research has investigated the possible clinical benefit of ACEI in different clinical conditions. Accordingly, these agents have been recommended for the treatment of heart failure, hypertension and acute and chronic myocardial infarction. The aim of the authors was to review the rationale and clinical evidence for the use of ACEI in patients with cardiovascular disease.

ACEI are indicated in the treatment of hypertension (class I, level of evidence A). Current guidelines strongly recommend reduction of blood pressure to different levels according to the risk profile (the higher the risk, the lower the ideal blood pressure) |7|. The primary objective in hypertensive patients is the control of blood pressure levels that can be achieved with different drugs that also reduce cardiovascular morbidity during long-term treatment. Based not only on the results of studies in hypertension but also on the information available from other sources (e.g. heart failure, myocardial infarction etc.), the selection of a specific drug can be based on the patient profile. Thus, ACEI may be considered as the first-choice therapy in patients with heart failure, reduced left-ventricular ejection fraction or diabetes, previous myocardial infarction or stroke in patients with high coronary disease risk, based on the efficacy of these drugs in these populations (Table 7.1). Taken in conjunction with the trials in heart failure and after myocardial infarction, the HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease studies argue persuasively for a general vascular protective effect of ACEI in patients with coronary and other forms of atherosclerotic arterial disease |8–9|. The use of ACEI to prevent sudden cardiac death in patients with left ventricular dysfunction or heart failure after myocardial infarction is considered as a class I indication, level of evidence A. The reduction in mortality observed in these trials varied from 20 to 54% |4|.

Interpretation. Based not only on the results of studies in hypertension but also on the information available from other sources, ACEI may be considered to be first-line therapy in patients with hypertension, heart failure, systolic dysfunction, coronary heart disease, diabetes and stroke.

Table 7.1 Use of ACEI in cardiovascular diseases

Indication	Class	Level
Blood pressure control	I	A
Secondary prevention: high-risk patients	I	A
Patients with CHF, class II–IV	I	A
LVSD after myocardial infarction	I	A
LVSD, no symptoms, no myocardial infarction	I	A
Diastolic heart failure	IIa	C
Acute myocardial infarction, first 24 h, high risk	I	A
All patients with myocardial infarction	IIa	A
MI, diabetes, or other high-risk patients	I	A
Prevention of sudden death: CHF, previous myocardial infarction	I	A
Dilated cardiomyopathy	I	B

Classes: I, evidence and/or general agreement that a given procedure/treatment is beneficial, useful and effective; IIa, weight of evidence/opinion is in favour of usefulness/efficacy.
Levels: A, data derived from multiple randomized clinical trials or meta-analyses; B, data derived from a single randomized clinical trial or non-randomized study; C, consensus of opinion of the experts and/or small studies.
CHF, chronic heart failure; LVSD, left ventricular systolic dysfunction.
Source: Lopez-Sendon *et al*. (2004).

Comment

Since their introduction, ACEI continue to be the first line of treatment not only for high blood pressure but also for other cardiovascular diseases related to hypertension. In addition to reducing blood pressure, ACEI reduce angiotensin II and aldosterone levels, exhibit antiproliferative effects and reduce ventricular remodelling after myocardial infarction, decrease renal vascular resistances and increase renal blood flow, retard the development of atherosclerosis, and also modulate the vascular fibrinolytic balance. Recently, a newly discovered action of these drugs in comparison with all other antihypertensive drugs, except for the angiotensin II antagonists, is the reduction of new-onset diabetes, which in itself represents a risk factor for subsequent cardiovascular disease. All of the above confirm the previous suggestions for the use of ACEI as first-line treatment in many cardiovascular diseases.

Relation of physical activity and body mass index to the risk of hypertension; a prospective study in Finland

Hu G, Baregno NC, Tuomilehto J, Lakka TA, Nissinen A, Jousilahti P.
Hypertension 2004; **43**: 25–30

Background. Overweight and obese people are usually less active than people of normal weight. Overweight, obesity and weight gain have been shown to be important and independent risk factors for the development of hypertension. There is good evidence that regular physical activity reduces the risk of cardiovascular disease. A

meta-analysis, which included 54 clinical trials and 2419 participants, assessed the effect of aerobic exercise on blood pressure. In a previous report aerobic exercise was associated with a significant reduction in mean systolic blood pressure by 3.8 mmHg and diastolic blood pressure by 2.6 mmHg |10|. This study sought to determine whether regular physical activity can reduce the risk of hypertension in both men and women and in subjects with and without excess weight. The authors followed 8302 Finnish men and 9139 women aged 25–64 years without a history of antihypertensive drug use, coronary heart disease, stroke and heart failure at baseline. During a mean follow-up of 11 years, there were 1600 cases of drug-treated hypertension. The authors found that regular physical activity was associated with significantly reduced risk of hypertension in men and women, independently of age, education, smoking habits, alcohol intake, history of diabetes, body mass index and systolic blood pressure at baseline. Overweight and obesity were also associated with an increased risk of hypertension. The prospective effect of physical activity was consistent in both overweight and normal-weight subjects (Fig. 7.1).

INTERPRETATION. Regular physical activity and keeping body weight normal will protect against the development of hypertension.

Comment

Lifestyle measures, including physical activity, should be instituted whenever appropriate in all patients, both in those with normal blood pressure and in patients who require drug treatment. The present study indicates that regular physical activity and weight control can reduce the risk of hypertension in both sexes regardless of the

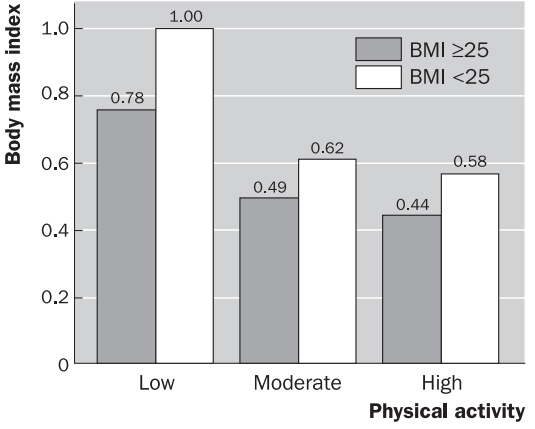


Fig. 7.1 Hazard ratios of hypertension according to the physical activity level (low, moderate and high) and body mass index (<25 and >25) among men. Adjusted for age, area, study year, education, smoking status, alcohol intake and diabetes. Source: Hu *et al*. (2004).

level of physical activity. There are some limitations of the study. The assessment of physical activity is always imprecise. Possible individual changes in the level of physical activity during follow-up may also have influenced the results. In addition, physically active people may have a healthier lifestyle in general when compared with sedentary people. Despite the above limitations, sedentary patients should be advised to take up a modest level of aerobic exercise on a regular basis, such as walking, jogging or swimming for at least 30–45 min, three or four times a week.

Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients

Muiesan ML, Salvetti M, Monteduro C, *et al*. *Hypertension* 2004; **43**: 731–8

BACKGROUND. LVH is initially a useful process compensating for abnormal loading conditions but it is also the first step towards the development of overt clinical disease, such as congestive heart failure, ischaemic heart disease, cardiac arrhythmias and stroke |6|. The purpose of the present study was to investigate the role of changes in left ventricular geometric patterns in the prediction of cardiovascular events in a large group of prospectively identified patients with essential hypertension with and without LVH, undergoing usual medical treatment. The authors followed 436 prospectively identified uncomplicated hypertensive subjects for a follow-up period of 42 ± 16 months. Persistence of left ventricular hypertrophy from baseline to the end-point was confirmed as an independent predictor of cardiovascular events. Cardiovascular morbidity and mortality were significantly greater in patients with concentric (relative wall thickness ≥0.44) than in those with eccentric geometry (relative wall thickness <0.44) in patients presenting with LVH ($P = 0.002$) and in those without LVH ($P = 0.002$) at the follow-up echocardiogram (Fig. 7.2). The incidence of cardiovascular events increased progressively from the first to the third tertile of left ventricular mass index at follow-up; however, for a similar value of left ventricular mass index, it was significantly greater in those with concentric geometry. Stepwise multiple logistic regression analysis showed that the occurrence of cardiovascular events was independently associated with increasing age, male gender, persistence of LVH and persistence of concentric geometry, whereas blood pressure did not enter into the equation.

INTERPRETATION. The results of this study support the concept that measurement of left ventricle mass and relative wall thickness after several years of treatment can help identify the subsequent level of risk in hypertensive patients.

Comment

The main result of this study is that there is prognostic value in changes not only in left ventricular mass but also in changes in the pattern of geometric adaptation of the left ventricle from baseline to follow-up. Therefore, when evaluating left ventricular mass by echocardiogram we must also assess the geometry of the heart, because this

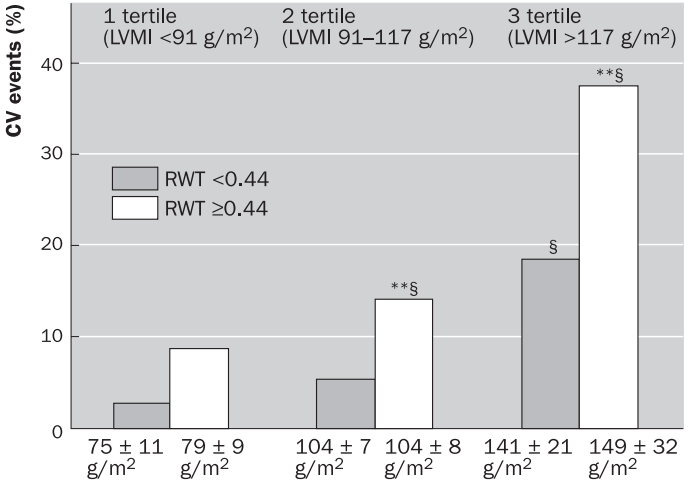


Fig. 7.2 Incidence of cardiovascular events in patients with concentric geometry compared with those with eccentric geometry is already higher, but not significantly different in the first tertile ($P = 0.146$) but the difference reaches statistical significance in the second ($P = 0.004$) and third ($P = 0.001$) tertiles. Incidence of cardiovascular events increases progressively from the first to the third tertile of left ventricular mass index at follow-up. The difference reaches statistical significance in the group of patients in the second tertile with concentric geometry and in both groups of patients in the third tertile, compared with the group of patients of the first tertile with eccentric geometry ($P < 0.001$). **Versus eccentric geometry; §versus first tertile with eccentric geometry. Source: Muiesan *et al*. (2004).

will help us to better stratify the risk of a future cardiovascular event. The association between concentric geometry and cardiovascular events may be explained by decreased myocardial contractility, severe diastolic filling abnormalities, increased oxygen requirement of myocardium, and greater risk of arrhythmias and sudden death. Also, because the incidence of carotid artery disease is higher in patients with concentric hypertrophy, this may be an indication to perform a study for the diagnosis of carotid disease. The results of this study are in keeping with previous studies demonstrating that regression of LVH is associated with improvement of the prognosis. There are some limitations to the above study. Blood pressure values at the baseline and end-point or their changes during follow-up did not correlate with cardiovascular risk in these patients. There are no data for atrial fibrillation or other arrhythmias that may influence cardiovascular outcome in patients with LVH. The authors did not assess the specific influence of antihypertensive drugs on outcome. Also, there was a small number of fatal cardiovascular events. However, the persistence of concentric geometry, even in the presence of normal left ventricular mass, should raise concern about appropriate blood pressure control, compliance with treatment or concomitant vascular disease in hypertensive patients, implying need for stricter clinical control.

Patients with a hypertensive response to exercise have impaired systolic function without diastolic dysfunction or left ventricular hypertrophy

Mottram PM, Haluska B, Yuda S, Leano R, Marwick TH. *J Am Coll Cardiol* 2004; **43**: 848–53

BACKGROUND. Cardiologists who perform exercise tolerance tests know that a hypertensive response to exercise is not uncommon. Previous studies have shown that a hypertensive response to exercise in normotensives is associated with an increased incidence of chronic hypertension during follow-up, and this has been proposed as a pre-clinical stage of hypertension |11|. According to other investigators, a delay in the decrease in blood pressure during the recovery period is accompanied by an increased probability of coronary heart disease. There are no data to demonstrate whether this hypertensive response is associated with hypertensive end-organ damage or other cardiovascular complications. Recently, new techniques, such as quantitative echocardiographic parameters with strain rate imaging and integrated backscatter, have become available. In this study the investigators, using these techniques, tried to determine whether patients with hypertensive response to exercise have detectable abnormalities of myocardial function and whether early systolic dysfunction is related to LVH and diastolic dysfunction. They screened 400 consecutive patients referred for exercise tolerance tests for chest pain evaluation. They studied only patients with normal ejection fraction and negative exercise tolerance tests, stratified into three groups: patients with a hypertensive response to exercise and hypertension, normotensives with a hypertensive response to exercise, and a control group without a hypertensive response to exercise. Although the patients with a hypertensive response to exercise had similar exercise capacity, cardiac dimensions and diastolic function, when compared with control subjects with a normotensive response to exercise, they demonstrated a mild decrease in left ventricular segmental deformation. This impairment of left ventricular long-axis systolic function was evident in both normotensives with a hypertensive response to exercise and patients with a history of resting hypertension (Fig. 7.3).

INTERPRETATION. According to this study, a hypertensive response to exercise is associated with subtle systolic dysfunction, even in the absence of resting hypertension. These changes occur before the development of LVH or detectable diastolic dysfunction and probably represent the earliest stages of hypertensive heart disease.

Comment

Previous studies have suggested that diastolic dysfunction develops relatively early in the course of hypertension, and clinical studies have suggested that diastolic dysfunction precedes systolic dysfunction in the progression of hypertensive heart disease. The findings in this study suggest that segmental systolic dysfunction occurs before global diastolic dysfunction and may be the earliest abnormality in hypertensive

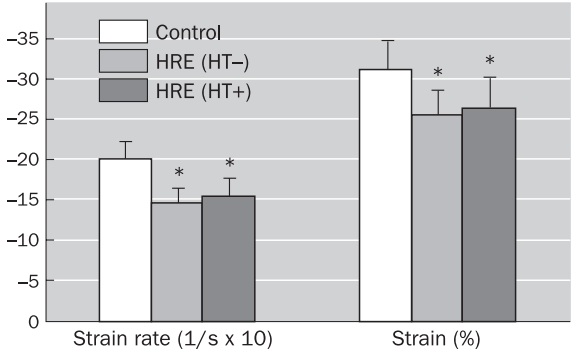


Fig. 7.3 Mean segmental strain rate and peak systolic strain at rest in patients with a hypertensive response to exercise (HRE) with and without hypertension (HT) and in control subjects. *P <0.001 versus controls using Bonferroni adjustment. Source: Mottram *et al*. (2004).

heart disease. Indeed, the authors found impaired systolic function in both hypertensive patients with minimal increase in left ventricular size and a hypertensive response to exercise and in patients with normal left ventricular mass and global diastolic dysfunction. Although it is not surprising that hypertensive patients with a hypertensive response to exercise have mildly abnormal left ventricular function, the detection of abnormal function in the normotensives is a significant finding. These findings suggest that the new techniques are promising quantitative tools for non-invasive myocardial characterization, which may help in the early detection of hypertensive heart disease. In a previous study we had similar findings |**12**|. It is of particular interest that a hypertensive response to exercise is associated with systolic dysfunction, even in the absence of resting hypertension. In the light of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) guidelines |**7**|, these results suggest that cardiac damage is probably already present in patients whom many observers would consider to be pre-hypertensives.

Adverse prognostic significance of new diabetes in treated hypertensive subjects

Verdecchia P, Reboldi G, Angeli F, *et al*. *Hypertension* 2004; **43**: 963–9

Background. The coexistence of hypertension and diabetes is frequent. Type 2 diabetes accounts for over 90% of cases and the cardiovascular risk is markedly increased when hypertension and diabetes coexist |13,14|. It is increasingly recognized that persons with hypertension have a high prevalence of insulin resistance and are at substantially higher risk of developing type 2 diabetes mellitus. Growing concern about the increased prevalence of the metabolic syndrome and type

2 diabetes has generated substantial interest in the metabolic effects of antihypertensive drugs. Historically, most of the focus has been on disturbances in carbohydrate and lipid metabolism associated with diuretics and β-blockers. However, the results of large-scale clinical trials have recently begun to shift attention to the possibility that some of the newer antihypertensive drugs may not only cause fewer metabolic side effects than diuretics and β-blockers, but may also decrease the overall risk of type 2 diabetes. This study investigated the prognostic value of new-onset type 2 diabetes in a cohort of hypertensive subjects without previous cardiovascular events, who had a number of diagnostic procedures repeated before and during treatment. Non-diabetic subjects, who developed diabetes during treatment and those with established diabetes at entry were compared for the subsequent incidence of cardiovascular events with the non-diabetic subjects who remained free of diabetes. First, the authors found that the baseline level of plasma glucose and the use of diuretics after a median follow-up of 6 years were independent predictors of the development of new-onset diabetes. Secondly, they observed that the occurrence of new-onset diabetes in treated hypertensive patients carried a risk of subsequent cardiovascular events that was not statistically different from the risk borne by those who already had diabetes and hypertension at the inception of the study. Indeed, both groups had much higher risk than those who remained free of diabetes (Fig. 7.4).

Interpretation. In treated hypertensive subjects, the occurrence of new diabetes portends a risk of subsequent cardiovascular disease that is not dissimilar from that of subjects with previously known diabetes. Baseline plasma glucose levels and the use of diuretics are independent predictors for the development of new-onset diabetes.

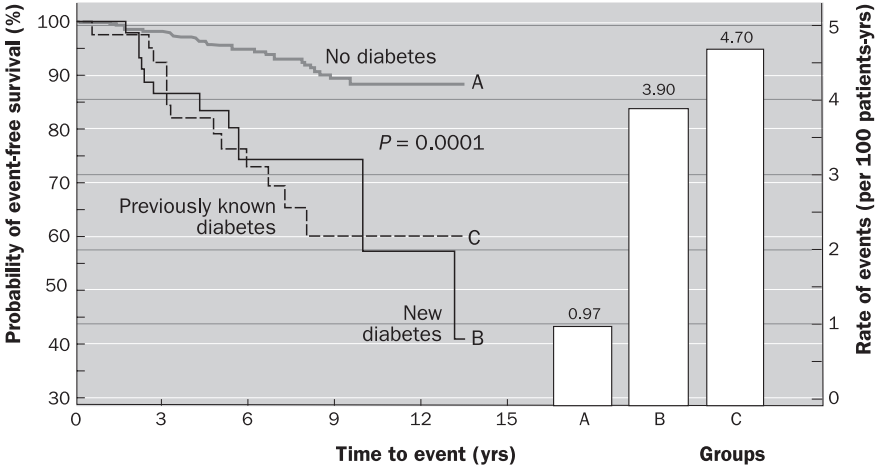


Fig. 7.4 Cardiovascular events in treated hypertensive subjects without diabetes (Group A), new-onset diabetes (Group B), and previously known diabetes (Group C). Source: Verdecchia *et al*. (2004).

Comment

This study provides new data on the adverse impact of new-onset diabetes in treated hypertensive subjects. Pre-treatment blood glucose and exposure to diuretic treatment during follow-up were independent predictors of new diabetes. After accounting for robust covariates, including age, 24-hour ambulatory blood pressure and LVH, subjects with new-onset diabetes were almost three times more likely to have a subsequent cardiovascular event over a long follow-up period than those who remained free of diabetes. A limitation of the study is the lack of control for occasional change in antihypertensive treatment over time. Also, there are no data regarding the potential effects of diet and physical activity. Previous studies, such as CAPPP, INSIGHT, LIFE, INVEST, CONVINCE, ALLHAT, STOP-2, HOPE, CHARM etc. |**15–18**|, have shown that the use of diuretics or β-blockers, compared with calcium antagonists, ACEI or angiotensin II antagonists, was associated with increased incidence of new-onset diabetes. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the combination of amlodipine–perindopril was associated with a 32% lesser relative risk of new onset of diabetes compared with atenolol–bendroflumethiazide, while in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial the relative risk of new-onset diabetes was 23% lower in those treated with valsartan in comparison with those treated with amlodipine. Recent studies have shown that angiotensin II may promote impaired glucose metabolism through its effects on insulin signalling pathways, tissue perfusion, oxidative stress, sympathetic activity and adipogenesis |**19–22**|. Thus, pharmacological interruption of the renin–angiotensin system with ACEI or angiotensin II antagonists might improve glucose metabolism by interfering with angiotensin II generation or angiotensin II receptor activation. In addition, ACEI may also act to improve insulin sensitivity via potentiation of bradykinin |**23**|. It is now generally recognized that microvascular disease starts long before the presentation of patients with clinical diabetes. These observations suggest that thiazide diuretics and β-blockers should be initiated cautiously in hypertensive patients with elevated fasting glucose or those who have a body mass index of 30 or greater. The risk of diabetes and associated cardiovascular disease should be factored into further recommendations of antihypertensive therapy. This will be increasingly important as the number of hypertensive patients with insulin resistance increases in parallel with increases in obesity and ageing of the essential hypertensive population throughout the world. The take-home message from this paper is that with agents that increase the propensity to type 2 diabetes there will eventually be partial reversal of the benefits expected from effective lowering of blood pressure. Despite claims to the contrary, there is no such thing as mild or benign diabetes mellitus, as the presence of diabetes increases the risk of cardiovascular hypertensive complications about 4- to 5-fold.

Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events

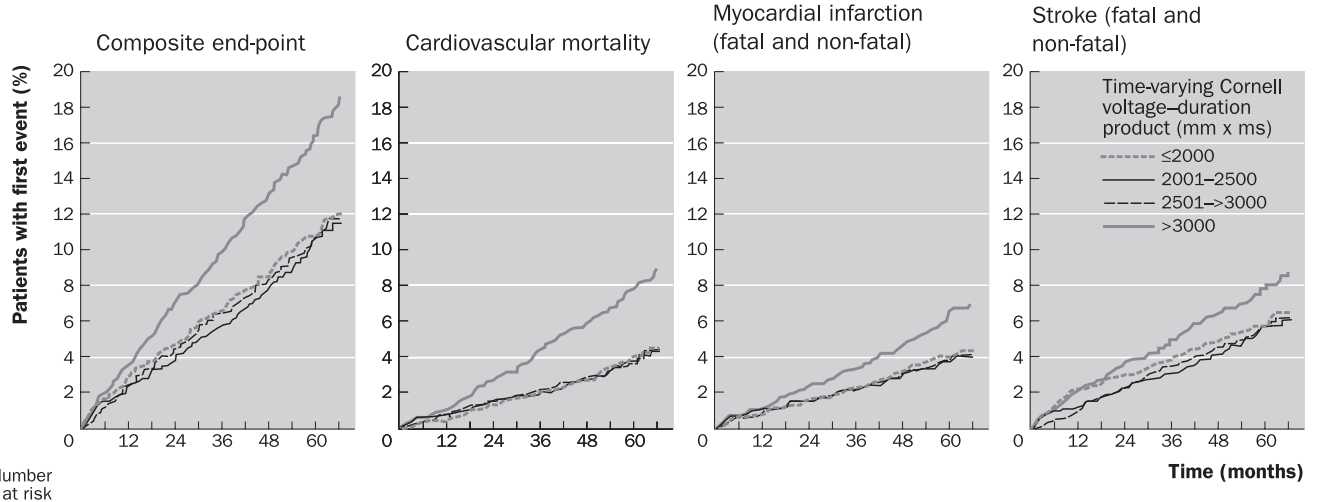
Okin PM, Deveraux RB, Jern S, *et al*. *JAMA* 2004; **292**: 2343–9

BACKGROUND. LVH detected by 12-lead ECG and by echocardiography are common manifestations of pre-clinical cardiovascular disease that strongly predict cardiovascular morbidity and mortality |23,24|. Antihypertensive therapy aimed at reducing blood pressure can produce regression of LVH and reduce, but not entirely eliminate, the increased risk of major cardiovascular events. In the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) study, the regression of LVH, measured by echocardiography, was accompanied by reduction of cardiovascular events. However, there are no data indicating whether regression of LVH measured by ECG is associated with an improved prognosis. The aim of the present study was to test the hypothesis that lesser severity of LVH measured by ECG during antihypertensive treatment is accompanied by decreased cardiovascular morbidity and mortality, independently of reduction of blood pressure levels and treatment modalities. Because the Cornell voltage criteria modestly improve ECG detection of LVH, and the product of Cornell voltage and QRS duration further enhances the sensitivity of the ECG while maintaining high specificity, with a sensitivity of 51 vs 31% for the Sokolow–Lyon criteria, the authors used both criteria in participants in the LIFE trial. The LIFE study was a prospective trial that demonstrated a greater reduction in cardiovascular events in patients taking losartan than in those taking atenolol. In the current analysis they found that lower values of electrocardiographic LVH by Cornell product and/or Sokolow–Lyon voltage criteria during antihypertensive treatment are associated with a lower likelihood of cardiovascular morbidity and mortality (cardiovascular death, myocardial infarction or stroke). This was independent of treatment modality and of decreases in blood pressure in a prospectively studied population of patients with hypertension selected to be at increased risk of cardiovascular events based on the presence of LVH on a screening ECG. In contrast, persistence of LVH or the development of more pronounced electrocardiographic LVH by these criteria was associated with increased risk of cardiovascular morbidity and mortality (Fig. 7.5).

INTERPRETATION. These findings support the use of ECG criteria (Cornell product and/or Sokolow–Lyon) for the measurement of LVH and for assessment of cardiovascular risk over time in hypertensive patients. They also suggest that antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH by these criteria may improve the prognosis.

Comment

The assessment of LVH either by echocardiography or ECG has advantages and disadvantages. The usefulness of ECG criteria for the detection of LVH and for serial evaluation of changes in left ventricular mass has been limited by the low sensitivity



Number at risk Cornell product mm x ms												
≤2000	1205	1956	2063	1205	2023	2181	1205	1987	2134	1205	1969	2085
2001–2500	2253	2552	2317	2253	2620	2448	2253	2581	2383	2253	2565	2387
2501–3000	2629	2034	1723	2629	2106	1818	2629	2073	1762	2629	2048	1772
>3000	2803	2010	1898	2803	2099	2054	2803	2045	1959	2803	2019	1913

Fig. 7.5 Rate of the composite end-point, cardiovascular mortality, stroke and myocardial infarction, by time-varying categories of Cornell voltage–duration product. Source: Okin *et al*. (2004).

of standard voltage criteria for the detection of the anatomical configuration of LVH. However, it is an inexpensive method, can be used widely and gives information regarding the presence of ischaemia, conduction defects and arrhythmias. Echocardiography has high specificity and sensitivity, is the preferred choice for the diagnosis of LVH, permits the quantitation of left ventricular mass, and gives important information about the functional significance of LVH. Disadvantages are the cost and the need for an expert in performing echocardiography studies. This study showed that even the inexpensive and widely used method of ECG can be useful not only for the diagnosis of LVH in hypertensive patients but also for the assessment of cardiovascular risk over time, as it provides important information. There are limitations to the study. The use of the Cornell product and the Sokolow–Lyon voltage criteria to select patients for the LIFE study resulted in the selection of a study population with increased baseline risk and, as a consequence, the present findings may not be representative of those with less severe disease. The prevalence of electrocardiographic LVH in ambulatory patients with hypertension was 9.8% in men and 5.7% in women for Sokolow–Lyon voltage and 14.9 and 18.8% respectively by the Cornell product criteria. Due to the selection process and the intrinsic variability of ECG measurements, it is likely that both the degree of ECG LVH at baseline and the subsequent decrease in ECG LVH during therapy were overestimated in some patients. However, improved outcome was associated with regression of ECG LVH despite these limitations. The results of this study have important implications for the management of patients with hypertension, independently of the drugs used. These data support the use of the Cornell product and/or Sokolow–Lyon voltage criteria for serial evaluation during treatment. This is particularly important in developing countries, where the use of echocardiography is not as widely available as in the developed world.

Effect of long acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina and hypertension: the ACTION trial

Lubsen J, Wagener G, Kirwan BA, de Brouwer S, Poole-Wilson PA. *J Hypertens* 2005; **23**: 641–8

BACKGROUND. Cardiovascular disease is the leading cause of death in the developed world and one of the main causes in developing countries. Hypertension contributes substantially to the risk of development of cardiovascular disease. The dihydropyridine calcium antagonists are the first-line treatment for hypertensive patients according to the European Society of Hypertension guidelines [25]. In addition to lowering blood pressure, calcium antagonists are known to be an effective treatment for symptoms of angina pectoris, and are widely used for this indication. However, in the 1990s there was a debate about the safety of the short-acting calcium antagonists, in particular in patients with coronary artery disease. The A Coronary disease Trial Investigating Outcome in Nifedipine (ACTION)

study was a placebo-controlled trial examining the effect of the nifedipine gastrointestinal therapeutic system (GITS) in 7665 patients with stable symptomatic coronary artery disease. The main results of the ACTION study have appeared in the *Lancet* |26|. A total of 52% of the 7665 ACTION patients were hypertensive. Follow-up blood pressures were reduced by nifedipine ($P < 0.001$), on average by 3.9/2.4 and 6.6/3.5 mmHg among normotensives and hypertensives respectively. Nifedipine GITS significantly reduced ($P < 0.05$) the combined incidence of all-cause mortality, myocardial infarction, refractory angina, heart failure, stroke and peripheral revascularization by 13% in hypertensives only. Nifedipine significantly reduced the incidence of any stroke or transient ischaemic attack by almost 30% in both subgroups and the need for coronary angiography by 21% in normotensives and 16% in hypertensives. Among hypertensives, the incidence of new overt heart failure was significantly decreased by 38% and that of debilitating stroke by 33%. Among normotensives, the need for coronary bypass grafting was significantly reduced by 32%. Nifedipine did not affect all-cause mortality, cardiovascular death and myocardial infarction in either normotensives or hypertensives, but decreased the need for peripheral revascularization (Fig. 7.6).

INTERPRETATION. The addition of nifedipine GITS, a long-acting dihydropyridine calcium antagonist, to the basic treatment regimen of patients with symptomatic coronary artery disease and hypertension is safe and results in a significant reduction of cardiovascular mortality.

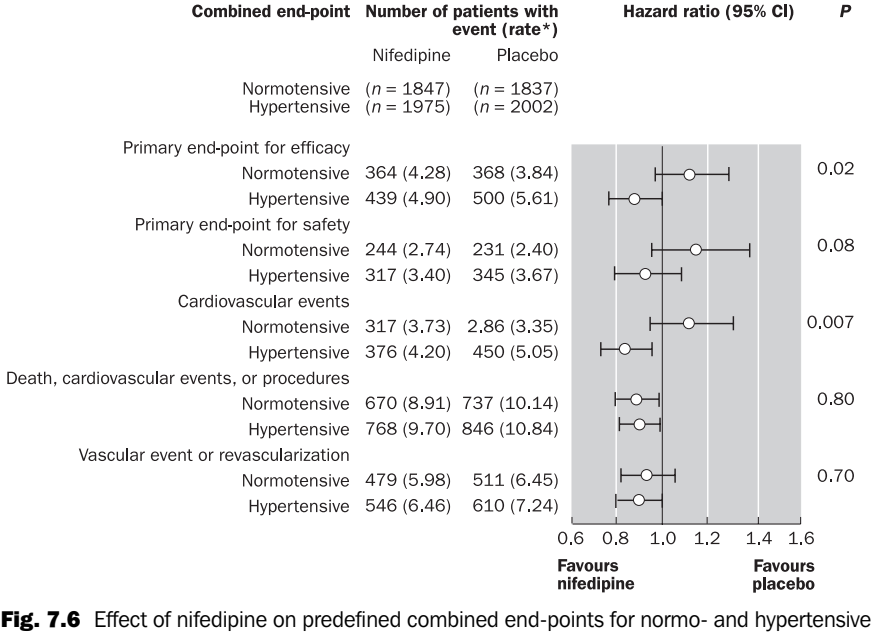


Fig. 7.6 Effect of nifedipine on predefined combined end-points for normo- and hypertensive subjects at baseline. *Number of events per 100 patient-years of follow-up at risk. *P*-values for effect modification (interaction test). CI, confidence interval. Source: Lubsen *et al*. (2005).

Comment

The ACTION trial showed that long-acting calcium channel blockers are not only safe in patients with coronary artery disease but also significantly decrease the incidence of new overt heart failure. Similar results have been found in the VALUE trial in high-risk hypertensive patients in whom heart failure was significantly and similarly decreased by 11% in the amlodipine-treated group as in the valsartan group, whose blood pressure had been normalized earlier. Another important finding of the above study was the presence of hypertension after 4 years of treatment in 47% of hypertensive patients, while 33% of normotensive patients at baseline were hypertensive at the end. These findings emphasize the need for blood pressure control, in particular in patients with target organ damage, such as established coronary artery disease.

Comparison of antihypertensive effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist and a diuretic in patients with hypertension not controlled by angiotensin receptor blocker monotherapy

Stergiou G, Makris T, Papavasiliou M, Efstathiou S, Manolis A. *J Hypertens* 2005; **23**: 883–9

Background. The majority of high-risk hypertensive patients will receive more than two drugs in order to achieve optimal blood pressure control. The proportion requiring combination therapy will depend on baseline blood pressure values. In previous trials in grade 1 hypertension, monotherapy was successful in about 60% of hypertensives, and in grades 2 and 3 monotherapy was successful in 25–40% of patients. In trials with diabetes the vast majority of patients were on at least two drugs, and in those with diabetic nephropathy an average of two to three drugs were required in addition to the baseline drug. It is now recognized that in order to reach the recommended blood pressure goal, treatment with combined antihypertensive drugs is required in the majority of hypertensive patients. The co-administration of agents from different classes results in multidimensional mechanisms of action that provide complementary cardiovascular effects. According to the last European Society of Hypertension/European Society of Cardiology [25] (ESH/ESC) guidelines and the JNC-7, some combinations are more effective than others for the reduction of blood pressure. Recently accumulating evidence suggests that the combination of an ACEI with an angiotensin receptor blocker provides a greater blood pressure decrease than either drug given as monotherapy. In other studies, the combination of the above drugs was effective in patients with target organ damage, such as myocardial infarction or congestive heart failure. In this study the investigators conducted a randomised crossover trial with ambulatory blood pressure monitoring in order to assess the additional antihypertensive effect of an ACEI compared with a dihydropyridine calcium antagonist or a thiazide diuretic in patients whose hypertension was not controlled by a full dose of angiotensin receptor blocker

monotherapy (valsartan 160 mg). The addition of amlodipine to valsartan 160 mg reduced systolic blood pressure by 15.2 mmHg compared with 13.5 mmHg with chlorthalidone 12.5 mg and 8.6 mmHg with benazepril 20 mg. Diastolic blood pressure decreased by 9.9 mmHg with the addition of amlodipine, 9.5 mmHg with chlorthalidone and 6.3 mmHg with benazepril (Fig. 7.7).

INTERPRETATION. According to the above study all combinations were effective in reducing blood pressure, but the combination of an angiotensin receptor blocker with a calcium blocker or a diuretic was superior to the combination with an ACEI.

Comment

Following the recent guidelines, many new studies, such as Perindopril Protection Against Recurrent Stroke Study (PROGRESS), INVEST, ASCOT and VALUE, have provided significant information for different combination treatments which have been shown to be effective in reducing blood pressure. Previous studies have shown that the combination of an ACEI with a diuretic is effective in reducing cardiovascular morbidity and mortality. The recent ASCOT study also showed that the combination of the ACEI perindopril with the calcium blocker amlodipine was more effective than the combination of a diuretic with a β-blocker in reducing cardiovascular morbidity and mortality. In this study, investigators found that the combination of a calcium channel blocker with a diuretic was associated with higher risk of cardiovascular mortality compared with the combination of a diuretic with a β-blocker or an ACEI in elderly women. Another significant finding of the ASCOT trial was the decreased relative risk of new-onset diabetes by 32% in those treated with the combination of an ACEI with a calcium blocker compared with the combination of a diuretic

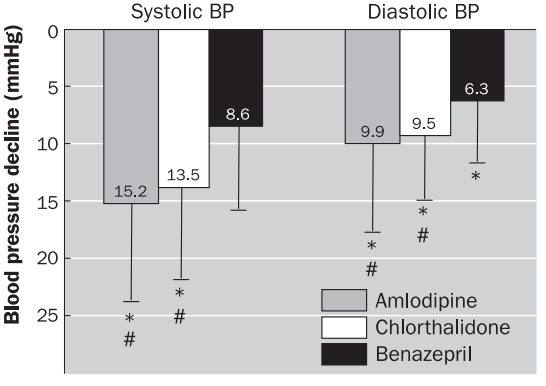


Fig. 7.7 Additional antihypertensive effect (24-h ambulatory blood pressure [ABP]) of amlodipine, chlorthalidone and benazepril when combined with valsartan monotherapy. *P <0.001 compared with valsartan monotherapy; #P <0.05 compared with valsartan–benazepril combination. Source: Stergiou *et al*. (2005).

with a β-blocker. The fact that this was a randomized crossover trial with the use of ambulatory blood pressure monitoring increases the validity of its findings. In view of the recent data of the VALUE trial, which showed that in high-risk patients the treatment of blood pressure should be aggressive in order to reduce blood pressure as soon as possible, it is very important for physicians to know the most effective combinations.

Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End-point Reduction in Hypertension (LIFE) study

Wachtell K, Lehto M, Gerdts E, *et al*. *J Am Coll Cardiol* 2005; **45**: 712–19

BACKGROUND. Atrial fibrillation, the most common cardiac arrhythmia encountered in clinical practice, is a growing public health problem. Patients with hypertension and heart failure are at high risk of developing atrial fibrillation, and in both conditions atrial fibrillation increases the risk of cardiovascular morbidity and mortality, particularly the risk of fatal and non-fatal stroke. The development and persistence of atrial fibrillation are associated with changes in cardiac structure, function and electrical properties, known as cardiac remodelling. Previous studies have shown that the renin–angiotensin–aldosterone system plays a major role in the pathogenesis of atrial fibrillation. Angiotensin II is not only a potent vasoconstrictor, but also causes cellular damage, necrosis and fibrosis. Atrial fibrosis is a frequent finding in patients with atrial fibrillation and may lead to intra-atrial conduction disturbances. Recent data suggest that ACEI attenuate this atrial remodelling in experimental models of atrial fibrillation, and in two recent trials (Trandolapril Cardiac Evaluation [TRACE], Studies of Left Ventricular Dysfunction [SOLVD]), compared with placebo, treatment with an ACEI markedly reduced the incidence of atrial fibrillation in patients with left ventricular dysfunction. In the present substudy of the LIFE study, patients treated with losartan developed 33% less atrial fibrillation than those treated with atenolol, despite similar blood pressure reduction. Patients receiving losartan tended to stay in sinus rhythm longer than those receiving atenolol. In those with a history of atrial fibrillation, the primary end-point (the occurrence of cardiovascular mortality, fatal and non-fatal stroke, and fatal and non-fatal myocardial infarction) was 42% less in those treated with losartan and the occurrence of stroke was 45% less than in those treated with atenolol (Fig. 7.8). In patients with sinus rhythm at entry, losartan-based therapy reduced the onset of atrial fibrillation by 33% and subsequent stroke by 51% compared with atenolol-based therapy, despite similar blood pressure reduction. Patients who developed new-onset atrial fibrillation in the losartan group had 40% fewer primary composite end-points and 51% fewer stroke events than those in the atenolol group.

INTERPRETATION. According to these new findings, in patients with electrocardiographically documented LVH treatment with losartan was associated with a reduction in new onset of atrial fibrillation compared with those treated with atenolol. The data also confirm that atrial fibrillation is a major risk factor for cardiovascular morbidity and mortality.

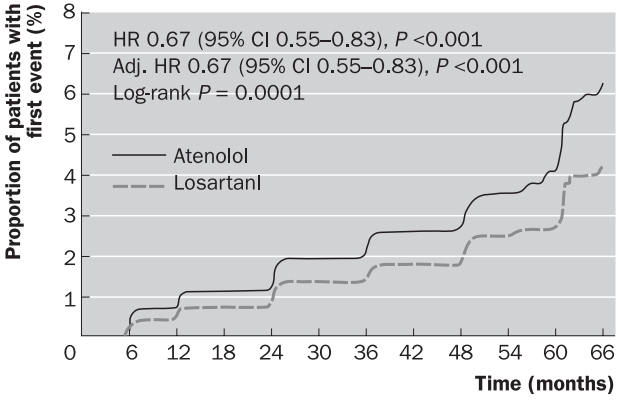


Fig. 7.8 Kaplan–Meier curves illustrating new-onset electrocardiogram-verified atrial fibrillation during follow-up. CI, confidence interval; HR, hazard ratio. Source: Wachtell *et al*. (2005).

Comment

This study is the first to show that, despite the fact that both losartan and atenolol reduce the blood pressure to a similar extent, the rate of new onset of atrial fibrillation was lower in those treated with losartan than in those treated with atenolol. According to recent guidelines, both drugs are equally effective in reducing blood pressure, and they are in the first line of treatment. The fact that losartan reduced the rate of new onset of atrial fibrillation by 33% compared with atenolol with similar blood pressure reduction is surprising, because traditionally β-blockade is considered the first-line therapy to prevent atrial fibrillation as well as the preferred treatment for rate control in established atrial fibrillation. In addition, patients receiving losartan-based therapy tended to stay in sinus rhythm longer. This study is in keeping with previous studies which have suggested that blockade of the renin–angiotensin system with ACEI or angiotensin II antagonists reduces the incidence of atrial fibrillation. One explanation for the added benefit of losartan in preventing new-onset atrial fibrillation and its consequences in hypertensive patients with LVH could be the parallel effects of losartan on regression of atrial and ventricular hypertrophy. The greater regression of LVH with losartan-based therapy compared with atenolol may have been paralleled by greater reduction of left atrial overload and dilatation, thereby reducing stimuli to new onset of atrial fibrillation. Limitations of the study include the fact that atrial fibrillation was not pre-specified, the electrocardiogram was performed annually, and the study comprised only patients with electrocardiographic LVH, but none of these diminish the validity of the results. The main findings of the original report of this study were that new onset of diabetes and subsequent stroke were significantly reduced by losartan compared with atenolol for similar blood pressure reduction.

Conclusion

A recurring theme in the cardiovascular literature of the last few years has been the influence of various antihypertensive treatments on metabolic parameters and the consequences of these effects for various aspects of cardiac structure and function. Earlier studies, by contrast, were limited to the demonstration of efficacy in lowering blood pressure and used surrogate end-points to justify the prediction of benefit. There is no doubt that blood pressure lowering capacity is the most important property of any antihypertensive agent and it would be unthinkable nowadays to conduct a placebo-controlled trial in which one group would receive no active treatment. Placebo in today's trials is an inactive pill added to a standard drug regimen with the same antihypertensive efficacy as the comparator regimen. The question is whether drugs with different mechanisms of action have differential effects on neurohumoral factors (e.g. the renin–angiotensin system, the sympathetic nervous system and numerous local tissue autacoids, such as endothelin and nitric oxide), on metabolic factors (most importantly insulin resistance, but also renal electrolyte handling, uric acid, etc) and on local haemodynamic and cellular alterations leading to cardiac and vascular remodelling. It is now recognized that some of these effects are independent cardiovascular risk factors, changes in which can improve or worsen the global cardiovascular risk in a manner additive to the benefit obtained by the normalization of blood pressure. This concept of blood pressure-associated risk and metabolic/humoral-associated risks as separate entities contributing to the global risk has emerged from the large controlled randomized outcome trials of recent years, in which final outcomes are widely different despite similar blood pressures at the end-point. As research has focused on the mechanisms that may explain such differences, our approach to treatment choices has evolved. While in earlier decades thiazide and β-adrenoceptor blockers were the staples of antihypertensive therapy, it is now increasingly apparent that alternative regimens may offer the added benefits of reversing the cardiac remodelling process and diminishing the incidence or progression of the metabolic syndrome, both of which have important long-term consequences.

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8

Hypertension and the autonomic nervous system

GUIDO GRASSI, FOSCA QUARTI TREVANO

Introduction

The hypothesis that essential hypertension has a pathophysiological link with a dysfunction in autonomic cardiovascular control dates back almost 80 years, when for the first time the Nobel prize-winner Dr Corneille Jean François Heymans was able to show in experimental animals a stable elevation in systolic and diastolic blood pressure values following surgical removal of the reflexogenic areas involved in the neural control of the cardiovascular system |**1**|. Since then, a huge number of experimental and clinical studies have confirmed this hypothesis, providing additional information on the role of neurogenic mechanisms in the development, maintenance and progression of the hypertensive state.

The information collected so far can be schematically summarized as follows. First, the 'hypertensive autonomic imbalance' includes not only a reduced vagal drive to the heart, but also enhanced sympathetic outflow to the cardiac muscle and the peripheral circulation |**2**|. Together, these neurogenic abnormalities represent the pathophysiological background of the main haemodynamic alterations commonly detectable in the hypertensive state, i.e. the marked increase in systemic and regional vascular resistance and the concomitant elevation in resting heart rate |**3**|. Second, the parasympathetic/sympathetic abnormalities appear to be important not only in favouring the increase in blood pressure but also in triggering the development of the end-organ damage frequently detectable in hypertension. This is because several studies have shown that sympathetic neural factors are involved in the development of left ventricular hypertrophy |**4**| and play a large part in determining the structural vascular alterations typical of the so-called hypertensive hypertrophic remodelling process |**5**|. This is also because adrenergic mechanisms promote the metabolic alterations (insulin resistance, hyperinsulinaemia, hypertriglyceridaemia) that frequently accompany a stable increase in blood pressure |**6**|. The adverse cardiovascular effects of the adrenergic overdrive are further increased when hypertension is associated with other pathological conditions known to be characterized by sympathetic overactivity, such as visceral obesity and congestive heart failure |**7**|. Finally, the autonomic imbalance, particularly the hyperadrenergic state described in hypertension, is becom-

ing a major target of the modern antihypertensive pharmacological approach, which aims not only at lowering the elevated blood pressure values but also at exerting sympathoinhibitory effects |**8–9**|. This new goal of antihypertensive treatment has received further support from the finding that, in a variety of cardiovascular diseases (such as congestive heart failure, myocardial infarction and renal failure), increased levels of sympathetic drive adversely affect the patient's prognosis as they are almost invariably associated with greater morbidity and mortality rates |**10–11**|.

During the past year, a number of studies that have focused on the clinical and therapeutic relevance of the autonomic dysfunction that characterizes essential hypertension have been published. Because of editorial constraints, this chapter will discuss the results of a small selection of the many worthwhile papers published in this research area. The choice is based on (beside the quality of the studies) the specific topic addressed. Thus, this chapter highlights the roles of the various components of the sympathetic nervous system in terms of the pathogenesis of hypertension and the development of its cardiovascular and metabolic complications, and as the target of the antihypertensive pharmacological intervention.

Hypertension and insulin resistance are not directly related in obese dogs

Rocchini AP, Yang JQ, Gokee A. *Hypertension* 2004; **43**: 1011–16

BACKGROUND. This study, performed in 36 dogs on a high-fat diet, was designed to examine the complex interrelationships between insulin resistance, hypertension and sympathetic overactivity in obesity-related hypertension. The experimental animals were instrumented for the chronic assessment of the blood pressure, heart rate and body weight changes induced by a 6-week period of the high-fat diet. This diet was capable of triggering, along with an overweight state, a blood pressure increase and a state of insulin resistance. The animals were then treated with different cardiovascular drugs, such as diuretics, α-blockers, β-blockers, clonidine and aspirin, in order to determine whether and to what extent pharmacological interference with the different neurogenic and metabolic processes involved in the control of cardiovascular homeostasis may prevent the development (or reverse the presence) of hypertension, insulin resistance, or both.

INTERPRETATION. Clonidine caused a marked sympathoinhibition coupled with a consistent blood pressure reduction and an improvement in insulin sensitivity. These effects were drug-specific because they were not detectable with other antihypertensive treatments (such as α- and β-blockers), which caused similar blood pressure reductions (Fig. 8.1). The haemodynamic and metabolic effects, however, were unrelated to each other, because a treatment based on high-dose aspirin improved insulin sensitivity but left blood pressure levels unmodified. These findings speak against the hypothesis that, in this specific animal model of obesity, insulin resistance and hypertension display a cause–effect relationship.

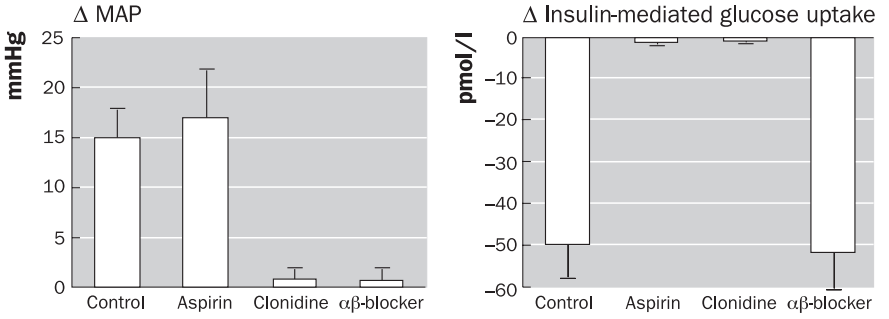

Fig. 8.1 Effects of placebo (control), aspirin, clonidine and combined α- and β-receptor blockade on mean arterial pressure (MAP) and insulin-mediated glucose uptake in experimental animals. Data are shown as mean ± SEM of differences compared with the no-drug condition. Source: Rocchini *et al*. (2004).

Comment

During recent years, growing attention has been devoted to the investigation of the mechanisms involved in the pathogenesis of the increase in blood pressure associated with obesity. The rationale for these studies stands on the evidence that obesity-related hypertension is a clinical condition that is difficult to treat adequately and to control satisfactorily. Evidence has been provided that at least two mechanisms, i.e. insulin resistance and adrenergic overdrive, may be, alone or combined, the main pathophysiological features responsible for the blood pressure increase. This is because insulin resistance and the concomitant hyperinsulinaemia may raise blood pressure by (i) increasing central sympathetic vasoconstrictor tone, (ii) enhancing sodium retention by the kidney, and (iii) causing vasoconstriction rather than vasodilatation in peripheral blood vessels. This chain of events might represent not only the pathophysiological background for obesity-related hypertension but also the target for specific pharmacological interventions aimed at lowering the elevated blood pressure regimens of the obese population. The study by Rocchini and colleagues tells us that the physiopathological events mentioned above may be somewhat unrealistic, because interventions aimed at improving insulin resistance (represented in the present study by aspirin treatment) are not always effective in reducing elevated blood pressure levels. The same conclusion applies to the opposite intervention, i.e. to the therapeutic approaches based on diuretics, α-blockers and β-blockers that are able to reduce blood pressure values but are ineffective on the metabolic profile. Taken together, these findings imply that the chicken-and-egg question related to the complex relationship between insulin resistance and elevated blood pressure still remains largely unanswered.

Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake and angiotensin neuromodulation

Schlaich MP, Lambert E, Kaye DM, *et al*. *Hypertension* 2004; **43**: 169–75

BACKGROUND. By using the microneurographic technique and the radiotracer dilution method, the authors investigated the contributions of central, peripheral, baroreflex and humoral (renin–angiotensin system) mechanisms to the sympathetic activation that characterizes essential hypertension. In 22 untreated hypertensive patients and 11 age-matched normotensive controls, systemic, muscle, cardiac and renal sympathetic outflows were evaluated in order to determine the patterns of regional neural discharge and the modulation exerted on it by baroreflex mechanisms and circulating neurohormones, such as angiotensin II. This was done by performing (i) computer-assisted spontaneous baroreflex sensitivity evaluation and (ii) biochemical determination of angiotensin II levels in the coronary circulation.

INTERPRETATION. There were four main findings of the study. First, essential hypertensives are characterized by marked sympathetic activation, which occurs in the muscle circulation and in the cardiac and renal vascular districts (Fig. 8.2). Second, spontaneous baroreflex control of sympathetic nerve traffic is not altered in hypertension. This is at variance with baroreceptor heart rate modulation, which undergoes a marked impairment proportional to the severity of the hypertensive state. Third, by using an infusion of desipramine the authors were able to demonstrate a decrease in the adrenergic reuptake process of the neurotransmitter by peripheral adrenergic nerve terminals. This was coupled with a lack of any significant relationship between circulating angiotensin II levels and plasma norepinephrine values in the coronary circulation.

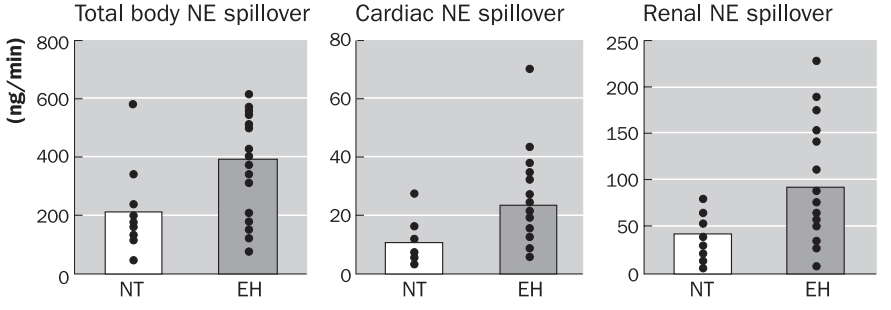

Fig. 8.2 Rates of norepinephrine (NE) spillover into plasma in the systemic (*left panel*), cardiac (*middle panel*) and renal (*right panel*) circulation. Individual and average data are shown for normotensives (NT) and essential hypertensive patients (EH). Source: Schlaich *et al.* (2004).

Table 8.1 Behaviour of regional sympathetic activity in different pathological states

Cardiovascular districts	Essential hypertension	Obesity	Obesity-related hypertension	Heart failure
Cardiac	≠	∅	≠	≠
Renal	≠	≠	≠	≠
Cerebral	?	?	?	?
Muscular	≠	≠	≠≠	≠
Cutaneous	∅	∅	?	∅

≠, increase; ∅, decrease; ?, no information.
Source: Grassi and Esler (2002) |**12**|.

Comment

The study by Schlaich and colleagues aimed to clarify the role of central, reflex and neurohumoral factors in determining the hypertension-related neuroadrenergic activation. The results suggest that, rather than being dependent on a baroreflex dysfunction and/or on the sympathomodulatory effects exerted by circulating angiotensin II, the adrenergic activation of essential hypertension is more likely related to (i) dysregulation in the central control of the sympathetic neural discharge, and/or (ii) a dysfunction in the peripheral mechanisms modulating norepinephrine turnover and causing a reduction in the reuptake process of the adrenergic neurotransmitter. In practical terms, this means that hypertension-related adrenergic activation is caused by enhanced central drive as well as by impaired function of the pathways regulating plasma norepinephrine catabolism.

Two further comments should be made. First, the data (and conclusions) mentioned above refer to specific cardiovascular districts, their generalization to the whole circulation being prevented by the heterogeneity of the sympathetic function in different cardiovascular beds |**3,6**|. This is confirmed by the evidence that, in various cardiovascular or non-cardiovascular diseases, the pattern of sympathetic activation undergoes profound regional differentiation (Table 8.1) |**12**|. Second, the absence of any effect of angiotensin II on sympathetic drive is probably dependent on the modest degree of renin–angiotensin–aldosterone activation seen in hypertension. In other conditions characterized by marked neurohumoral activation, such as heart failure and ischaemic heart disease, there is evidence for potentiation by angiotensin II of sympathetic cardiovascular influences |**13**|. Finally, the present findings strengthen the concept that modulation of central and peripheral adrenergic drive via sympatholytic agents should be one of the goals of pharmacological strategies aimed at lowering elevated blood pressure values |**14**|.

Adrenal medullary overactivity in lean, borderline hypertensive young men

Reims HM, Fossum E, Hoieggen A, Moan A, Eide I, Kjeldsen SE. *Am J Hypertens* 2004; **17**: 611–18

BACKGROUND. Data related to the participation of the adrenal medulla in the sympathetic dysfunction characterizing borderline hypertension are scanty and controversial. To better define the role of the adrenal medulla in the pathogenesis of the essential hypertensive state, plasma catecholamines and heart rate were assessed at rest and during mental stress in 62 lean and 29 overweight patients with borderline hypertension and in 36 lean and seven age-matched overweight normotensive controls. The aim of the study was to determine the involvement of epinephrine in the early phases of the hypertensive state.

INTERPRETATION. No significant difference in resting heart rate was found between the four groups. With the exception of lean borderline hypertensives (displaying greater circulating levels of the adrenergic neurotransmitters), no significant difference in plasma norepinephrine and epinephrine values was found between the four groups. However, the plasma catecholamine responses to mental stress were potentiated in lean hypertensives and only in part (norepinephrine) in obese subjects displaying a blood pressure elevation (Fig. 8.3).

Comment

The study results provide evidence that hypertension is associated with augmented responsiveness of the adrenal medulla to sympathetic stimuli. This is particularly the case for lean subjects, the concomitant presence of an overweight condition or of an

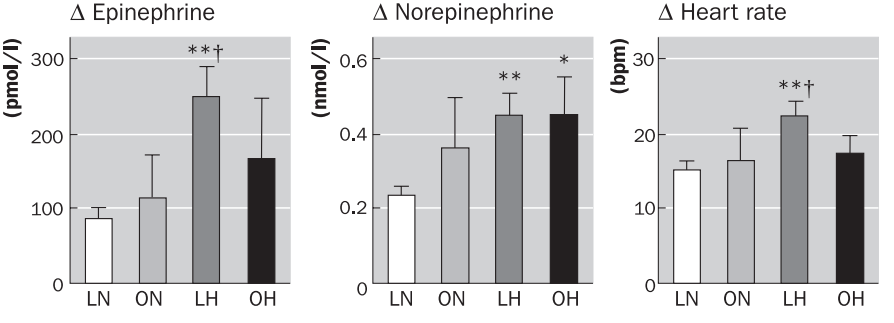

Fig. 8.3 Plasma catecholamines and heart rate responses to mental stress in lean normotensives (LN), obese normotensives (ON), lean borderlines (LH) and obese borderline subjects (OH). Symbols refer to the statistical significance of the difference between LH and LN (**P <0.01), LH and ON (†P <0.05), and OH and ON (*P <0.05). Data are mean ± SEM. Source: Reims *et al.* (2004).

overt obese state attenuating the between-group differences. In commenting on the study's findings, two considerations should be made. First, the study has the merit that it represents the first comprehensive attempt to systematically investigate the function of the adrenal medulla in the hypertensive state complicated or not by obesity. The study also has some weaknesses. They include the fact that the haemodynamic and neuroadrenergic responses to mental stress are poorly reproducible and often differ according to the cardiovascular district examined. Second, the results support, at least in part, the so-called epinephrine hypothesis, which emphasizes the pathophysiological relevance of adrenal medulla stimulation as the primary source of the blood pressure elevation.

Relationship between central sympathetic activity and stages of human hypertension

Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DASG. *Am J Hypertens* 2004; **17**: 217–22

BACKGROUND. Single-unit and multiunit microneurographic recordings of efferent postganglionic sympathetic nerve traffic were obtained in 90 untreated patients classified as subjects with high normal blood pressure, white-coat and borderline hypertension. Further classification was based on the assessment of the severity of the hypertensive state, making it possible to differentiate high blood pressure stages 1 and 2–3 (Joint National Committee VI criteria). Other measurements included 24-hour ambulatory blood pressure monitoring and echocardiographic determination of left ventricular mass index. Thirteen age-matched normotensive subjects served as controls.

INTERPRETATION. The group of hypertensive patients was characterized by a marked increase in both single-unit and multiunit sympathetic neural discharge (on average, an increase of 30%). The degree of sympathetic activation was proportional to the severity of the hypertensive state, greater blood pressure values being associated with more pronounced levels of sympathoexcitation. The early prehypertensive stages (high normal blood pressure and borderline hypertension) were also characterized by sympathetic activation (on average, an increase of 20%), which appeared, however, to be of lesser magnitude than that found in established hypertension. White-coat hypertension (i.e. the condition characterized by normal 24-hour blood pressure profiles but elevated sphygmomanometric values) also displayed a hyperadrenergic state.

Comment

The unique feature of the study was the systematic evaluation of cardiovascular adrenergic drive in different clinical conditions, characterized by a lesser or by a more pronounced increase in clinic and ambulatory blood pressure values. The study conclusions strengthen previous findings |**15**| by providing evidence that the magnitude of the hypertension-related sympathetic activation closely mirrors the severity of the hypertensive state, greater levels of sympathetic nerve traffic characterizing

patients with severe hypertension and/or those with left ventricular hypertrophy. The most intriguing result of the study, however, is the evidence that, even in the prehypertensive stages, sympathetic drive is increased. This finding supports the hypothesis that neurogenic mechanisms contribute to the early development of the disease. A final comment refers to the evidence that sympathetic overactivity also characterizes white-coat hypertension. Considering the recent data indicating that this condition is not an innocent phenomenon but carries an increased cardiovascular risk [**16**], the findings of the present study identify in the sympathetic activation one of the possible factors contributing to the elevated risk profile of these patients.

Morning blood pressure surge and hypertensive cerebrovascular disease

Kario K, Pickering TG, Hoshide S, *et al*. *Am J Hypertens* 2004; **17**: 668–75

BACKGROUND. The study was designed to assess the possible relationships between the morning rise in blood pressure mediated by α-adrenergic receptor stimulation and the occurrence of silent cerebrovascular disease. Ninety-eight elderly hypertensive patients underwent a complex study protocol which included the performance of (i) 24-hour ambulatory blood pressure monitoring to determine the magnitude of the early morning blood pressure surge; (ii) brain magnetic resonance imaging to detect the presence of silent cerebral infarcts; and (iii) echocardiography to quantify left ventricular mass index. The 24-hour blood pressure monitoring was repeated twice at baseline to obtain more reproducible values and was performed again after effective α-blockade (doxazosin). α-adrenergic drive was assessed on the basis of the magnitude of the doxazosin-induced attenuation of the morning blood pressure peak.

INTERPRETATION. The patients displaying greater early morning blood pressure surges (systolic blood pressure increase during the first 2 morning hours after waking of magnitude ≥45 mmHg) had a prevalence of left ventricular hypertrophy and multiple silent cerebral infarcts significantly greater than that displayed by the non-surge patients (morning systolic blood pressure increase <45 mmHg). In the so-called blood pressure surge group, subjects showing greater hypotensive responses to α-blockade (and thus with more elevated morning sympathetic drive) had a significantly greater incidence of multiple silent cerebral infarcts (57 vs 39%; $P < 0.05$). Similar results were obtained when the data were adjusted for age, 24-hour systolic blood pressure load, smoking and body mass index.

Comment

The study findings provide important information on the role of factors other than the blood pressure overload in the pathogenesis of silent hypertensive cerebrovascular disease in elderly individuals. In particular, Kario and colleagues demonstrate that patients with an augmented morning blood pressure surge are characterized by greater prevalence of left ventricular hypertrophy as well as of silent cerebral infarcts. It is likely that these cardiac and cerebrovascular complications depend on the haemo-

dynamic overload seen in the first hours of waking time, since an excessive morning blood pressure elevation may facilitate microvascular remodelling in the small cerebral arteries through an increase in shear stress or potentiated platelet aggregability, favouring microthrombus formation. The results of the present study, however, provide an additional pathophysiological explanation for the elevated prevalence of cerebrovascular abnormalities described in the early morning hours. They show that an increase in vascular α-adrenergic drive might be the neurogenic mechanism responsible for the phenomenon. The clinical implication is clear, since the data do underline the usefulness of α-blockade in reducing and/or preventing the blood pressure rise and thus the waking-related cerebrovascular complications. Further studies, however, are needed to clarify the specificity of this pharmacological effect.

Sympathetic neural activation in non-diabetic metabolic syndrome and its further augmentation by hypertension

Huggett RJ, Burns J, Mackintosh AF, Mary D. *Hypertension* 2004; **44**: 847–52

BACKGROUND. In order to assess the behaviour of the sympathetic nervous system in the metabolic syndrome, 36 normotensive and hypertensive subjects complicated by this pathological state were evaluated using the microneurographic technique to obtain single-unit and multiunit recordings of sympathetic nerve traffic. An index of spontaneous baroreflex sensitivity was also obtained. Data were compared with those obtained in normotensive or hypertensive subjects without any metabolic abnormality. Diagnosis of metabolic syndrome was based on the criteria of the Adult Treatment Panel III, i.e. on the presence of at least three of the following abnormalities: (i) blood pressure ≥130/85 mmHg; (ii) abdominal obesity; (iii) hypertriglyceridaemia; (iv) low levels of high density lipoprotein; and (v) fasting hyperglycaemia.

INTERPRETATION. The sympathetic nerve firing rate was increased in normotensive subjects with metabolic syndrome, the degree of sympathetic activation being similar to that found in uncomplicated and hypertensive patients of normal weight (Fig. 8.4). The additional presence of hypertension was associated with a further potentiation of the adrenergic activation (on average +20%). With the exception of insulin and HOMA index, which were significantly related to the sympathetic nerve traffic values (r always >0.41; $P<0.05$), all other variables did not display any significant link with the adrenergic function.

Comment

In recent years, metabolic syndrome has become a major health problem, affecting about 25–30% of the adult population in European and non-European countries, with greater prevalence in aged individuals. The clinical interest in this pathological condition is related to the evidence that an increased incidence of vascular complications of an atherogenic nature does characterize the disease, adversely affecting the patient's prognosis. The present findings suggest that one of the mechanisms through which metabolic syndrome increases the cardiovascular risk profile is the

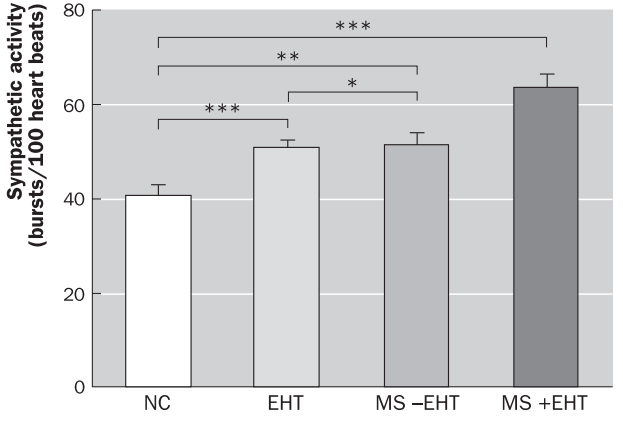

Fig. 8.4 Resting values of multiunit muscle sympathetic nerve traffic in normotensive controls (NC), hypertensive controls (HT) and normotensive (MS –EHT) and hypertensive (MS +EHT) patients with metabolic syndrome. Asterisks refer to the statistical significance of differences between groups: *P <0.05, **P <0.01, ***P <0.001. Data are mean ± SEM. Source: Huggett *et al.* (2004).

sympathetic overactivity that, when combined with other cardiovascular or metabolic abnormalities, may potentiate the adverse impact of the disease on circulation. The study findings once again underline the importance of the relationship between sympathetic activation and insulin resistance, showing that neural and metabolic abnormalities may not infrequently go hand in hand.

Sympathetic and baroreflex function in hypertensive or heart failure patients with ventricular arrhythmias

Grassi G, Seravalle G, Dell'Oro R, Facchini A, Ilardo V, Mancia G. *J Hypertens* 2004; **22**: 1747–53

BACKGROUND. Results of animal studies emphasize the relevance of the pro-arrhythmogenic role of the sympathetic nervous system. The present study was designed to evaluate the behaviour of sympathetic nerve traffic, directly quantified via the microneurographic approach, in heart failure or essential hypertension complicated by premature ventricular contractions. In 28 essential hypertensive patients, without or with monofocal ventricular extrasystolic beats (Lown class I) and in 30 age-matched arrhythmic or non-arrhythmic heart failure patients (Holter monitoring), sympathetic nerve traffic was measured at rest and during phenylephrine and nitroprusside infusions capable of stimulating and deactivating arterial baroreceptors.

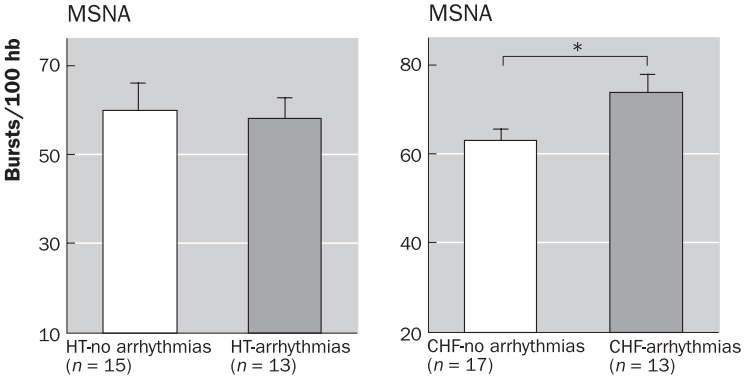

Fig. 8.5 *Left panel*: muscle sympathetic nerve traffic (MSNA) in hypertensive patients without (HT–no arrhythmias) or with (HT+arrhythmias) ventricular ectopic beats (Lown I). *Right panel*: muscle sympathetic nerve traffic in congestive heart failure patients without (CHF–no arrhythmias) or with (CHF+arrhythmias) ventricular ectopic beats (Lown I). Data are mean ±SEM. *P <0.05. Source: Grassi *et al.* (2004).

Interpretation. Resting sympathetic nerve traffic was similar in hypertensive patients with or without cardiac arrhythmias (Fig. 8.5). In contrast, in heart failure patients, displaying at Holter monitoring ventricular extrasystolic beats, sympathetic nerve traffic was increased by about 25% as compared to that found in age-matched patients with impaired cardiac function but without arrhythmic events (Fig. 8.5). In the two diseases, however, baroreflex modulation of both heart rate and sympathetic nerve traffic was impaired, a greater baroreceptor dysfunction being detected in patients with heart failure syndrome.

Comment

Studies in experimental animals have shown conclusively that sympathetic neural factors as well as baroreflex mechanisms exert a pro-arrhythmogenic effect. The present study suggests that this may also be the case in humans, particularly when there is an impairment in the inotropic properties of the left ventricle, such as happens in the heart failure syndrome. In this instance it is likely that baroreflex mechanisms participate in the development of the adrenergic activation, through impairment of the inhibitory effects exerted by this reflexogenic area on central adrenergic outflow. The present study does not allow any definite conclusion about the participation of sympathetic neural mechanisms in the development of cardiac arrhythmias in the hypertensive state. This is because the study involved only patients in Lown class I. This leaves unanswered the question of whether adrenergic activation does occur in more severe and life-threatening ventricular arrhythmias.

Improvement of insulin resistance by troglitazone ameliorates cardiac sympathetic nervous dysfunction in patients with essential hypertension

Watanabe K, Komatsu J, Kurata M. *J Hypertens* 2004; **22**: 1761–8

BACKGROUND. The study was planned to examine the effects of improving insulin sensitivity, by chronic administration of an insulin sensitizer, on cardiac sympathetic function, as evaluated by the ^{123}I-metaiodobenzyl guanidine imaging technique. Insulin sensitivity (steady-state plasma glucose method), blood pressure, metabolic markers and cardiac norepinephrine uptake and washout were evaluated before and after a 6-month treatment with troglitazone in 34 mild essential hypertensives and 17 normotensive controls.

INTERPRETATION. When compared with the normotensive group, the essential hypertensives displayed, along with an increase in blood pressure and in echocardiographically measured left ventricular mass, an insulin resistance state coupled with scintigraphic evidence of delayed cardiac norepinephrine turnover. As shown in Table 8.2, troglitazone administration significantly decreased systolic and diastolic blood pressure values and left ventricular mass index, and improved insulin sensitivity. These effects were accompanied by a 20% improvement in insulin sensitivity and lipid and cholesterol profiles.

Comment

Troglitazone and the related thiazolinedione compounds exert a number of non-metabolic effects |**17**|. The drug may (i) improve stroke volume and cardiac index in type 2 diabetics; (ii) favour a regression in left ventricular mass; (iii) lower peripheral vascular resistance and thus blood pressure; (iv) normalize the impairment in the endothelium-mediated vasodilatation detected at the level of the brachial artery; and (v) inhibit vascular smooth muscle cell proliferation and migration, thereby exerting

Table 8.2 Haemodynamic, cardiac and metabolic effects of troglitazone (mean ± SD)

	Control	6 months	*P*<
Systolic blood pressure (mmHg)	142.6 ± 12.5	135.2 ± 11.4	0.01
Diastolic blood pressure (mmHg)	78.4 ± 7.2	72.6 ± 6.5	0.05
Heart rate (beats/min)	74.0 ± 9.9	71.3 ± 8.3	ns
Total cholesterol (mg/dl)	191.3 ± 17	182.6 ± 15	0.05
Triglycerides (mg/dl)	147.9 ± 27	135.4 ± 23	0.01
Left ventricular mass index (g/m^2)	146.2 ± 25.6	139.4 ± 19	0.01
Heart to mediastinum washout rate of ^{123}I (arbitrary units)	2.12 ± 0.04	2.27 ± 0.05	0.05

Source: Watanabe *et al*. (2004).

antiatherogenic effects. The new finding of the study by Watanabe and colleagues is the demonstration that long-term treatment with troglitazone also exerts sympathoinhibitory effects by reducing the uptake of the adrenergic neurotransmitter from cardiac sympathetic nerve terminals and increasing its myocardial tissue clearance and turnover. These findings strengthen the clinical relevance of insulin–sympathetic interactions. They suggest that therapeutic intervention aimed at improving insulin sensitivity may exert favourable extrametabolic effects, which include improvement in coronary microcirculatory function. Despite these important clinical outcomes, this study does not clarify the chicken-and-egg question of insulin–sympathetic interaction. This is because the effects of insulin on norepinephrine turnover mentioned above may be in part secondary phenomena, independent of the insulin-related sympathetic effects but related to improvement in myocardial perfusion.

Effects of low-dose nifedipine GITS on sympathetic activity in young and older patients with hypertension

Ruzicka M, Coletta E, Floras J, Leenen FHH. *J Hypertens* 2004; **22**: 1039–44

BACKGROUND. This study investigated the effects of a 4-week treatment with low-dose nifedipine gastrointestinal therapeutic system (GITS) on two indices of sympathetic neural function, i.e. muscle sympathetic nerve traffic and plasma norepinephrine levels. After a 4-week placebo run-in period, mild to moderate essential hypertensive patients were randomly assigned to placebo treatment or to nifedipine. Measurements included, along with the two above-mentioned indices of adrenergic function, blood pressure values and hormonal assay of plasma renin activity and angiotensin II levels.

INTERPRETATION. The study results were analysed by subdividing the patients into two groups according to their age. As shown in Fig. 8.6 this age-related analysis led to a number of intriguing results. First, it showed that dihydropyridines have no clear-cut blood pressure lowering effects in younger patients, whereas a significant systodiastolic blood pressure reduction (on average 10/7 mmHg) was observed in older individuals. Second, these haemodynamic effects were accompanied in young patients by sympathetic activation, which was virtually absent in older individuals.

Comment

Although it has always been accepted that antihypertensive drug treatment indicates that calcium channel blockers almost invariably exert sympathoexcitatory effects, in recent years a number of observations have clearly shown that this may not always be the case. This is because, in experimental animals, intracerebral administration of lipophilic and long-acting calcium antagonists may lower rather than increase adrenergic drive. This finding therefore suggests that the effects of calcium antagonists on

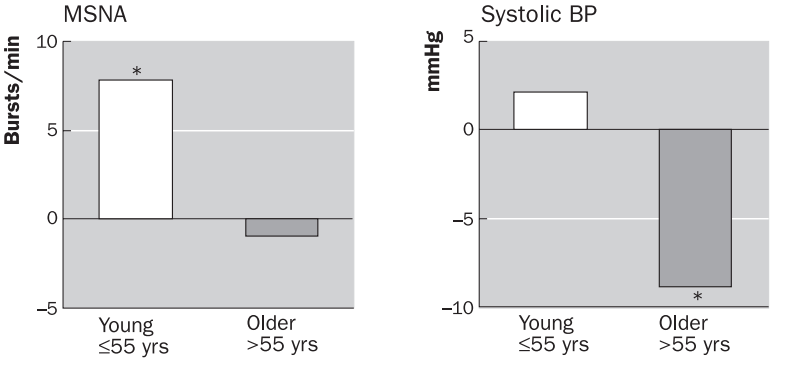

Fig. 8.6 Effects of long-term nifedipine GITS administration in young and older hypertensive patients on sympathetic nerve traffic (MSNA) and systolic blood pressure (BP). *P <0.05 between groups. Source: Ruzicka *et al.* (2004).

sympathetic outflow are heterogeneous, depending largely on the pharmacodynamic as well as the pharmacokinetic profile of the drug. The present study supports this notion, by showing that in elderly subjects nifedipine GITS does not activate the sympathetic nervous system, which is at variance with what can be seen in young subjects. This points to the usefulness of calcium channel blockade as a therapeutic measure in the treatment of systodiastolic or isolated hypertension of the elderly.

Effect of losartan on muscle sympathetic activity and baroreceptor function in systemic hypertension

Bechir M, Enseleit F, Chenevard R, Luscher TF, Noll G. *Am J Cardiol* 2005; **95**: 129–31

Background. To determine whether and to what extent pharmacological interference with the renin–angiotensin system may affect autonomic function, sympathetic nerve traffic and arterial baroreflex control of cardiac vagal drive were evaluated in ten hypertensive patients before and after 3 months of treatment with the angiotensin II receptor blocker losartan. Assessment of baroreceptor sensitivity was based on the spectral analysis technique and fast Fourier transformation, obtained by plotting spontaneous changes in the R–R interval and systolic blood pressure in relation to each other.

Interpretation. Long-term administration of losartan caused, as expected, a significant reduction in systodiastolic blood pressure, coupled with an increase in circulating levels of angiotensin II, thus providing evidence for the effective drug-induced blockade of angiotensin II receptors. These haemodynamic and humoral effects were associated with a

significant, albeit modest, reduction in sympathetic nerve traffic (about 10%), which was coupled with a 50% increase in the baroreflex control of sinus node activity and thus of heart rate.

Comment

A number of studies performed in the past decade have examined the effects of different antihypertensive agents on sympathetic neural function. At variance with results obtained with angiotensin-converting enzyme inhibitors, which appear to be sympathetically neutral in hypertension |**18**|, the present findings do suggest that sympathoinhibition, although of modest degree, also characterizes the long-term administration of angiotensin II receptor antagonists. As previously mentioned, these sympathoinhibitory effects appear to be potentiated in heart failure and in renal insufficiency—conditions in which cardiovascular homeostasis, and thus autonomic balance, depends to a large extent on the renin–angiotensin activation |**19,20**|. The sympathomodulating properties of losartan may represent one of the mechanisms explaining the more favourable effects of the angiotensin II receptor blockers compared with atenolol on cardiovascular morbidity and mortality observed in the Losartan Intervention For End-point reduction in hypertension (LIFE) study |**21**|.

Conclusion

Assessment of neuroadrenergic cardiovascular influences has become a demanding task in man because it requires a number of sophisticated approaches. These include, along with plasma norepinephrine and epinephrine assays, (i) the cardiac neuroimaging technique; (ii) sympathetic nerve traffic analysis; and (iii) the norepinephrine method. As discussed in this chapter, all these techniques have been employed extensively in the investigations published in the past year to clarify the autonomic profile of the hypertensive patient. From the studies described and commented on in this review, it appears clear that the investigators have made considerable efforts to better quantify adrenergic drive and its modifications by diseases and pharmacological treatments. These efforts, however, needs to be balanced against the objective difficulty of quantifying regional sympathetic cardiovascular drive, which appears largely heterogeneous in its behaviour.

Analysis of the studies included in this review shows that a growing interest is focused on the investigation of the complex relationships between sympathetic function and metabolic profile. These attempts hope to define better the sequence of events triggering a blood pressure increase in obese patients and in subjects with metabolic disease. The goal of these investigations is to achieve a clear-cut pathophysiological feature of the specific pathologic state and thus to properly guide therapeutic intervention.

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9

Hypertension and the vascular tree

EDOUARD BATTEGAY, ROK HUMAR, ALAIN BERNHEIM

Introduction

Increased blood pressure is associated with endothelial dysfunction, microvascular rarefaction, increased peripheral resistance and arterial remodelling. Microvascular rarefaction and arterial remodelling lead to further increases in blood pressure; arterial remodelling increases arterial stiffness and thus raises pulse pressure, i.e. it elevates systolic blood pressure while it tends to decrease diastolic blood pressure. This contributes to isolated systolic hypertension, a condition especially prevalent among the elderly. Treating isolated systolic hypertension substantially reduces cardiovascular events. Microvascular rarefaction, on the other hand, contributes to elevation of peripheral resistance and thus increases both systolic and diastolic blood pressure. This combined systolic and diastolic hypertension is more common in the middle-aged. Recently, impaired angiogenesis, i.e. impaired formation and reconstitution of microvessels, has been found to be a characteristic of arterial hypertension and impaired nitric oxide (NO) formation |**1**|. Also, some antihypertensive drugs seem to improve the capacity of tissues to form new vessels and to recreate more adequate tissue oxygenation |**1**|.

We have chosen papers about the vascular tree in hypertension that essentially address three areas:

- endothelial dysfunction
- angiogenesis and microvascular rarefaction
- arterial stiffness.

We feel that aspects of the chosen papers are essential for future developments in hypertension.

Endothelial dysfunction in nascent hypertension

Endothelial dysfunction is currently and widely discussed as a prognostic factor in arterial hypertension and in cardiovascular diseases |**2**|. The term 'endothelial dys-

function' relates to the decreased capacity of the endothelium to induce vasodilation upon a stimulus such as acetylcholine, bradykinin or flow. This endothelially driven vasodilation is mediated by the release of NO. Impaired NO biosynthesis, in turn, may lead to arterial remodelling, impaired angiogenesis and, in consequence, microvascular rarefaction. Thus, endothelial dysfunction may also play an important causative role in the transition between youthful, healthy arteries and microvessels to dysfunctional, stiffened arteries and rarefied microvessels.

Flow-mediated vasodilation and the risk of developing hypertension in healthy post-menopausal women

Rossi R, Chiurlia E, Nuzzo A, Cioni E, Origliani G, Modena MG. *J Am Coll Cardiol* 2004; **44**: 1636–40

BACKGROUND. Cardiovascular events increase significantly after menopause. At the same time the incidence of endothelial dysfunction and arterial hypertension rises. However, it is not clear whether endothelial dysfunction follows as a consequence or precedes arterial hypertension. This study prospectively assessed the relationship between endothelial vasomotor function, evaluated by ultrasound, and the incidence of arterial hypertension among apparently healthy, normotensive post-menopausal women. Endothelial-dependent vasodilation was measured as flow-mediated dilation of the brachial artery using high-resolution ultrasound. It independently predicted the future development of hypertension in healthy, normotensive post-menopausal women; during follow-up of 3.6 ± 0.7 years, 112 of 952 women (11.8%) developed hypertension. The adjusted relative risk for women with a percentage of flow-mediated dilation of 3.5 or less was 5.77 (95% confidence interval [CI] 2.34–8.10) compared with women with a value of 5.5% or greater. The relative risk increased steadily with decreasing percentage of flow-mediated dilation (Fig. 9.1).

INTERPRETATION. These prospective data indicate a significant increase in the relative risk of arterial hypertension with decreasing flow-mediated vasodilation (i.e. endothelial dysfunction). This risk is independent of age, baseline systolic and diastolic blood pressure, and numerous other well-known risk factors. Therefore, endothelial-dependent vasodilation independently predicts the future development of arterial hypertension in healthy, normotensive post-menopausal women. This could suggest that impaired endothelial vasodilation may be an early sign and predictor of the development of arterial hypertension in post-menopausal women, and it also suggests that impaired endothelial vasodilation may contribute causally to hypertension.

Comment

This strictly observational study investigated relatively young women (53 ± 5 years) who were free of cardiovascular risk factors or cardiac illness. Therefore, the results cannot be applied to older women at higher risk or to men. The ultrasound measurement of endothelial-dependent flow-mediated vasodilation of the brachial artery is an attractive technique to assess endothelial function non-invasively and repeatedly.

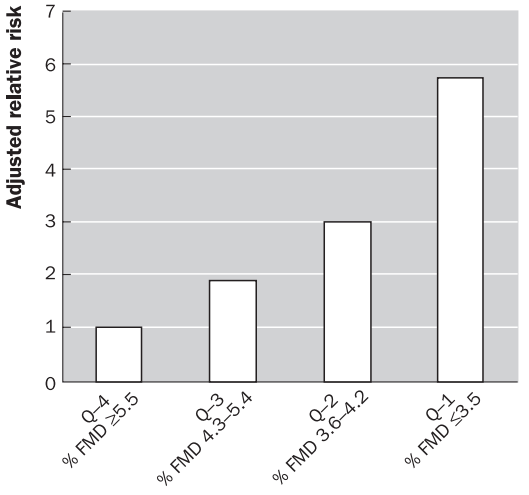


Fig. 9.1 Relative risk of developing hypertension in relation to the percentage of flow-mediated dilation (FMD) quartiles in healthy post-menopausal women. The fourth quartile must be considered as the referent one (see bar on the left of the figure). Source: Rossi *et al*. (2004).

However, despite its widespread use, this technique is reported to have methodological limitations related to the biological and technical variability of the measurements. Results should therefore be interpreted cautiously. Nevertheless, endothelial dysfunction may be considered not only a consequence but also a precursor of arterial hypertension. Therefore, normotensive patients with impaired flow-mediated dilation should be considered as a high-risk population for development of arterial hypertension. Such patients should be advised to initiate measures that prevent hypertension, such as modifications of their lifestyle.

Hypertension and angiogenesis

Rarefaction of capillaries and arterioles is a well-established abnormality in many tissues of hypertensive patients |**1**|. Several antihypertensive drugs, including compounds that inhibit the renin–angiotensin–aldosterone–system improve altered structure of arteries and rarefied microvascular networks |**1**|. Possibly, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers improve the oxygenation of hypoxic tissues by increasing angiogenesis; for example, in the ischaemic myocardium of patients with coronary heart disease |**3**|, hypertensive animals with left ventricular hypertrophy |**4,5**|, or in retinal and hind limb ischaemia in diabetes.

The question asked in the study by Toblli and colleagues was whether the ACE inhibitor perindopril has a beneficial effect on myocardial angiogenesis in a rat model of hypertension, obesity and non-insulin-dependent diabetes mellitus. The study by Ebrahimian and colleagues asked whether the ACE inhibitor perindopril and the angiotensin receptor 1 blocker candesartan induce angiogenesis and reverse ischaemia in the hind-limb. Because angiogenesis can also be harmful in specific situations, they also investigated whether these substances affect angiogenesis in retinal ischaemia at the same time.

Angiotensin-converting enzyme inhibition and angiogenesis in myocardium of obese Zucker rats

Toblli JE, Cao G, DeRosa G, Di Gennaro F, Forcada P. *Am J Hypertens* 2004; **17**: 172–80

BACKGROUND. Three groups of rats were used in this study: obese Zucker (OZ) rats with or without perindopril, and control lean Zucker (LZ) rats without perindopril. Perindopril was given for 6 months. Perindopril lowered blood pressure, heart weight, improved the insulin/glucose ratio and increased myocyte and capillary density (Table 9.1). Perindopril-treated myocardium showed increased presence of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) compared with untreated OZ rats. VEGF and eNOS correlated with the number of capillaries.

INTERPRETATION. ACE inhibition by perindopril improves myocardial angiogenesis and parameters such as heart weight and myocyte density. The pathway eliciting this response may involve eNOS and VEGF. The effects of perindopril observed in this animal model of human metabolic syndrome may be associated with improved cardiac function.

Table 9.1 Morphological and immunohistochemical parameters after 6 months of treatment

Mean ± SD	Group 1 (n = 10) OZ rats	Group 2 (n = 10) OZ rats with perindopril	Group 3 (n = 10) LZ rats
Heart weight (g)	2.14 ± 0.09*	1.29 ± 0.07†	0.95 ± 0.06
Heart weight (g)/100 g body weight	0.36 ± 0.04*	0.22 ± 0.02	0.25 ± 0.02
Myocyte density (no. per mm^2)	847 ± 91*	2044 ± 67	2031 ± 50
Myocyte diameter (μm)	32.7 ± 2.6*	21.2 ± 1.0	20.9 ± 0.5
Capillary density(no. per mm^2)	436 ± 78*	1348 ± 118	1356 ± 135
Myocyte/capillary ratio	1.99 ± 0.4*	1.52 ± 0.1	1.50 ± 0.1

* Versus groups 2 and 3, P <0.01.
† Versus group 3, P <0.01.
Source: Toblli *et al*. (2004).

Dual effect of angiotensin-converting enzyme inhibition on angiogenesis in Type 1 diabetic mice

Ebrahimian TG, Tamarat R, Clergue M, Duriez M, Levy BI, Silvestre JS. *Arterioscler Thromb Vasc Biol* 2005; **25**: 65–70

BACKGROUND. Diabetic mice (streptozotocin, 40 mg/kg) were treated with or without an ACE inhibitor (perindopril, 3 mg/kg per day) or an angiotensin receptor 1 (AT_1) blocker (candesartan, 20 mg/kg) for 4 months. Hind-limb ischaemia was induced by right femoral artery ligature for one additional month. In the ischaemic leg, angiographic score, capillary density and foot perfusion were increased by 2.7-, 2.0- and 1.6-fold respectively in ACE inhibitor-treated diabetic mice compared with untreated diabetic animals. ACE inhibitor also raised the concentration of VEGF 1.4-fold in ischaemic diabetic legs. This ACE inhibitor's pro-angiogenic effect was totally abolished in diabetic animals deficient in bradykinin B2 receptor, suggesting that it was mediated by the bradykinin pathway. In the diabetic retina, angiotensinogen and ACE mRNA levels were increased 2.8- and 4.1-fold respectively ($P < 0.01$ versus non-diabetic mice), suggesting local activation of the renin–angiotensin system. Diabetes also raised the VEGF protein level 1.5-fold ($P < 0.05$ versus non-diabetic mice). Treatments with the ACE inhibitor and the AT_1 blocker hampered diabetes-induced VEGF upregulation and retinal neovascularization.

INTERPRETATION. ACE inhibition improves neovascularization in the diabetic ischaemic leg through activation of bradykinin signalling, whereas it reduces neovascular growth in the diabetic retina through inhibition of an overactivated angiotensin II pathway. Treatments with ACE inhibitor and AT1 receptor blocker decreased diabetes-induced VEGF upregulation and retinal neovascularization.

Comment

The articles by Toblli and colleagues and Ebrahimian and colleagues confirm that inhibition of ACE increases microvascular density in rodent models of hypertension (Fig. 9.2) and diabetes (Fig. 9.3), i.e. in the myocardium and the ischaemic hind-limb, respectively. The effects of the AT_1 blocker candesartan are not clearly described in the paper of Ebrahimian and colleagues.

Both groups show that ACE inhibition increases VEGF concentration, a potent angiogenic molecule. Ebrahimian and colleagues show that an ACE inhibitor's pro-angiogenic effect is abolished in bradykinin B2 receptor-deficient animals. This suggests that ACE inhibitors trigger the growth of new microvessels by inducing bradykinin, which also induces VEGF. Bradykinin has been previously associated with VEGF-dependent angiogenesis. Stimulation of the bradykinin B2 receptor leads to activation of VEGF and eNOS, thereby inducing tube formation in human coronary endothelial cells |**6,7**|. Correspondingly, Toblli and colleagues report increased eNOS expression in myocardial capillaries in OZ rats treated with perindopril.

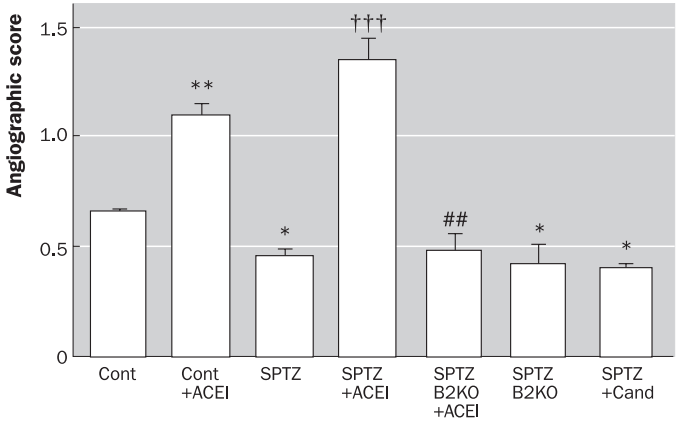


Fig. 9.2 Quantitative evaluation of ischaemic/non-ischaemic angiographic score by high-definition microangiography using barium sulphate injected in the abdominal aorta, followed by image acquisition with a digital X-ray transducer and computed quantification of vessel density. Values are mean ± SEM, $n = 6$ per group. *P <0.05, **P <0.01 versus control mice; P <0.01, P <0.001 versus diabetic animals (SPTZ); ##P <0.01 versus ACE inhibitor-treated diabetic animals. Cont, non-diabetic control; ACEI, animals treated with ACE inhibitor; SPTZ, streptozotocin-treated mice; B2KO, B2-deficient mice receiving ACE inhibitor; Cand, mice treated with AT1 receptor blocker. Source: Ebrahimian *et al*. (2005).

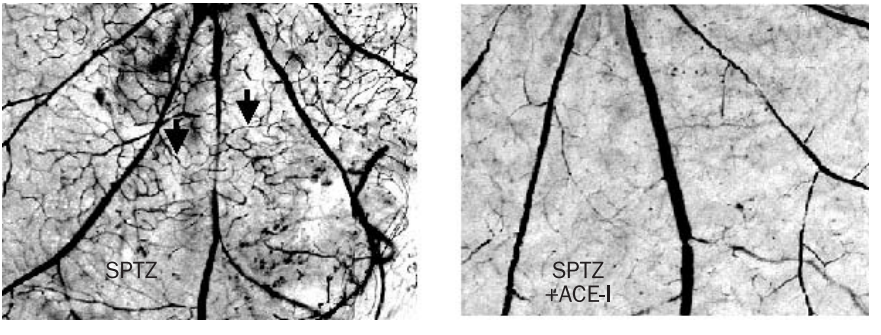


Fig. 9.3 Representative photomicrographs of vessel density in the retina of ACE inhibitor-treated (+ ACE-I) and untreated diabetic mice (SPTZ). Source: Ebrahimian *et al*. (2005).

Both groups mention that the changes in vessel density observed after ACE inhibition may be related to reduction in systemic hypertension. In primary (genetic) forms of hypertension, rarefaction can occur at very early stages before significant elevation of pressure |**1**|. As mentioned by Toblli and colleagues, another study examining the effects of perindopril used two different doses of perindopril:

0.2 mg/kg per day, which did not alter blood pressure, and 2.0 mg/kg per day, which decreased systolic pressure by 40 mmHg. Treatment with either dose of perindopril significantly augmented angiogenesis of the ischaemic limb in spontaneous hypertensive rats (SHR) |**8**|. Thus, perindopril's effects on angiogenesis may be hypertension-independent. Therefore, involution or expansion of the microvasculature may be an important factor in the development of hypertension and its treatment. The development of new microvessels may significantly contribute to the antihypertensive effect of drugs that inhibit the renin–angiotensin–aldosterone system. Interestingly, Ebrahimian and colleagues also show that ACE inhibitors may inhibit angiogenesis in other settings: ACE inhibitors reduced excess vessel growth in the diabetic retina through inhibition of an overactivated angiotensin II pathway (Fig. 9.3). Perindopril has previously been shown to inhibit tumour growth by suppression of VEGF-induced angiogenesis *in vivo*. The anti-angiogenic activity of perindopril in tumours is mediated at least partially by angiotensin II inhibition |**9,10**|. Thus, the local environment may influence the final biological response.

Fascinatingly, new anti-angiogenic therapies for the treatment of metastatic colorectal cancer using an anti-VEGF antibody (bevacizumab; Avastin®) result in hypertension in a significant proportion of patients |**11,12**|. Thus, reduction of microvascular networks and/or haemodynamic effects, as seen with the use of anti-VEGF antibodies in cancer treatment, may result in hypertension.

Effects of arterial hypertension and antihypertensive drugs on vascular wall properties and atherosclerosis

The increase in peripheral vascular resistance and blood pressure in hypertension leads to vascular remodelling. Contrariwise, remodelling of large and small arteries elevates blood pressure, because of the vessels' reduced elasticity and loss of Windkessel function. Large arteries have a stiffened, thickened, less elastic media, which contributes to elevated systolic blood pressure and pulse pressure.

The clinical relevance of arterial stiffness is widely debated. Clinical assessment of arterial stiffness reflects both structural vessel wall characteristics and haemodynamic circumstances, such as left ventricular stroke volume and heart rate. Thus, it is not always easy to separate effects on the vascular wall from effects on blood pressure and haemodynamics, especially if indirect measures of vessel wall characteristics are used. Nevertheless, it seems clear that a high central pulse pressure and pulse wave velocity (PWV) are associated with worse prognosis for cardiovascular events independently of other cardiovascular risk factors |**13**|. Similarly, hypertension complicated by atherosclerosis is associated with a worse prognosis. Treatment of mild hypertension may be of greater benefit in hypertensive subjects with atherosclerosis or other signs of vascular remodelling than in others. In addition, some therapies may be more efficient in reducing parameters of vascular remodelling or prognosis in these

patients. Thus, preferential treatment of these patients with inhibitors of the renin–angiotensin–aldosterone system are currently being discussed |**14**|.

The architecture of the vessel wall is also markedly altered in response to vascular injury. A neointima forms as part of a reparative response to injury that involves thrombosis, migration and proliferation of vascular cells, matrix production, and inflammatory cell infiltration.

In addition to the changes in the vascular wall, luminal dimensions are changed. Active restructuring of cellular and non-cellular components of the vessel wall can result in apparent changes in luminal dimensions with relatively small changes in wall thickness. For example, vascular dilatation associated with sustained high blood flow or cell loss and matrix proteolysis can result in aneurysm formation. Conversely, a reduction of the vascular mass and calibre results from a long-term reduction in blood flow.

Nebivolol increases arterial distensibility *in vivo*

McEniery CM, Schmitt M, Qasem A, *et al*. *Hypertension* 2004; **44**: 305–10

BACKGROUND. Arterial stiffness independently predicts cardiovascular mortality in hypertensive patients. β-blockers appear to be less effective than other drugs in improving some outcomes in hypertensive patients. A potential explanation may be that β-blockers reduce arterial stiffness less effectively. Nebivolol, a relatively new vasodilating β-adrenoceptor antagonist, differs from conventional non-vasodilating β-blockers, such as atenolol, in that it stimulates NO biosynthesis, which leads to vasodilation. The aim of this study was to test the hypothesis that nebivolol, in contrast to atenolol, directly increases arterial distensibility *in vivo* through stimulation of NO production. For the assessment of arterial distensibility, intravascular PWV was measured in sleep. The reason for using a peripheral vascular model was to determine the local actions of the two β-blockers on vessel properties, while avoiding systemic effects with changes in mean arterial pressures. The main finding was that nebivolol reduced PWV by 6 ± 3% at a dose of 500 nmol/min ($P < 0.001$), whereas an equimolar concentration of atenolol showed no comparable effect (Fig. 9.4). The effect of nebivolol on PWV was significantly attenuated during co-infusion of *NG*-monomethyl-*L*-arginine (L-NMMA) and also during co-infusion of butoxamine, indicating that the effect of nebivolol on arterial distensibility is mediated by endothelial release of NO, at least in part via a β_2-receptor-dependent mechanism.

INTERPRETATION. The study demonstrates in an ovine hind-limb model that nebivolol, but not atenolol, acts directly on the arterial wall to improve arterial distensibility. This effect of nebivolol is mediated through the release of NO, at least in part via a β_2-adrenoceptor-dependent mechanism. The NO pathway appears to be an effective therapeutic target in conditions of increased large artery stiffness, such as isolated systolic hypertension. Therefore, in these conditions, vasodilating agents like nebivolol may be of greater benefit than conventional β-blockers.

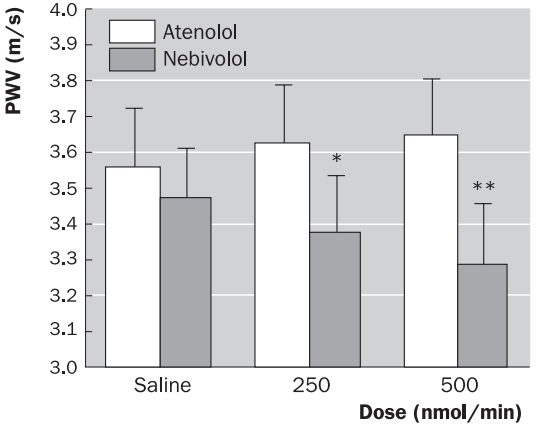


Fig. 9.4 Effect of intra-arterial infusion of atenolol ($n = 6$) and nebivolol ($n = 6$) via the catheter on ovine iliac PWV. Values are means ± SEM. $P < 0.001$, ANOVA, nebivolol versus atenolol. *$P < 0.05$, **$P < 0.01$, Bonferroni test. Source: McEniery *et al*. (2004).

Comment

In the present study an ovine iliac artery served as a model for large arteries in humans. In contrast to proximal parts of the aorta, the iliac artery is predominantly a muscular rather than an elastic artery. Therefore, applicability of the results to central arteries in humans requires confirmation by clinical investigations assessing aortic distensibility. Atenolol, the non-vasodilating β-blocker used in the study, has recently been suggested to reduce cardiovascular risk in hypertension less effectively than other antihypertensive drugs |**15**|. It is not clear whether this is due to the lack of a beneficial influence of atenolol on arterial wall properties and whether other β-blockers differ in this regard. However, NO-mediated vasodilation caused by nebivolol appears to separate this substance from conventional β-blockers. This NO-dependent mechanism may contribute to improvements in the macrovascular structure and may be particularly essential in conditions associated with increased arterial stiffness, such as isolated systolic hypertension.

Large artery stiffness is not related to plasma cholesterol in older subjects with hypertension

Dart AM, Gatzka CD, Cameron JD, *et al*. *Arterioscler Thromb Vasc Biol* 2004; **24**: 962–8

Background. Previous studies have demonstrated a prognostic role for large artery stiffness in hypertensive patients. Increased stiffness is associated with the presence of coronary artery disease and is possibly useful as an early predictor of coronary risk. This study investigated whether there is a correlation between plasma

cholesterol levels and large artery properties among elderly hypertensive patients. Subjects were recruited from the participants of the Australian Comparative Outcome Trial of Angiotensin-Converting Enzyme Inhibitor- and Diuretic-Based Treatment of Hypertension in the Elderly (ANBP2). The non-invasively assessed arterial parameters were central augmentation index, systemic arterial compliance and transverse expansion of the aortic arch (aortic distensibility). Large artery measurements were performed in 1089 subjects. Arterial wave forms acceptable for analysis of the augmentation index and systemic arterial compliance were obtained in around 80% of cases. Aortic distensibility was assessed in 63% of investigated subjects. In those patients the mean total cholesterol level was 5.5 ± 1.0 mmol/l and mean high-density lipoprotein (HDL) cholesterol concentration was 1.4 ± 0.5 mmol/l. In multiple regression analysis, parameters of stiffness and total or HDL cholesterol did not correlate with each other significantly.

INTERPRETATION. In elderly hypertensive subjects there was no independent association between plasma total cholesterol or HDL cholesterol levels and parameters of large artery stiffness. This may increase the value of assessment of arterial properties in predicting cardiovascular risk.

Comment

As mentioned above, parameters of arterial stiffness could not be obtained in a relevant number of study subjects. According to the authors, selection bias is unlikely, given the similarity in cholesterol levels observed between the patients analysed in this substudy and the main ANBP2 cohort of 6083 subjects.

Blood sample collections performed in this study were not restricted to the fasting state. Therefore, LDL cholesterol levels could not be calculated. However, previous investigations in healthy subjects have revealed comparable associations between aortic stiffness parameters and both low-density lipoprotein (LDL) cholesterol and total cholesterol/HDL cholesterol. This implies that the study results would have been similar had LDL cholesterol been available.

Theoretically, elevated cholesterol levels should affect large artery stiffness via impaired endothelial function and atheroma formation. On the other hand, cholesterol values correlate only marginally with cardiovascular risk in elderly patients without coronary heart disease. The authors suggest that the lack of an association between large artery properties and cholesterol can be explained, at least in part, by the older age and hypertension, two major determinants of arterial stiffness present in all the subjects studied.

Pulse pressure and coronary atherosclerosis progression in post-menopausal women

Nair GV, Waters D, Rogers W, Kowalchuk GJ, Stuckey TD, Herrington DM. *Hypertension* 2005; **45**: 53–7

BACKGROUND. Pulse pressure is an index of large artery stiffness and a predictor of coronary artery disease outcomes, including myocardial infarction and

restenosis after percutaneous coronary intervention. In this study, the relationship between pulse pressure and progression of coronary atherosclerosis and the influence of hormone replacement therapy (HRT) were examined in post-menopausal women with angiographically confirmed coronary artery disease (Estrogen Replacement in Atherosclerosis [ERA] trial). Post-menopausal women (n = 309) aged 66 ± 7 years with coronary artery disease were randomized to oestrogen, oestrogen plus progestin, or placebo and followed for 3.2 years. In each patient the mean minimum diameter of ten standardized coronary segments was assessed by quantitative coronary angiography at baseline and follow-up. Changes in mean minimum diameter were related to baseline pulse pressure values. Additionally, the effect of HRT on follow-up pulse pressure values was assessed. At follow-up, a stepwise increase in coronary disease progression was observed with increased levels of baseline pulse pressure (P for trend = 0.0001; Fig. 9.5). Neither oestrogen nor the combination of oestrogen plus progestin influenced pulse pressure values significantly during the course of the study (Fig. 9.6).

INTERPRETATION. In post-menopausal women with angiographically documented coronary artery disease, increased levels of baseline pulse pressure are associated with subsequent progression of coronary atherosclerosis, independently of baseline coronary artery diameter, cardiovascular risk factors, and haemodynamic factors known to influence pulse pressure. HRT did not influence pulse pressure.

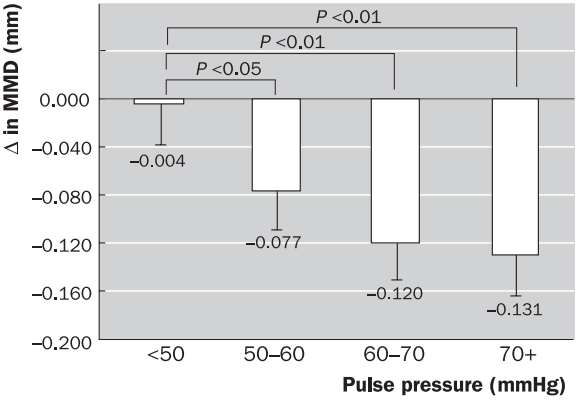


Fig. 9.5 Impact of baseline pulse pressure on coronary disease progression. Adjusted for baseline mean minimum diameter (MMD), location of artery segment, length of follow-up, clinic site, imputed measures, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, early events, study treatment, non-steroid anti-inflammatory drug (NSAID) use, lipid treatment, age, race, cardiovascular disease, risk factors, mean arterial pressure, heart rate and height. Source: Nair *et al*. (2005).

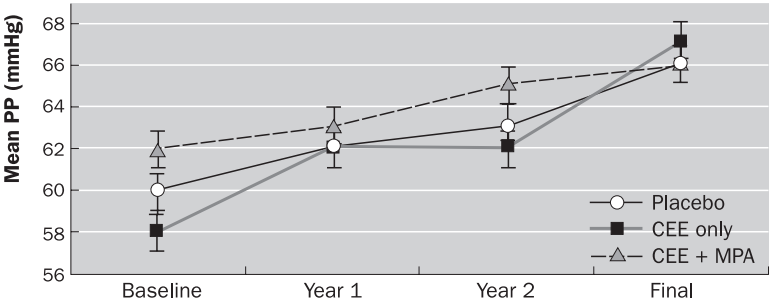


Fig. 9.6 Effects of HRT (conjugated equine oestrogen [CEE] only and CEE plus medroxyprogesterone acetate [CEE+MPA]) on pulse pressure. Adjusted for time, mean arterial pressure and baseline pulse pressure. Source: Nair *et al*. (2005).

Comment

These findings again suggest that arterial stiffness is a risk factor for the progression of coronary disease. It remains to be elucidated whether an increase in pulse pressure also promotes vulnerability to coronary atheroma with subsequent plaque rupture and cardiovascular events. The absence of an effect of HRT on arterial stiffness is in line with previous studies in older post-menopausal women with established coronary artery disease. Hormone substitution influences progression of neither atherosclerosis nor pulse pressure.

Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol

London GM, Asmar RG, O'Rourke MF, Safar ME, on behalf of the REASON Project Investigators. *J Am Coll Cardiol* 2004; **43**: 92–9

Background. The combination of the ACE inhibitor perindopril with the diuretic indapamide has been shown to reduce cardiovascular morbidity and mortality. In hypertensive patients, the combination of perindopril plus indapamide more effectively reduces systolic blood pressure than atenolol for the same reduction of diastolic blood pressure. The aim of this study was to evaluate whether a low-dose combination of perindopril plus indapamide reduces central as well as brachial systolic blood pressure more than atenolol. Furthermore, haemodynamic factors independently influencing peripheral and central systolic blood pressure were evaluated. Low-dose perindopril plus indapamide decreased systolic blood pressure more than atenolol, especially in central arteries. After 1 year, the difference between peripheral and central systolic blood pressure was maintained in the patients treated with perindopril plus indapamide (8.28 ± 1.53 mmHg) and

significantly attenuated in the patients treated with atenolol (0.29 ± 1.61 mmHg). The difference in reduction of brachial systolic blood pressure under perindopril plus indapamide versus atenolol became significant at the end of the 1-year follow-up only. Under atenolol, the reduction of systolic blood pressure was principally due to a decrease in mean blood pressure. Under perindopril plus indapamide, mean blood pressure reduction played a minor role. The pronounced decrease in central systolic blood pressure with perindopril plus indapamide was mainly due to improved large artery function, i.e. reduction of large artery stiffness and favourable alteration of wave reflections.

Interpretation. Low-dose perindopril plus indapamide reduces systolic blood pressure more than atenolol. This differential effect is more pronounced in central than peripheral arteries. The accentuated decrease in central systolic blood pressure may be due to an improvement in large artery function and a changing pattern in pressure waves reflected from distal arterial and arteriolar territories, where perindopril plus indapamide, but not atenolol, is known to improve vessel wall structure.

Comment

The findings of the present study regarding the action of atenolol on systolic blood pressure are in accordance with recent data showing that atenolol failed to improve arterial distensibility and, possibly, cardiovascular events. Whether this is a drug-specific disadvantage of atenolol remains unclear. Therefore, future trials comparing the low-dose combination of perindopril plus indapamide with antihypertensive treatments different from atenolol are needed. Potent blood pressure reduction and the positive influence on arterial stiffness with the low-dose combination of perindopril plus indapamide suggests that this treatment may be an attractive alternative to conventional high-dose monotherapies in hypertensive subjects.

Effects of amlodipine and lisinopril on intima–media thickness in previously untreated, elderly hypertensive patients (the ELVERA trial)

Terpstra WF, May JF, Smit AJ, de Graeff PA, Meyboom-de Jong B, Crijns HJ. *J Hypertens* 2004; **22**: 1309–16

Background. An increase in intima–media thickness can be an early sign of atherosclerosis. Reduction of cardiovascular risk factors has been shown to reduce the progression of intima–media thickness. This study compared the effects of the calcium channel blocker amlodipine and the ACE inhibitor lisinopril on intima–media thickness during a 2-year follow-up in elderly, previously untreated hypertensive individuals. The primary end-point of the ELVERA trial was the change in combined mean maximum far wall intima–media thickness of ten segments of the carotid and femoral arteries after 2 years of treatment with amlodipine 5–10 mg versus lisinopril 10–20 mg. The two drugs reduced overall intima–media thickness and blood pressure (Table 9.2) to similar extents. Secondary end-points were changes in intima–media

Table 9.2 Impact of amlodipine and lisinopril on combined maximum intima–media thickness

		Combined maximum intima–media thickness (mm)				
	n	Mean	SD	Median	Minimum	Maximum
Amlodipine						
Baseline	71	1.210	0.281	1.153	0.736	2.224
Year 1	64	1.121*	0.257	1.101	0.733	1.789
Year 2	63	1.166*	0.236	1.163	0.828	1.756
Lisinopril						
Baseline	77	1.194	0.282	1.124	0.795	2.212
Year 1	65	1.116*	0.212	1.091	0.751	1.740
Year 2	63	1.129*	0.232	1.084	0.751	1.698

* Significant difference compared with baseline ($P < 0.0001$). No significant differences between amlodipine and lisinopril were observed ($P = 0.18$).
Source: Terpstraa *et al*. (2004).

thickness in the common carotid and common femoral arteries. A significant treatment benefit for amlodipine was observed in the intima–media thickness of the elastic common carotid artery. For the femoral artery, on the other hand, the effects of the two drugs were identical.

INTERPRETATION. In this long-term study the calcium channel blocker amlodipine and the ACE inhibitor lisinopril exhibited similar effects on the primary end-point, the change in combined intima–media thickness of ten segments of the carotid and femoral arteries. Differential effects of the two drugs in favour of amlodipine were only observed in the elastic common carotid artery, an arterial segment that is usually not susceptible to atherosclerosis.

Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis; principal results of PHYLLIS—a randomized double-blind trial

Zanchetti A, Crepaldi G, Bond MG, *et al*. *Stroke* 2004; **35**: 2807–12

BACKGROUND. The Plaque Hypertension Lipid-Lowering Italian Study (PHYLLIS) trial aimed to test whether antihypertensive therapy with the ACE inhibitor fosinopril is more effective than hydrochlorothiazide on the progression of asymptomatic carotid atherosclerosis in hypertensive, hypercholesterolaemic patients. Additionally, lipid-lowering with pravastatin in association with either fosinopril or hydrochlorothiazide was evaluated against placebo. Carotid intima–media thickness, measured by ultrasound, was used to assess the progression of asymptomatic atherosclerosis.

A total of 508 hypertensive, hypercholesterolaemic patients with asymptomatic carotid atherosclerosis were randomized to treatment with hydrochlorothiazide, fosinopril, hydrochlorothiazide plus pravastatin, and fosinopril plus pravastatin respectively and were followed up blindly for 2.6 years. The primary outcome was the change in mean maximum intima–media thickness of the common carotids and bifurcations (CBM_{max}). CBM_{max} progressed significantly with hydrochlorothiazide but not with fosinopril. Progression was also prevented by adding pravastatin to hydrochlorothiazide. Combination of fosinopril and pravastatin exhibited no synergistic effect (Fig. 9.7). Blood pressure reduction was similar for the two antihypertensive drugs. Fosinopril and pravastatin exerted their benefits predominantly at the bifurcation, a preferred location for the development of atherosclerosis.

INTERPRETATION. Carotid atherosclerosis progressed with hydrochlorothiazide but not with fosinopril or with a combination of pravastatin with either drug. Fosinopril and pravastatin exerted their effects predominantly at the bifurcation, a site preferably affected by the haemodynamic consequences of hypertension and prone to the development of atherosclerosis. In conclusion, fosinopril and pravastatin prevent the progression of carotid atherosclerosis.

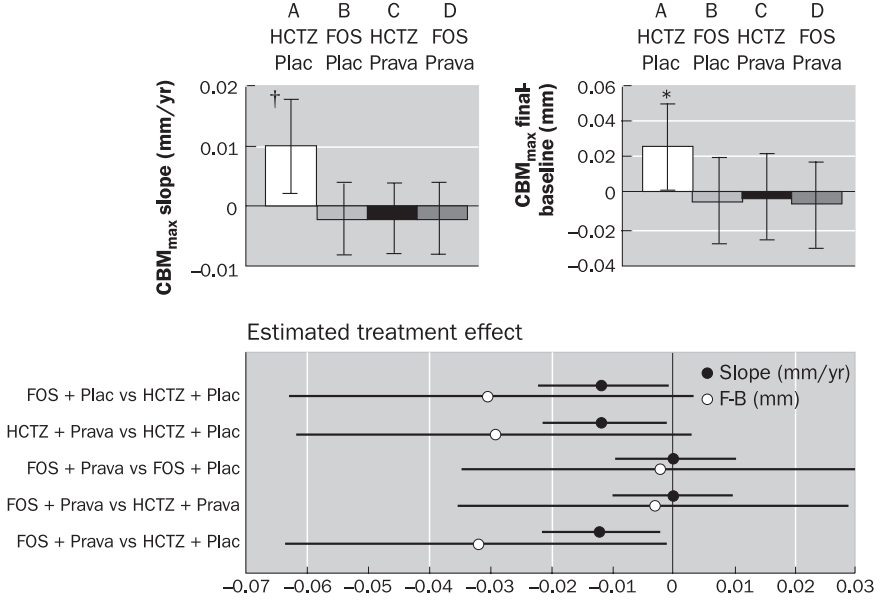
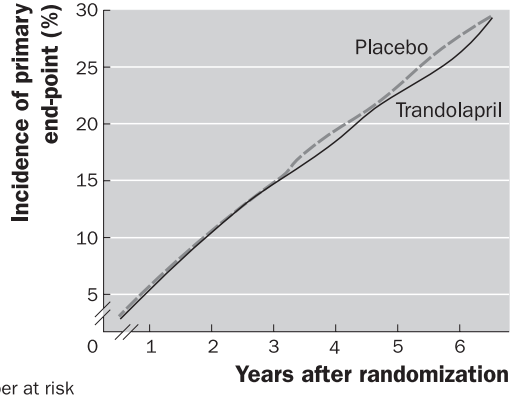


Fig. 9.7 Changes in slopes of mean maximum intima–media thickness of the common carotids and bifurcations (CBM_{max}) (top left) and between final and baseline measurements (top right) in the four treatment groups (top). Mean ± 95% CIs. HCTZ, hydrochlorothiazide; FOS, fosinopril; Plac, placebo; Prava, pravastatin. *P <0.05, †P <0.01. Source: Zanchetti *et al*. (2004).

Angiotensin-converting-enzyme inhibition in stable coronary artery disease

Braunwald E, Domanski MJ, Fowler SE, *et al.*; the PEACE Trial Investigators. *N Engl J Med* 2004; **351**: 2058–68

Background. ACE inhibitors effectively reduce the risks of heart failure, myocardial infarction and death from cardiovascular causes in patients with left ventricular systolic dysfunction or heart failure. ACE inhibitors have also been shown to reduce atherosclerotic complications in patients who have vascular disease without heart failure. The goal of the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial was to test whether ACE inhibitor therapy, when added to modern extensive therapy, would reduce the rate of non-fatal myocardial infarction, death from cardiovascular causes, or revascularization in low-risk patients with stable coronary artery disease and normal or slightly reduced left ventricular function. The PEACE trial is a double-blind, placebo-controlled cardiovascular outcome study. A total of 8290 patients with stable coronary artery disease and with normal or slightly reduced left ventricular function were randomly assigned either to trandolapril or to placebo. Trandolapril was given at a dose previously shown to reduce mortality and cardiovascular morbidity in patients with reduced left ventricular systolic function after myocardial infarction. Patients assigned to receive the ACE inhibitor failed to exhibit a beneficial effect on the primary end-point, which comprised death from cardiovascular causes, non-fatal myocardial infarction, and revascularization (Fig. 9.8).



Number at risk

Trandolapril	4158	4017	3752	3506	3079	1963	969
Placebo	4132	3990	3719	3486	3027	1929	891

Fig. 9.8 Cumulative incidence of the primary end-point (death from cardiovascular causes or non-fetal myocardial infarction or coronary revascularization) according to treatment group. Source: Braunwald *et al.* (2004).

Interpretation. In patients with stable coronary heart disease and preserved left ventricular ejection fraction who are receiving intensive current standard therapy, usually including coronary revascularization and lipid-lowering agents, and in whom the rate of cardiovascular events is already quite low, there is no evidence that the addition of an ACE inhibitor provides further benefit with regard to death from cardiovascular causes, myocardial infarction or coronary revascularization. Therefore, ACE inhibitors may not be necessary in all such patients to reduce their cardiovascular risk.

Comment

These three trials concentrate on the question of whether there is a direct effect of specific antihypertensive drugs on vascular wall properties and atherosclerosis beyond blood pressure lowering. Studies in experimental models suggest such effects for drugs such as calcium channel blockers and ACE inhibitors. Some data derived from interventional trials in humans support the possibility of a favourable effect of calcium channel blockers that is independent of blood pressure. These investigations, however, focused mainly on the progression of intima–media thickness of the carotid arteries. Therefore, a more generalizable benefit concerning cardiovascular disease remains speculative. As to anti-atherogenic properties of ACE inhibitors, clinical trials published to date are not conclusive. The three trials presented here, ELVERA, PHYLLIS and PEACE, contribute to the discussion mentioned above. ELVERA and PHYLLIS investigate the direct influence of specific drugs on the progression of intima–media thickness. PEACE is an outcome trial focusing on the effect of an ACE inhibitor on the clinical consequences of atherosclerosis.

The results of the two trials investigating the influence of antihypertensive drugs on intima–media thickness – ELVERA and PHYLLIS – suggest direct anti-atherogenic properties for calcium antagonists and ACE inhibitors, whereas thiazide diuretics appear to lack a beneficial action on the progression of atherosclerosis that is independent of blood pressure. In the PHYLLIS trial, the beneficial effect of treatment with an ACE inhibitor was equalized by adding a statin to the thiazide. Furthermore, the combination of ACE inhibitor plus statin failed to exhibit a synergistic effect on the progression of intima–media thickness. These findings imply that blood pressure-independent benefits achieved by ACE inhibitors may become marginal if the patient is simultaneously treated with a statin. This interpretation is in line with the results of the PEACE trial. The frequent use of statins (70%) observed in that study may have led to the failure of ACE inhibition to benefit the investigated normotensive patients who were suffering from relatively low-risk cardiovascular disease. Findings from previous trials investigating the effect of ACE inhibitors in patients with coronary disease and preserved left ventricular systolic function support this hypothesis. In these studies, ACE inhibitors improved endothelial function or reduced the progression of coronary artery disease only among patients with elevated concentrations of LDL cholesterol.

The three trials imply that some antihypertensive drugs may have a beneficial effect on the progression of atherosclerosis beyond the lowering of blood pressure. However, such an effect appears to shrink in relevance if patients are treated aggressively for other risk factors, such as cholesterol.

Conclusion

Endothelial dysfunction, microvascular rarefaction and accelerated arterial stiffness are essential changes of the micro- and macrovasculature in patients with arterial hypertension. Importantly, these alterations in vascular properties are not only a prognostically relevant consequence of hypertension. In addition, they may cause further development and progression of hypertension. This leads to new pathophysiological and therapeutic concepts. An important question is whether these functional and morphological changes of big and small vessels can be improved by specific antihypertensive drugs independently of blood pressure.

Nebivolol, a relatively new vasodilating β-adrenoceptor antagonist, differs from conventional β-blockers by its ability to stimulate substantial NO biosynthesis. This beneficial effect on endothelial function, i.e. the resulting NO-mediated vasodilation, may also be important in conditions associated with increased arterial stiffness, such as systolic hypertension. Antihypertensive drugs may also contribute to the redeployment of microvascular networks. ACE inhibition increases microvascular density in animal models. This effect appears to be mediated by activation of bradykinin signalling, resulting in the induction of VEGF. Thus, ACE inhibitors may counteract microvascular rarefaction and its consequences. Also, some antihypertensive drugs may improve arterial wall properties; arterial hypertension leads to vascular remodelling and increased thickening of the vessel walls, which contributes to enhanced stiffening of large arteries. Increased arterial stiffness and the consecutively elevated pulse pressure are supposed to be an independent risk factor in atherosclerotic diseases. Arterial stiffness and arterial wall thickening have been shown to be improved by antihypertensive drugs such as ACE inhibitors and calcium antagonists. In conclusion, some antihypertensive drugs may have benefits that are independent of blood pressure, i.e. effects on the macro- and microvasculature, and that affect the further development and progression of hypertension and atherosclerosis. However, the antiatherogenic effects of such drugs beyond the lowering of blood pressure appear to be marginal in a clinical setting in which patients are treated aggressively for other cardiovascular risk factors, such as dyslipidaemia.

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10

Hypertension among children and adolescents

BONITA FALKNER

Introduction

Measurement of blood pressure (BP) in children and adolescents has become part of routine healthcare in the young. BP measurement techniques that are especially important in the young, including BP cuff size, and the BP levels that define high BP in the young are becoming established in paediatric clinical practice. While secondary causes of hypertension occur more frequently in young children than in adults, primary, or essential, hypertension can be diagnosed in children and adolescents. As in adults, primary hypertension in children is often associated with other comorbidities. Consequently, the evaluation and care of a child with primary hypertension often requires evaluation for other risk factors in addition to the high BP.

This chapter will discuss recent publications on the diagnosis and management of childhood hypertension, BP trends in the young and evidence of target organ damage associated with high BP in the young. Recent articles on birth weight and BP in newborns will also be reviewed.

Diagnosis and management of high blood pressure in children and adolescents

In 1976 the National Heart, Lung, and Blood Institute of the National Institutes of Health issued a report on high BP in children and adolescents |**1**|. The report provided, for the first time, some normative data on childhood BP level according to age and sex. Based on these data, it was apparent that the normal BP range in children was much lower than in adults. It was also apparent that the adult definition of hypertension – a BP level that exceeded 140/90 mmHg – was inappropriate for children. An alternative definition of hypertension in childhood was developed, based on BP percentile. Abnormal, or high, BP was defined as a BP level that exceeded the 95th percentile of the normal BP distribution at a given age. The 95th percentile of BP for a 4-year-old boy of average height would be 111/69 mmHg whereas the BP 95th

percentile for a 14-year-old boy of average height would be 126/82 mmHg. With the development of BP data in healthy children, the shift in the normal BP range throughout childhood growth and development became clear and the ability to detect high BP became more precise. Over the next decades, additional BP data on healthy children and adolescents were added to the national data and the BP distribution curves were further refined. Subsequent reports in 1987 and 1996 recommended measurement of BP as part of routine healthcare in all children, beginning at age 3 years. This practice has been largely adopted by physicians who care for children. As a result, hypertension is detected in children and adolescents more frequently and at less severe levels of hypertension. Concurrently, there have been secular changes in childhood lifestyles and behaviours that have resulted in a global childhood obesity epidemic. The current recommendations on the detection and management of high BP in the young and the impact of obesity on BP will be discussed in this section.

The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. *Pediatrics* 2004; **114**(2 Suppl 4th Report): 555–76

BACKGROUND. The purpose of this report |2| is to update clinicians on the latest scientific evidence regarding BP in children and to provide recommendations for the diagnosis, evaluation and treatment of hypertension based on available evidence. The report includes the following information. New data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) have been added to the childhood BP database, and the BP data have been re-examined. The revised tables now include the 50th, 90th, 95th and 99th percentiles by gender, age and height. Hypertension in children and adolescents continues to be defined as systolic BP and/or diastolic BP that is, on repeated measurement, at or above the 95th percentile. BP between the 90th and 95th percentiles had been designated 'high normal'. To be consistent with the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) |3|, this level of BP will now be termed 'prehypertensive' and is an indication for lifestyle modifications. The evidence of early target organ damage in children and adolescents with hypertension is evaluated, and the rationale for early identification and treatment is provided. Based on recent studies, revised recommendations for the use of antihypertensive drug therapy are provided. Treatment recommendations include an updated evaluation of non-pharmacological therapies to reduce additional cardiovascular risk factors. Information is included on the identification of hypertensive children who need evaluation for sleep disorders.

INTERPRETATION. The Working Group that developed this Fourth Report concludes that while secondary causes of hypertension are identifiable more frequently in the young,

primary, or essential, hypertension is also detectable in childhood. The evaluation of childhood hypertension should include basic diagnostic studies for possible secondary causes of hypertension, and also include an evaluation for comorbidities and target organ damage.

Comment

This report moves beyond the previous guidelines on the diagnosis, evaluation and treatment of high BP in children and adolescents. Methods for accurate BP measurement are reviewed. BP measurement by auscultation continues to be the recommended method of measurement. Where mercury column instruments are not available, aneroid instruments are acceptable. The use of ambulatory BP monitoring for diagnosis of 'white-coat hypertension' is discussed. Additional BP data have been added to the total childhood database. The additional data have not changed the BP level at the 90th and 95th percentiles. However the BP tables have been expanded to include the 50th percentile and the 99th percentile. The 50th percentile provides the BP level at the mid-point of the BP distribution for age, gender, and height, which gives an approximation of average normal BP. The 99th percentile is added to provide numbers for BP stratification of severity of hypertension. Stage 1 hypertension is defined as systolic or diastolic BP that is, on repeated measurement, between the 95th percentile and 5 mmHg above the 99th percentile. Stage 2 hypertension is defined as systolic or diastolic BP that is greater than 5 mmHg above the 99th percentile. The guidelines for the extent of the evaluation and institution of antihypertensive therapy are related to the stage of hypertension. Children who have BP levels that are between the 90th and 95th percentiles have prehypertension. Because the 90th percentile may be above the adult definition of prehypertension at >120/80 mmHg, adolescents with BP >120/80 mmHg (but less than the 95th percentile) are also considered prehypertensive. Children with hypertension, particularly those who have primary hypertension, may also have associated comorbidities, including abnormal plasma lipids, impaired glucose tolerance, obesity, or sleep disorders. Recommendations on evaluation for comorbidities are provided in the report.

There is now evidence that hypertensive children may also have target organ damage as a consequence of the elevated BP. More than 25% of hypertensive children and adolescents may have left ventricular hypertrophy. Currently, the most useful and reliable method for determination of target organ damage in childhood is echocardiography for measurement of left ventricular mass. Information on ascertainment of left ventricular mass and criteria for left ventricular hypertrophy are provided in the report.

Guidelines for treatment, including the application of therapeutic lifestyle changes and indications for pharmacological therapy are discussed in the report. The number of drugs that have been studied with clinical trials in children has increased, largely because of incentives provided to the pharmaceutical industry under the 1997 Food and Drug Administration Modernization Act and the 2002 Best Pharmaceuticals for

Children Act |**4–6**|. Although still limited, clinical trial data in children on antihypertensive medication are becoming available. These data are now providing evidence on which to base management decisions. The report contains the most current information on paediatric labelling for dosage, along with some guidelines for the choice of drug class on beginning pharmacological therapy.

Figure 10.1 is a BP management algorithm for children and adolescents. The figure provides a pathway for preventive care, evaluation and treatment according to BP status. For normotensive children, healthy lifestyle counselling is appropriate. For prehypertensive children, therapeutic lifestyle changes and BP monitoring are recommended. Further diagnostic evaluation should be considered for a prehypertensive child if he or she is overweight or has other comorbidity. For Stage 1 hypertension, verification of the BP elevation with repeated measurements is recommended, followed by diagnostic studies. Children found to have secondary hypertension should have treatment for specific causes, whereas children with primary hypertension may benefit from initial treatment with therapeutic lifestyle changes. If insufficient BP

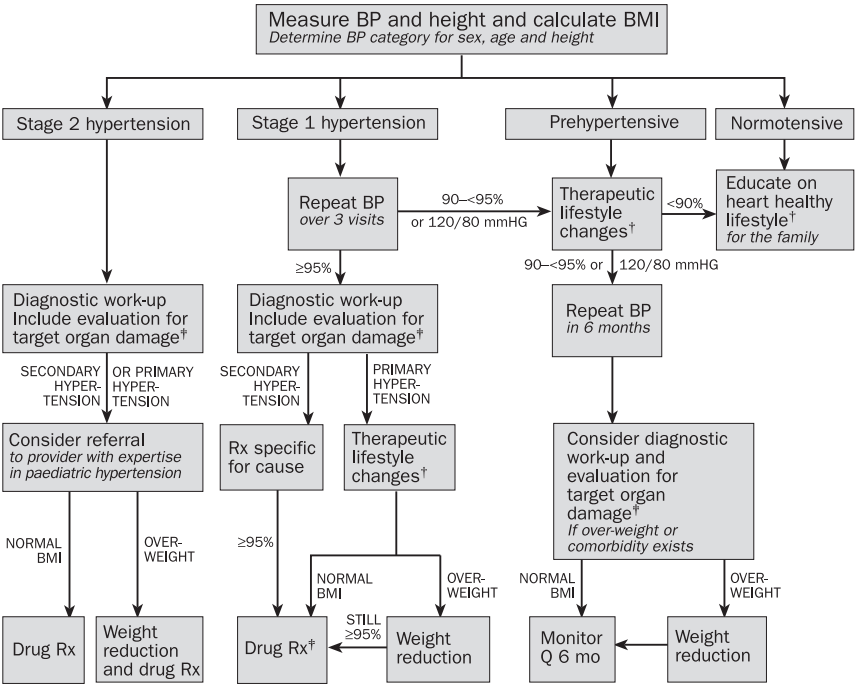

Fig. 10.1 Management algorithm. BMI, body mass index; BP, blood pressure; Rx, prescription; Q, every. †Diet modification and physical activity; ‡especially if younger, very high BP, little or no family history, diabetic, or other risk factors. Source: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) |**2**|.

reduction is achieved with lifestyle changes, pharmacological therapy can be indicated. Children with Stage 2 hypertension should have a more immediate evaluation and treatment, including drug therapy as well as weight reduction if overweight.

Secondary causes of hypertension occur more frequently in children than adults. Essential hypertension can also be identified in the young. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents provides more information on evaluation and management than previous reports. The Fourth Report is accessible at the National Heart Lung and Blood Institute website at www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm.

Trends in blood pressure among children and adolescents

Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. *JAMA* 2004; **291**: 2107–13

BACKGROUND. The prevalence of overweight among children and adolescents increased between 1988 and 2000. While excess body weight is known to have an effect on BP, the change in BP over that time has not been examined. The objective of this study was to examine trends in systolic and diastolic BP among children and adolescents between 1988 and 2000. The authors analysed two serially conducted cross-sectional studies using nationally representative samples of children and adolescents, aged 8–17 years, from NHANES III, conducted in 1988–1994 (n = 3496), and NHANES 1999–2000 (n = 2086). Main outcome measures were systolic and diastolic BP levels. In 1999–2000, the mean (SE) systolic BP was 106.0 (0.3) mmHg and diastolic BP was 61.7 (0.5) mmHg. After adjustment for age, mean systolic BP was 1.6 mmHg higher among non-Hispanic black girls (P = 0.11) and 2.9 mmHg higher among non-Hispanic black boys (P <0.001) compared with non-Hispanic whites. Among Mexican-Americans, systolic BP of girls was 1.0 mmHg higher (P = 0.21) and that of boys was 2.7 mmHg higher (P <0.001) than in non-Hispanic whites (P <0.001). With further adjustment for body mass index (BMI), these differences were attenuated. After standardization for age, race/ethnicity and sex, systolic BP was 1.4 (95% confidence interval [CI] 0.6–2.2) mmHg higher (P <0.001) and diastolic BP was 3.3 (95% CI 2.1–4.5) mmHg higher in 1999–2000 (P <0.001) than in 1988–1994. With further adjustment for differences in the BMI distribution in 1988–1994 and 1999–2000, the increase in systolic BP was reduced by 29% and diastolic BP was reduced by 12%.

INTERPRETATION. BP has increased over the past decade among children and adolescents. This increase is partially attributable to an increased prevalence of overweight.

Comment

This report is the result of a detailed biostatistical analysis of epidemiological data. The data that are available on serial measurements of BP in children are limited. The data used for this report are not based on repeat measurement of BP in the same

individuals. The investigators compared two separate sets of BP data in children that were obtained in two separate time periods. The time interval between the two sets of measurements is only about 10 years. The 1988–1994 NHANES sample included 3496 children between the ages of 8 and 17 years, and the 1999–2000 NHANES sample included 2086 children. Considering the normal shift in BP distribution with childhood growth and development, the number of children in each set of data is not very large. However, a statistically significant upward trend in BP was detected. While the absolute increase in BP may not seem very large (a systolic BP increase of 1.4 mmHg and a diastolic BP increase of 3.3 mmHg), the public health implications are substantial for a population increase in BP of a few mmHg. This degree of increase in BP predicts a marked increase in the prevalence of hypertension, especially in young adults, followed by an increase in the rates of hypertensive morbidity, including heart failure, renal failure and strokes.

Publications that draw on national childhood data avoid applying the term 'obesity' in children. To avoid stigma associated with obesity, the term 'overweight' is used as an alternative and is defined as BMI at or above the 95th percentile on the age and gender tables. Children with BMI above the 85th percentile but below the 95th percentile are considered at risk of being overweight. In 2002, Ogden and colleagues |**7**| compared the prevalence of overweight (BMI $\geq$95th percentile), in the 1999–2000 NHANES data with the prevalence in previous NHANES data periods. Their analyses verified the increase in prevalence of childhood obesity (termed 'overweight'). In their analysis of the serial sets of NHANES BP data, Muntner and colleagues determined that the upward trend in childhood BP level was largely due to the increase in overweight children and adolescents. Thus, there is now evidence that childhood obesity is having consequences for health, beginning in the young. Obesity with hypertension in children and adolescents is both a public health issue and a common problem confronted by primary care physicians. Recognition of the extent of this health problem is an important first step, to be followed by development of more effective management strategies.

Prevalence and trends of a metabolic syndrome phenotype among US adolescents, 1999–2000

Duncan GE, Li SM, Zhou XH. *Diabetes Care* 2004; **27**: 2438–43

BACKGROUND. The objective of this study was to determine the prevalence of a metabolic syndrome phenotype among US adolescents using the most recent national data and to examine trends in the prevalence of metabolic syndrome. An analysis of data was conducted on 991 adolescents (aged 12–19 years) who had fasted for at least 6 hours, from NHANES. The metabolic syndrome was determined using the National Cholesterol Education Program (Adult Treatment Panel III) definition modified for age. The overall prevalence of the metabolic syndrome phenotype among US adolescents increased from 4.2% in NHANES III (1988–1992) to 6.4% in NHANES 1999–2000 (P <0.001). The syndrome was more prevalent

($P < 0.01$) in male than female adolescents (9.1 vs 3.7%) and was found in 32.1% of overweight adolescents (BMI ≥95th percentile for age and sex), compared with 7.1% of adolescents at risk of overweight (BMI between the 85th and 95th percentiles) ($P < 0.001$). Based on population-weighted estimates, more than 2 million US adolescents currently have the metabolic syndrome phenotype.

INTERPRETATION. The prevalence of a metabolic syndrome phenotype has increased significantly over the past decade among US adolescents and is particularly prevalent (>39%) in overweight adolescents. These findings have important implications for public health because of the well-known health risks associated with the metabolic syndrome in adults.

Comment

The metabolic syndrome is a clustering of cardiovascular risk factors that is associated with both type 2 diabetes mellitus and cardiovascular disease. The core abnormality of the metabolic syndrome is insulin resistance, or impairment of insulin's glucoregulatory action. Many factors are associated with the syndrome, including central (or visceral) obesity, dyslipidaemia, high BP, impaired glucose tolerance, and microalbuminuria, along with abnormalities in fibrinolysis and inflammation |**8,9**|. The metabolic syndrome has been defined for clinical application in adults by the National Cholesterol Education Panel (NCEP) |**10**| and the World Health Organization (WHO) |**11**|. Current estimates indicate that the age-adjusted prevalence of the metabolic syndrome is approximately 24% among US adults |**12**|. Previously, Cook and colleagues |**13**| examined NHANES III data from 1988–1992 to determine the prevalence of the metabolic syndrome in adolescents. They used the NCEP criteria for the definition of the metabolic syndrome, with some adjustments for adolescent age, including BP at or above the 90th percentile as high BP and a plasma triglyceride level above 110 mg/dl as elevated triglyceride. They found that approximately 4% of US adolescents had the metabolic syndrome. Among adolescents with BMI above the 95th percentile for age and sex, the prevalence of the metabolic syndrome was 29%. In the present report, the authors examined the subsequent set of NHANES data, from 1999–2000, for the prevalence of the metabolic syndrome in adolescents and compared the results with the previous estimates from 1988–1992. Figure 10.2 depicts the upward shift in the prevalence of the metabolic syndrome for all adolescents and shows an increase from 4.2% in the 1988–1992 period to 6.4% in the 1999–2000 period. The figure also shows the greater prevalence among males compared with females. Among adolescents who were overweight (obese), the prevalence of the metabolic syndrome increased from 29% in 1988–1992 to 32.1% in 1999–2000.

The metabolic syndrome is a significant health issue that markedly increases the risk of cardiovascular disease. Obesity is the major driver in development of the metabolic syndrome. Using population estimates, over two million adolescents in the US currently have the metabolic syndrome. Comparable numbers of younger children may also have the metabolic syndrome or are likely to have it as they become adolescents. This health problem is not limited to the US, but is also being recognized in both Western and developing countries.

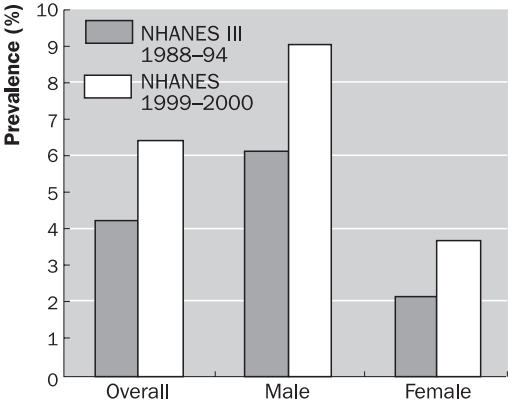

Fig. 10.2 Prevalence of a metabolic syndrome phenotype among US adolescents aged 12–19 years. Differences shown are between NHANES III (1988–1994) and NHANES 1999–2000, overall and by sex. All comparisons between surveys are significant at $P < 0.001$. Source: Duncan *et al*. (2004).

Overweight, ethnicity, and the prevalence of hypertension in school-aged children

Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. *Pediatrics* 2004; **113**: 475–82

BACKGROUND. The objective of this study was to describe the current prevalence of paediatric hypertension and the relationships between gender, ethnicity, overweight and BP. School-based screening was performed in 5102 children (13.5 ± 1.7 years). Age, gender, ethnicity, weight and height were ascertained and BMI was calculated. Overweight was defined as BMI at or above the 95th percentile. Students with BP above the 95th percentile on the first screening underwent a second screening 1–2 weeks later, and then a third screening if BP was above the 95th percentile at the second screening. Ethnicity distribution was 44% white, 25% Hispanic, 22% African-American and 7% Asian. Overall, the prevalence of overweight was 20%, which varied significantly by ethnicity (31% Hispanic, 20% African-American, 15% white and 11% Asian). The prevalence of elevated BP after the first, second and third screenings was 19.4, 9.5 and 4.5% respectively. Elevated BP on first screening was highest among Hispanics (25%) and lowest among Asians (14%). Ethnic differences in the prevalence of hypertension (elevated BP in three screenings) were not significant after controlling for overweight. The prevalence of hypertension increased progressively as the BMI percentile increased from below the 5th (2%) to at or above the 95th (11%). After adjustment for gender, ethnicity, overweight and age, the relative risk of hypertension was significant for gender (1.50; 95% CI 1.15–1.95) and overweight (3.26; 95% CI 2.50–4.24).

Interpretation. These results confirm an evolving epidemic of cardiovascular risk in youth, as evidenced by an increase in the prevalences of overweight and hypertension, notably among ethnic minority children.

Comment

Unlike the previous two reports, which were based on NHANES data, this report is based on data obtained from children in a school setting, indicating that the sample represents healthy individuals. The age range is early adolescents and the sample size of 5102 adolescents exceeds the number of adolescents in the NHANES samples. The high rates of obesity are again verified. In fact, the 20% prevalence of obesity (overweight) is somewhat higher than in the NHANES 1999–2000 data. The prevalence of obesity is known to be greater in minority children. Over 50% of the total sample were Hispanic and African-American, which may explain the higher prevalence of obesity that was found in this study. A very important part of this report lies in the BP data. The BP distribution curves in the Fourth Report |**2**| and the BP data in NHANES are based on measurements made on one occasion in each case. It is well known, however, that BP measurements in childhood are not always consistent in repeat measurements because of the normal variability of childhood BP and the phenomenon of regression to the mean. Therefore, the clinical diagnosis of hypertension requires average BP levels that are at or above the 95th percentile on at least three separate occasions. The authors applied this standard to children who were found to have elevated BP on the first screening measurement. After the third BP measurement, 4.5% of the children were found to have hypertension. Moreover, among the obese (BMI >95th percentile), 11% were hypertensive. The 11% of the obese children with hypertension already have two components of the metabolic syndrome. The Fourth Report |**2**|, discussed above, recommends that these children be evaluated for additional comorbidities, including abnormalities in glucose or lipid metabolism, which would designate the metabolic syndrome and also heighten their risk of cardiovascular injury.

The publications discussed above document the dramatic increase in childhood obesity. Concurrent with the increase in obesity is an increase in BP level in children and adolescents, along with an increase in the metabolic syndrome among adolescents. Together, these reports indicate that the likely consequences of the rising rates of obesity in the young are greater rates of cardiovascular disease and also earlier onset of cardiovascular injury. These trends represent significant issues in both public health and clinical practice.

Target organ damage from hypertension in the young: emerging evidence

Detectable injury to blood vessels or to the heart or kidneys from high BP indicate that target organ damage has occurred and the risk of subsequent cardiovascular events is

heightened. Hypertensive adults who have left ventricular hypertrophy (LVH) are at greater risk of cardiovascular events than hypertensive patients without LVH. Other clinical measures in adults of target organ damage include aortic stiffness, an increase in the intimal–medial dimension of the carotid artery, and microalbuminuria. Evidence is now emerging which indicates that target organ damage in young adulthood is linked with higher BP in childhood. There is also considerable data on left ventricular mass (LVM) in the young, as measured by echocardiography. The following reports provide important new information on this issue.

The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association

Hanevold C, Waller J, Daniels S, Portman R, Sorof J; International Pediatric Hypertension Association. *Pediatrics* 2004; **113**: 328–33

BACKGROUND. The objective of this project was to determine the prevalence of LVH in a multiethnic group of children and adolescents with hypertension. Pooled data obtained between 1998 and 2001 from three sites belonging to the International Pediatric Hypertension Association were examined. Patients undergoing echocardiography to detect LVH as part of the evaluation for hypertension were included for analysis. LVM was calculated from two-dimension guided M-mode echocardiographic measurements of the left ventricle. Left ventricular mass index (LVMI) was calculated as LVM/height$^{2.7}$. LVH by adult criteria was defined as LVMI greater than 51 g/m$^{2.7}$ and by paediatric criteria as LVMI greater than 38.6 g/m$^{2.7}$. Left ventricle geometry was classified as concentric, concentric remodelling, eccentric or normal. Data on 129 patients with a mean age of 13.6 ± 3.6 years were analysed. The population was 67% male, 46.5% white, 38% African-American and 15.5% Hispanic. The prevalence of LVH was 15.5% using adult criteria and 41.1% using paediatric criteria. Increasing BMI was associated with a higher LVMI. Using either paediatric or adult criteria, LVH was associated with BMI at or above the 95th percentile for age and gender. LVH and concentric hypertrophy were identified most frequently in Hispanic children.

INTERPRETATION. LVH occurs commonly in children with hypertension and is associated with increased BMI. LVH may be more prevalent in Hispanic children than in other ethnic groups. Prevention and treatment of obesity are important in reducing the cardiovascular risk for children with hypertension. Further evaluation of the frequency of LVH in multiethnic populations is needed.

Comment

Echocardiography is considered superior to the electrocardiogram in the assessment of LVM in children and adolescents. Previous paediatric studies have reported variable rates of LVH in children with hypertension, ranging from 8 to 38% |**14,15**|. The

difference in the reported frequencies of LVH in children with hypertension may be due to differences in the method used to calculate LVM and the definition of LVH. In addition, most studies on LVM in children and adolescents have been conducted in a single centre. This report adds considerable important information regarding the prevalence of LVH among children and adolescents with hypertension. The sample of hypertensive children was drawn from three different centres. Although the study is a retrospective review of pooled data, the study includes an exceptionally large number of hypertensive children, and the data were also multiethnic and included Caucasian, African-American and Hispanic children.

There is a normal increase in LVM during childhood growth and development. Therefore, the normal ranges of cardiac size in children need to be defined within the context of body size. The methods for correcting LVM for body size have varied, and include adjustments for height, body surface area, weight and height raised to various powers. In this study, the investigators used height$^{2.7}$ (in metres). Height$^{2.7}$ is the recommended method of indexing LVM in children because it has been validated as an indicator of lean body mass and also minimizes the effects of age, gender and race |**2**|.

Two criteria for LVH were examined in this study. Among adult patients with hypertension, an LVMI above 51 g/m$^{2.7}$ is associated with a fourfold greater risk of cardiac events. Using this adult definition, the prevalence of LVH among hypertensive children and adolescents was 15.5%. However, adult criteria for the categorical classification of physical measurements are generally not appropriate for children and adolescents, which is why the 95th percentile is used as the cut point for abnormal BP and abnormal BMI. The authors also applied the 95th percentile method to the LVMI in this sample of hypertensive children. The 95th percentile for LVMI in children and adolescents (based on normative data) is 36.88 g/m$^{2.7}$ for females and 39.36 g/m$^{2.7}$ for males |**16**|. When the LVMI at or above the 95th percentile was used to define LVH, 41.1% of the hypertensive children had LVH. Obesity was found to be strongly associated with increased LVM, and LVH was detected more frequently among children with BMI above the 95th percentile.

This report provides impressive evidence that childhood hypertension is not a benign problem. LVH, ascertained by echocardiography, occurs frequently in hypertensive children and is indicative of target organ damage. These results strongly support the guidelines published in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents which recommend an echocardiogram for measurement of LVM in children and adolescents with hypertension |**2**|.

Increased left ventricular mass in obese adolescents

Friberg P, Allansdotter-Johnsson A, Ambring A, *et al*. *Eur Heart J* 2004; **25**: 987–92

BACKGROUND. An increase in LVM has been reported in obese adolescents in previous studies using echocardiography. The aim of this study was to determine the

extent of the increase in LVM and correlation to other risk factors using cardiac magnetic resonance in obese and lean adolescents. Nineteen obese and 20 lean adolescents were examined. After resting BP measurements and blood sampling for insulin triglycerides and cholesterol levels, all subjects underwent cardiac magnetic resonance examination to assess LVM. Adjusted for body height, LVM was 16% greater in obese than in lean adolescents (median 66 g/m; $P = 0.0042$). Obese subjects had higher resting systolic BP than controls (median 115 vs 110 mmHg; $P = 0.0077$) and higher fasting triglyceride and insulin levels. High-density lipoprotein cholesterol levels were lower in the obese group than in the lean group.

INTERPRETATION. Obese adolescents had a higher LVM than age-matched lean subjects, and there was a statistically significant correlation of LVM with BMI and systolic BP. These findings add to the established cardiovascular risk profile of obese adolescents.

Comment

In this study, cardiac imaging and measurement of LVM was performed with cardiac magnetic resonance. Although the number of adolescents that were examined was relatively small, compared with the above study by Hanevold *et al.*, the quality and precision of the cardiac measurements were superb. Rather than comparing hypertensive with normotensive adolescents, the intention in this study was to compare obese adolescents with age-matched lean adolescents. Other risk factors, including BP, were analysed. The effect of obesity on cardiac size was clearly demonstrated, with LVM significantly greater in the obese than in the lean adolescents. Moreover, an additional effect of BP on LVM was also detected that increased LVM in addition to the effect of obesity. This report is consistent with other recent publications that are providing evidence that high BP and obesity are serious health issues in the young. Children and adolescents with both obesity and high BP frequently have LVH, indicative of cardiovascular injury. Obese children with high BP should be carefully evaluated and treated.

Childhood blood pressure as a predictor of arterial stiffness in young adults; the Bogalusa Heart Study

Li S, Chen W, Srinivasan SR, Berenson GS. *Hypertension* 2004; **43**: 541–6

BACKGROUND. Increased arterial stiffness is an independent predictor of cardiovascular disease and mortality in middle-aged and older adults. Limited data are available regarding the relationship of arterial stiffness in young adults with risk factors measured in childhood or adulthood, or as a cumulative burden from childhood to adulthood. This aspect was examined in a sample of 835 black and white young adults (72% whites, 44% men) aged 24–44 years who had at least four measurements of traditional risk factors over an average follow-up period of 26.5 years since childhood. Brachial–ankle pulse wave velocity (baPWV), measured by a simple automatic oscillometric technique, was used as an index of arterial stiffness. The cumulative burden of risk factors since childhood was measured as

area under the curve divided by follow-up years. In young adults, the baPWV was higher in males than in females ($P < 0.001$) and in blacks than in whites ($P < 0.001$). In multiple regression analyses, independent predictors of baPWV in young adults were systolic BP in childhood; systolic BP, high-density lipoprotein cholesterol, triglycerides and smoking in adulthood; and the cumulative burden of systolic BP and triglycerides and duration of smoking years from childhood.

Interpretation. Systolic BP beginning in childhood is a consistent predictor of arterial stiffness in free-living, asymptomatic young adults. These findings underscore the importance of childhood BP in the evolution of arterial stiffness and the need to begin preventive cardiology early in life.

Comment

The Bogalusa Heart Study is a community-based longitudinal cohort study that has many advantages, including the biracial composition, and the cohort is without the selection bias that occurs with patient samples. The results of this study show that systolic BP in childhood, in adulthood or as a cumulative systolic BP burden since childhood is a consistent predictor of arterial stiffness in young adults. These data demonstrate that systolic BP is the leading determinant in the evolution of arterial stiffness, a measure of target organ damage. The baPWV measures were not available in childhood, so that it cannot be determined if there was a relationship between systolic BP level and vascular stiffness, even in the young. High-density lipoprotein cholesterol and triglycerides also contribute to the development of arterial stiffness. The results of this study provide even more support to the importance of measuring and monitoring BP in childhood. When BP is elevated, interventions to lower BP may have future benefit.

Fetal programming: birth weight and future blood pressure

Inverse associations between fetal growth and disease in later life have provided the basis for the original 'fetal origins' hypothesis |**17**|. According to this theory, an impaired intrauterine environment that deprives the fetus of optimal nutrient delivery programmes the fetus to express, in later life, ischaemic heart disease, type 2 diabetes mellitus, hypertension and stroke. Suboptimal intrauterine nutrition would restrict fetal growth and result in lower birth weight. Thus, low birth weight has become the clinical marker of a suboptimal intrauterine environment and a possible risk factor for future hypertension. Although the birth weight concept has been an appealing theory and has been supported by data from retrospective studies, it remains controversial. Recent investigations that have applied a prospective longitudinal design have not detected the inverse association of birth weight with subsequent BP.

Indicators of fetal growth do not independently predict blood pressure in 8-year-old Australians: a prospective cohort study

Burke V, Beilin LJ, Blake KV, *et al*. *Hypertension* 2004; **43**: 208–13

BACKGROUND. Inverse associations between size at birth and BP in later life are commonly statistically significant only after adjustment for current size, consistent with change in size as the determinant. Few studies have been prospective or have included a range of potential confounders. Using regression models, including maternal and demographic variables, an examination was conducted on associations between size at birth and BP in Australian children followed from week 16 of gestation to the age of 8 years. BP measurements were available from 1417 children born after 37 weeks of gestation without congenital abnormalities. In models adjusted only for sex, the birth weight, birth length, ponderal index, head circumference, chest circumference, abdominal girth, mid-arm circumference, triceps skin fold, placental weight or birth/placental weight ratio did not significantly predict systolic BP in 8-year-olds. With adjustment for current size, associations were inverse but not statistically significant (regression coefficients: birth weight –1.11; 95% confidence limits [CL] –2.22 to 0.01; birth length –0.25; 95% CL –0.52 to 0.24) and remained non-significant after adjustment for confounders. Current weight, height or BMI significantly predicted systolic BP and diastolic BP ($P < 0.001$) with a difference of 8/4 mmHg between upper and lower quartiles; effects were similar in infants with lower and higher birth weight.

INTERPRETATION. These findings are consistent with post-natal change in size as the major determinant of BP in 9-year-olds and are important in the context of the world-wide epidemic of obesity in childhood as a likely precursor of increasing rates of hypertension in adults.

Comment

In most of the reports that support the birth-weight theory, birth weight has been found to be a statistically significant predictor of later BP only when the statistical analysis includes an adjustment for later weight. In this study on 8-year-old children, there was no statistically significant association between birth weight and BP, with or without adjustment for current weight or with adjustment for the range of other possible confounders. The dominant measure that was correlated with current BP was current weight. These results indicate that post-natal weight and change in weight are major determinants of the BP level in childhood. These results also support the importance of weight control and avoidance of being overweight in childhood.

Effect of birth weight on blood pressure and body size in early adolescence

Falkner B, Hulman S, Kushner H. *Hypertension* 2004; **43**: 203–7

BACKGROUND. The fetal programming theory – that birth weight contributes to BP or body size in later life – was examined in this study. A prospective longitudinal study was conducted on subjects who were examined as newborns and prospectively interviewed and re-examined at 11–14 years of age. Low birth weight (<2500 g) was present in 36% of the sample. The adolescent examination included measurements of BP, using both auscultation and oscillometric methods; anthropometrics (height, weight and BMI); health status; and health behaviours. Data were analysed on 250 subjects. Correlation coefficients of birth weight with all BP measures were non-significant, except for the last auscultated diastolic BP ($r = 0.19$; $P < 0.01$), which had a positive relationship. The simple correlation coefficients of birth weight with adolescent body size were significant and positive for weight and BMI. After multiple linear regression analyses with adjustments for age, Tanner stage and gestational age, there was no significant effect of birth weight on adolescent weight or BMI. No significant correlations were detected for ponderal index at birth with adolescent measures.

INTERPRETATION. This study, which included a substantial portion of low-birth-weight cases (36%), indicates that birth weight does not correlate negatively with later BP. These results do not support the low-birth-weight theory and indicate that childhood factors that are more proximal have a greater effect on adolescent BP than intrauterine factors.

Comment

This is another prospective longitudinal study that, in examining the relationship of birth weight to BP in early adolescence, did not detect a significant inverse relationship of birth weight with subsequent BP. The number of children in this study was not as large as in the previous report discussed. However, the children in this sample included a large proportion (35%) who had low birth weight. Thus, even when the group of children under study was weighted with more high-risk cases, an effect of birth weight on future BP could not be detected.

Maternal age and other predictors of newborn blood pressure

Gillman MW, Rich-Edwards JW, Rifas-Shiman SL, Liberman ES, Kleinman KP, Lipshultz SE. *J Pediatrics* 2004; **144**: 240–5

BACKGROUND. The objective of this study was to investigate perinatal predictors of newborn BP. Among 1059 mothers and their newborn infants participating in Project Viva, a US cohort study of pregnant women and their offspring, five systolic BP

measurements were obtained on a single occasion in the first few days of life. Using multivariate linear regression models, the extent to which maternal age and other pre- and perinatal factors predicted newborn BP level were examined. The mean (SD) maternal age was 32.0 (5.2) years, and mean (SD) newborn systolic BP was 72.6 (9.0) mmHg. A multivariate model showed that for each 5-year increase in maternal age, newborn systolic BP was 0.8 mmHg higher (95% CI 0.2–1.4). In addition to maternal age, independent predictors of newborn BP included maternal third trimester BP (0.9 mmHg; 95% CI 0.2–1.6, for each increment in maternal BP); infant age at which BP was measured (2.4 mmHg; 95% CI 1.7–3.0, for each additional day of life); and birth weight (2.9 mmHg per kg; 95% CI 1.6–4.2).

INTERPRETATION. Higher maternal age, maternal BP and birth weight were associated with higher newborn systolic BP. Whereas BP later in childhood predicts adult hypertension and its consequences, newborn BP may represent different phenomena, such as pre- and perinatal influences on cardiac structure and function.

Comment

There has been an abundance of publications on the possible association of newborn weight with BP at a later time in life. However, there have been few studies and few reports on newborn BP. This paucity of information has been largely because measurement of BP is infrequently done in healthy newborn infants. With advances in neonatology along with the supportive instrument technology, BP measurement is now a standard part of care in the critically ill newborn infant. BP is usually measured in the newborn infant with oscillometric instruments, or when an umbilical artery catheter is in place a direct intra-arterial measurement of BP can be obtained. The available data on newborn BP indicate that, along with the haemodynamic transition from intrauterine to extrauterine life, there is a sharp upward shift in systolic BP |**18**|. In newborn infants, as well as children and adults, body size is a major determinant of BP level |**19**|. This report is important because newborn BP is an area in which there is still limited information. The interesting issue addressed by these authors is the point at which maternal and intrauterine factors determine BP level and the life phase at which post-natal factors determine BP level. At present, far more normative data are necessary to determine the normal range of newborn BP and to develop a better estimate of abnormal BP in the newborn.

Treatment of hypertension in children and adolescents

Children with hypertension, particularly those with evidence of target organ damage, can benefit from treatment to lower BP. Therapeutic lifestyle changes are recommended for all children with hypertension and for children with pre-hypertension. There are indications for pharmacological therapy in children with high BP; these indications include symptomatic hypertension, secondary hypertension, evidence of

target organ damage, types 1 and 2 diabetes mellitus, and persistent hypertension despite non-pharmacological measures |**2**|. Until recently, the clinical trial data on children that were available to guide antihypertensive drug treatment were limited to small case series and clinical experience. In the past few years some paediatric clinical trials on antihypertensive medications have been performed and these new clinical trial data are now being published. The following report is an example of this new and emerging information.

A randomized, placebo-controlled trial of amlodipine in children with hypertension

Flynn JT, Newburger JW, Daniels SR, *et al*; PATH-1 Investigators. *J Pediatrics* 2004; **145**: 288–90

BACKGROUND. The purpose of this study was to evaluate the efficacy and safety of amlodipine in hypertensive children. A randomized, double-blinded, placebo-controlled, parallel-group, dose-ranging study was conducted at 49 centres in North and South America. The primary end-point was the effect of amlodipine on systolic BP; secondary end-points included the effect of amlodipine on diastolic BP, the effect of amlodipine as a function of dose and body size, and an evaluation of safety. The study enrolled 268 hypertensive children (mean age 12.1 ± 3.3 years); 84 (31.3%) had primary hypertension and 177 (66%) were boys. Amlodipine produced significantly greater reductions in systolic BP than placebo; these were –6.9 mmHg for 2.5 mg daily ($P = 0.045$ vs placebo) and –8.7 mmHg for 5 mg daily ($P = 0.005$ vs placebo). The underlying cause of hypertension had no effect on the response to amlodipine. There was a significant dose–response effect of amlodipine on both systolic and diastolic BP, beginning at the dose of 0.06 mg/kg per day. Systolic BP at or below the 95th percentile was achieved in 34.6% of subjects with systolic hypertension. Amlodipine was well tolerated, with just six children withdrawn from treatment because of drug-related adverse events.

INTERPRETATION. Amlodipine effectively lowers systolic BP in a dose-dependent manner in hypertensive children who require drug treatment.

Comment

Amlodipine is a dihydropyridine calcium channel blocker that has appeal for use in children because it has a gradual onset of action and is long-acting, which means that it can generally be given once daily. This study demonstrates that amlodipine is effective in lowering BP, there is a progressive dose response, and amlodipine is generally safe for use in children. The study design is critical in proving efficacy and safety. The design in this study contains the critical elements of a trial; it is double-blind, randomized, and has a placebo arm. Because the benefits of BP reduction have been very well demonstrated in adults, clinical trials in adults on antihypertensive drugs no longer include a placebo arm. It is considered unethical to treat hypertensive patients with a placebo in a clinical trial, and generally one drug is compared with

another drug class in contemporary antihypertensive clinical trials on adults. In children, the issues are somewhat different. There is little information on cardiovascular event rates due to hypertension in children, with the exception of very severe hypertension. The BP-lowering effect and dose response are key issues to be determined in children with hypertension. However, there continue to be ethical concerns with regard to the use of placebo rather than some other active agent. The clinical trial design used in this study was created to manage these issues. In this study, all children received treatment with amlodipine, with randomization to different doses, for 4 weeks. After 4 weeks of active therapy there was another randomization, at which point some children were changed to placebo for an additional 4 weeks. Using this strategy, all hypertensive children received active treatment, after which some received placebo for a relatively short period of 4 weeks. More reports on antihypertensive clinical trials in children are expected to be published in the next few years. As these data develop, clinicians will have better information on which to make clinical management decisions.

Conclusion

Recent publications on hypertension in children and adolescents have established that primary, or essential, hypertension is present and identifiable in childhood. The expression of childhood hypertension and the prevalence of hypertension in young adulthood are increasing, largely driven by the childhood obesity epidemic. This condition is not benign, because, when evaluated, the presence of target organ damage is not uncommon. The roles of birth weight and intrauterine factors in determining future hypertension are likely to be less important than those of postnatal factors. Childhood lifestyles, including diet and physical activity patterns, that lead to obesity have a major effect on rising BP level. The prevention of obesity will contribute to hypertension prevention. With the publication of paediatric clinical trial data, clinicians will become more informed about the use of antihypertensive medication in children when drug therapy is indicated.

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Part III

New diagnostic strategies

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11

Genetics of hypertension and related disorders

FRANÇOIS ALHENC-GÉLAS

Introduction

Blood pressure is a genetically determined trait with a strong added influence of so-called environmental, lifestyle-related factors, such as salt and food intake and alcohol consumption. There is also a gender effect in the regulation of blood pressure, which is probably largely independent of environmental factors but interferes with the physiological effect of genes that control blood pressure. In some instances these genes can have gender-specific effects. Blood pressure level is strongly and causally linked to the incidence of major cardiovascular events, especially myocardial infarction and stroke, and to the progression of renal insufficiency towards end-stage renal failure, making it a well-documented genetic risk factor for these diseases. Familial transmission and epidemiological studies suggest that a relatively large number of genes, probably several tens, are involved in determining high blood pressure level in the general population. The search for blood pressure-related genes is a major endeavour in cardiovascular research, and proceeds from different and complementary experimental strategies, which can be schematically presented as follows. The first two approaches are the testing of candidate genes selected on the basis of established pathogenic hypotheses, and the identification of loci associated with blood pressure by positional cloning in large kindreds. The reliability of these two approaches relies strongly on the clinical design of the studies, which should be adequately powered and include well-phenotyped subjects. The third approach is the study of spontaneously hypertensive animals, especially rats, or of the development of strains of rats or mice with contrasted blood pressure levels, and the study, by linkage and segregation analysis in these paucigenic models, of candidate genes and blood pressure-associated loci. Hypotheses generated by these animal experiments can then be tested in human populations. The fourth approach is the study of monogenic forms of hypertension identified in selected families, generally on the basis of associated disorders such as ionic balance abnormalities, and the identification of the gene responsible by positional cloning or the candidate gene method. This approach has been very successful in the past, and has allowed the generation of new hypotheses concerning the regulation of blood pressure, and the identification of

new, rare, forms of hypertensive diseases. Its relevance to the genetics of essential hypertension has been limited so far, however.

Over the past 18 months or so, there have been a large number of publications illustrating these different approaches to the discovery of genes involved in blood pressure regulation, and some interesting new data. The selection below is arbitrary and based on the estimated relevance of these findings to human hypertension. In addition, some studies concerning the genetic basis of endothelial dysfunction, which is generally considered to be an early abnormal phenotype leading to cardiovascular diseases and hypertension, will be analysed.

Identification of new monogenic forms of hypertension

A cluster of metabolic defects caused by mutation in a mitochondrial tRNA

Wilson FH, Hariri A, Farhi A, *et al*. *Science* 2004; **306**: 1190–4, and supplementary material available online

BACKGROUND. A large kindred with hypertension, hypercholesterolaemia, hypomagnesaemia, either isolated or associated in the same subject with diverse patterns of association, was identified, and 142 subjects in this kindred over four generations were investigated clinically and biologically. A striking feature of this syndrome was the pure maternal transmission of the abnormal traits. Hypomagnesaemia was investigated and found to be of renal origin, with features – increased fractional magnesium excretion and decreased urinary calcium excretion – suggestive of distal tubule dysfunction. The maternal transmission pattern was suggestive of inheritance via the mitochondrial genome. This genome was sequenced across the kindred and a new mutation located within the mitochondrial $tRNA^{Ile}$ gene was observed in the maternal lineage of the proband. This mutation, a T→C transition, changes an otherwise well-conserved uridine in tRNAs for a cytidine, near the anticodon loop, and markedly impairs ribosome binding of the affected tRNA and presumably isoleucine incorporation into mitochondrial proteins. Features of abnormal mitochondrial function were observed by studying a striated muscle of a member of the maternal lineage histologically.

INTERPRETATION. A new form of mitochondrial disease was identified and its molecular basis established. One major feature of this disease is hypertension, present in 19 of the 41 members of the maternal lineage aged under 60, and in only seven of 52 members of the non-maternal lineage, the difference being highly significant. This mutation has been found only in this peculiar kindred so far. But because, besides hypertension and hypomagnesaemia, the mutation is also associated in some subjects with hypercholesterolaemia, the authors speculate that the association of hypertension and hypercholesterolaemia, which is frequent in the general population, might have a common genetic basis and be related to

the decrease in mitochondrial function with age. As far as tubular dysfunction and hypomagnesaemia are concerned, the cells of the distal tubule have the highest energy consumption rate in the nephron, and mitochondria play an important role in energy production, thus providing a putative physiological basis for this new phenotype related to mitochondrial dysfunction.

Comment

This is a very interesting observation by a group that has already contributed much to the description of the monogenic forms of hypertension and their molecular basis (see below). However, this is so far a rare disease. The causal mutation is homoplastic and yet the phenotype is highly variable among affected subjects, ranging from no change to high blood pressure and complex metabolic abnormalities. This suggests a pleiotropic effect of this mutation, also observed in other mitochondrial diseases. The study raises many questions pertaining to the mechanism of hypertension (there was no detectable effect of the mutation on renin or aldosterone levels), and that of hypercholesterolaemia. These questions may be difficult to study in animal models because of the human-specific pattern of cholesterol metabolism. Hypertension is not a recognized phenotype of mitochondrial diseases, but mitochondrial function has not been studied extensively in hypertension. This avenue is worth exploring, and this is a consequence of the study that nicely expands current hypotheses for the pathogenesis of essential hypertension and hypercholesterolaemia. The hypothesis that mitochondrial dysfunction may be related to the development of insulin resistance and may participate in the so-called metabolic syndrome has also been proposed in studies of type 2 diabetes, but none of the subjects studied in the present kindred had features of insulin resistance. This underlines the complexity of mitochondrial dysfunction and the large spectrum of its consequences, illustrated again by the present study.

Pseudohyperaldosteronism type II

WNK4 regulates apical and basolateral Cl^- flux in extrarenal epithelia

Kahle KT, Gimenez I, Hassan H, *et al*. *Proc Natl Acad Sci USA* 2004; **101**: 2064–9

Paracellular Cl^- permeability is regulated by WNK4 kinase: insight into normal physiology and hypertension

Kahle KT, Macgregor GG, Wilson FH, *et al*. *Proc Natl Acad Sci USA* 2004; **101**: 14877–82

The kidney specific WNK1 isoform is induced by aldosterone and stimulates epithelial sodium channel-mediated Na^+ transport

Naray-Fejes-Toth A, Snyder PM, Fejes-Toth G. *Proc Natl Acad Sci USA* 2004; **101**: 17434–9

BACKGROUND. These three articles deal with another monogenic form of hypertension, pseudohypoaldosteronism type II (PHAII) or Gordon syndrome, in which hypertension, and hyperkalaemia are associated. The molecular basis of PHAII was described in 2001, by positional cloning in two large affected kindreds, by Lifton, Jeunemaitre and their collaborators (Wilson *et al*. (2001) |1|). PHAII was found to be caused by mutations in members of the WKN family of serine–threonine kinases, either WNK1 or WNK4. These kinases are present in the distal nephron in the kidney. However, the mechanisms linking WNK1 and WNK4 to blood pressure regulation and potassium metabolism remain to be established. This has been done in a series of subsequent studies *in vitro* that suggest that WNK4 inhibits the activity of both the NaCl cotransporter (NCCT) and the inwardly rectifying-K^+ channel (ROMK) by reducing their membrane expression, through both kinase- and non-kinase-mediated mechanisms (Kahle *et al*. 2004 |2|, paper by Wilson *et al*. discussed above). The WNK4 mutation in the affected kindred suppressed the inhibition of NCCT, while reinforcing the inhibition of ROMK thus leading to sodium retention and hypertension, and concomitantly to potassium wasting. The present studies go beyond these first observations by suggesting additional mechanisms by which WNK4 can influence sodium, potassium and chloride metabolism, and affect blood pressure. The first study shows that WNK4, like WNK1, is not restricted to the kidney, has a wide distribution in the body, and also that it inhibits anion transporters, suggesting its involvement in chloride secretion and reabsorption. The second study, also by Lifton's group |3|, shows that WNK4, which is present in tight junctions, affects not only transcellular but also paracellular ionic transfer, providing additional hypotheses for its sodium chloride-retaining and hypertensive effect. The third study attempts to link WNK1, the other WNK implicated in PHAII, to aldosterone. The role of WNK1 in the control of electrolyte metabolism and in blood pressure regulation remains less studied than WNK4. It has been suggested that this kinase interacts with WNK4 and attenuates its inhibitory effect on NCCT.

INTERPRETATION. WNK4 gene expression was found, to various extents, in every organ tested, but the protein was characterized immunologically in tissues where it was found to be the most abundant: the absorptive epithelia in the kidney, exocrine glands, colon and epididymis. WNK4 was also detected, though in low abundance, in the vascular endothelium, except at the level of the blood–brain barrier, where endothelial WNK4 was especially abundant. Interestingly, WNK4 inhibits *in vitro* the activities of the $Na^+K^+2Cl^-$ cotransporter NKCC, which has a structure close to that of NCCT, and the apical Cl^-/base exchanger SLC26A, and therefore probably regulates chloride and anion absorption in these epithelia. Because WNK4 was abundant in tight junctions, the hypothesis that it can control paracellular flux was tested in transfected kidney epithelial cells. WNK4 increases the paracellular flux of chloride, and solute, in these cells, and the PHAII mutant of WNK4 has an

enhanced effect on these transfers. Thus, WNK4 seems to be a regulator of both transcellular and paracellular ion transport. While transcellular transfers are the major pathways for sodium reabsorption and potassium secretion, paracellular transfer is responsible for most of chloride reabsorption in the distal tubule. The gene for WNK1 is abundantly expressed in the distal tubule, where a shorter mRNA, transcribed by a specific promoter and coding for an N-terminal truncated protein devoid of kinase activity, has been identified |**4**|. Naray-Fejes-Toth *et al*. show that aldosterone specifically increases the abundance of this transcript in a cortical collecting duct cell line overexpressing the mineralocorticoid receptor. The WNK1 isoform coded by this short transcript was shown to increase Na^+ transport in cortical collecting duct cells and in another cell line, cotransfected with Enac- and WNK1. These data suggest that WNK1 is regulated by aldosterone and increases sodium reabsorption at least in part through Enac. It may be involved in the tubular effect of aldosterone, as Enac is a known target of this hormone.

Comment

These studies contribute to the description of new cellular regulatory pathways for electrolyte metabolism in the kidney. The relevance of these pathways to blood pressure regulation is attested by the hypertensive phenotype, probably due to sodium retention, of subjects carrying functional mutations. The roles of WNK4 and WNK1 in electrolyte transport in the kidney seem to be multiple, as these proteins are involved, at least *in vitro*, in several aspects of distal tubule function, sodium reabsorption, chloride reabsorption and potassium secretion, by acting on different molecular targets and different cellular and extracellular electrolyte transport pathways. Moreover, some of their actions are independent of their kinase activity, which suggests new protein–protein interactions. Also, the mutations in PHAII seem to confer a gain of function in WNK1 and a loss of function in WNK4 action, suggesting different mechanisms of action for these two proteins. However, these studies clarify the mechanism of hypertension in PHAII, as they suggest that both mutations can promote sodium retention through activation of either NCCT or Enac. These data were, however, generated *in vitro* in cellular models and their extension to *in vivo* studies using genetically modified animals is awaited. Also, the relevance of these observations for essential hypertension is not evident, unless studies of distal tubule function in essential hypertensive patients suggest that subtle dysfunction occurs commonly in these patients, or unless genetic association is observed at the WNK locus, for example in low-renin hypertension. Nevertheless, this story is a nice illustration of the major potential interest for renal and electrolyte physiology of studying the genetic basis of hypertension.

Genome-wide scans for blood pressure and hypertension

There have been several studies in large and well-phenotyped populations reporting the outcome of genome-wide scans for genetic association with blood pressure. The United States National Heart, Lung and Blood Institute Family Blood Pressure

program (NHLBI-FBPP) comprises several substudies concerning the genetics of hypertension: the GenNet, GENOA HyperGEN and SAPPHIRe studies, which include subjects of different ethnic backgrounds. African-Americans have a high prevalence of hypertension and constitute a significant part of the studied population. A genome scan for hypertension in non-obese African-American, conducted in 275 families of the NHLBI-FBPP studies, found a high score for linkage on chromosome 2q |**5**|. Also using African-American families included in the NHLBI-FBPP studies, and considering that the African-American population is an admixed population, Zhu *et al.* (below) developed an interesting approach of 'admixture mapping' by genome scan, and they identify several candidate loci. This study will be discussed in more detail below. Finally, besides systolic and diastolic blood pressures, which are both directly linked to cardiovascular mortality in epidemiological studies, pulse pressure is an indicator of arterial stiffness, and may be another predictor of major cardiovascular events. A genome scan for loci associated with pulse pressure has been conducted in another major study, the Framingham's heart study (DeStefano *et al.*, 2004, below).

Admixture mapping for hypertension loci with genome-scan markers

Zhu X, Luke A, Cooper RS, *et al. Nat Genet* 2005; **37**: 177–81 and supplementary material online

See also: The beauty of admixture

Darvasi A, Shifman S (comment on the study of Zhu *et al.*). *Nat Genet* 2005; **37**: 118–19

Background. The experimental approach relies on the assumption that African-Americans have roughly 75% African and 25% European ancestry. African and European alleles can be distinguished with appropriate sets of markers by comparison with reference populations. If the hypertensive phenotype is carried by ancestral African genes, then an excess of African ancestry at the corresponding loci will be found in hypertensive compared with normotensive subjects. This hypothesis has been tested by studying a common set of 269 microsatellite markers in 737 hypertensive and 573 normotensive African-American subjects belonging to three subpopulations of the NHLB-FBPP. The excess of African ancestry in hypertensives occurred mostly at a limited number of loci: 1q, 2p, 3q, 4q, 6q, 8q, 11q and 21q. The effect was especially apparent at 6q24 and 21q21, observed for several adjacent markers and across several subpopulations studied.

Interpretation. The study suggests that genes for high blood pressure susceptibility are located at these two loci in African-American subjects. Appropriate analyses were carried out to estimate the effect of variance among subpopulations and that of sampling, and the observation remained robust.

Comment

This well-conceived and well-carried-out study has several aspects of potential interest, and also a limitation. First, it is the first time that the concept of admixture mapping has been applied to the identification of genes involved in a complex trait. Hypertension in African-American is, because of the strong heritability of the trait and the estimated level of admixture of the African-American population, a favourable setting for this application. The degree of admixture in European populations would probably preclude the use of this approach in these populations. Secondly, loci related to high blood pressure were identified, by a new approach, and it is interesting to note that 6q24 was already proposed in other studies, albeit in European-American and Mexican-American populations. This region, like 21q, contains a large number of candidate genes, which can be further studied. Replication is, however, not perfect in the classical genome scan approach conducted in the same population by Morrison *et al.* (2004) |**6**|, and mentioned above, which pinpointed only chromosome 2q. By its design, the study identifies genes related to a peculiar form of genetic hypertension with a strong founder effect. The relevance of these findings to other forms of essential hypertension, in either Africans or Europeans, may be limited. In any case, this study is likely to open new avenues in the genetics of complex disease, and adds to progress in identifying new genes related to high blood pressure.

Genome-wide scan for pulse pressure in the National Heart, Lung and Blood Institute's Framingham Heart Study

DeStefano AL, Larson MG, Mitchell GF, *et al. Hypertension* 2004; **44**: 152–5

Background. Pulse pressure is an indirect indicator of arterial stiffness, and may be a good predictor of cardiovascular disease risk, especially in older people. However, its heritability is considered to be low. The present study was conducted to evaluate heritability in a large population and to perform linkage analysis by genome scanning on a subset of this population. The Framingham Heart Study is a reference study for cardiovascular epidemiology and genetics. Repeated measurements of blood pressure over 50 years are available. Heritability was calculated using long-term average pulse pressure data for 6421 subjects in 1593 families and was found to be higher than expected from previous studies, averaging 0.52 ± 0.03. Genome scanning was performed at 10 centimorgan (cM) density in 2492 individuals belonging to 345 pedigrees. The highest lod (log of the odds) score (2.94) was obtained for chromosome 15 at its distal end (122 cM), with weaker evidence for linkage on chromosomes 5, 7 and 10.

Interpretation. This study suggests that pulse pressure has a relatively strong inherited component. However, the genome scan analysis is somehow disappointing, because the evidence for linkage remains of borderline statistical significance. Several candidate genes can, however, be mapped in the chromosomal region identified, and further studies focusing on these genes may provide more definitive information.

Comment

This study further illustrates the interest of the Framingham Heart Study in cardiovascular genetic epidemiology. Because the heritability study was performed on a large number of pedigrees and with data generated from repeated blood pressure measurements, the observation is robust, and probably gives an accurate estimate of the heritability of pulse pressure. This information is a necessary basis for designing linkage or association studies aimed at unravelling the genetic mechanisms determining pulse pressure level, and the link between pulse pressure level, arterial stiffness and cardiovascular risk. However, this may require the study of an even larger number of pedigrees than included in the present study, and/or the refinement of the phenotypic traits studied. Linkage analysis for other haemodynamic parameters more directly reflecting arterial stiffness is being pursued in the Framingham study |**7**|.

Candidate genes for hypertension

The candidate gene approach is clearly powerful and is still widely used. The two human studies below have been selected on the basis of the originality of the hypotheses tested, appropriate design and power, study of functional variants, and coherence with studies performed in genetically modified animals.

Angiotensin-converting enzyme, sleep-disordered breathing, and hypertension

Lin L, Finn L, Zhang J, Young T, Mignot E. *Am J Respir Crit Care Med* 2004; **170**: 1349–53

Background. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II and inactivates kinins. ACE levels are considered critical for the regulation of vascular tone and blood flow in certain circulations, such as the renal and coronary circulations. ACE levels are genetically determined. However, ACE levels and a common genomic variation in the ACE gene (I/D polymorphism) that is strongly associated with these levels do not seem to influence blood pressure significantly in white populations, and most studies have not found any association of the ACE gene with essential hypertension in these populations. Sleep-disordered breathing (SDB) is an established risk factor for the development of hypertension. Genetic influence on the development of hypertension in the setting of SDB is likely but is not well documented. The present study analysed 1100 SDB-affected subjects of the Wisconsin Sleep Cohort for genetic polymorphism of ACE. The ACE I/D polymorphism was dose-dependently associated with blood pressure or established hypertension in this cohort, independently of confounding variables. Furthermore, there was an interaction between the severity of SDB and this polymorphism in predicting hypertension. The effect of the ACE gene on hypertension was more pronounced for patients with moderate severity of SDB.

Interpretation. The study suggests that the genetic polymorphism of ACE level modulates the risk of hypertension in SDB, as the D allele, associated with higher ACE levels, was associated with both higher systolic and diastolic blood pressures and a higher prevalence of hypertension. As in every genetic association study, this may be a chance finding. However, the large number of subjects studied, the level of significance observed and the gene dose effect suggest a true association. The mechanism linking ACE to blood pressure in this setting remains obscure, but both angiotensin II and kinins may amplify or counteract, respectively, other hypertensive mechanisms, especially the influence of the central or sympathetic nervous system.

Comment

This study refreshes the old issue of ACE and blood pressure and supports the hypothesis that, although ACE is not a major determinant of blood pressure in resting conditions, it can amplify the effect of other antihypertensive stimuli. Interestingly, the ACE gene has repeatedly been found to be associated with blood pressure or hypertension in black populations, contrary to white populations, and this could be explained, among other hypotheses, by an interaction of ACE with the effects of the exaggerated sodium retention occurring in these populations. Similarly, a modest increase in gene expression in genetically modified mice raises blood pressure in the setting of diabetes, and the genetic polymorphism of ACE levels has almost consistently been found in large populations and cohorts of type I diabetes to be associated with the development of vascular and renal complications |**8**|. These complications are genetically determined and lead to hypertension. SDB may be another setting in which genes otherwise having a modest effect on blood pressure can become pro-hypertensive. Because SDB, like type I diabetes, is a relatively homogeneous disease clinically, the identification of minor or 'helper' hypertensive genes may be easier in these diseases. The whole story of the genetic polymorphism of ACE levels and blood pressure, further illustrated by the present study, underlines the complexity of the genetic determinism of blood pressure.

Functional variant of CYP4A11 20-hydroxyeicosatetraenoic acid synthase is associated with essential hypertension

Gainer JV, Bellamine A, Dawson EP, *et al*. Circulation 2005; **111**: 63–9

See also: Cytochrome P-450 under pressure: more evidence for a link between 20-hydroxyeicosatetraenoic acid and hypertension

Fleming I. *Circulation* 2005; **111**: 5–7

Background. The cytochrome P450 4A arachidonic acid monooxygenases catalyse the oxidation of endogenous arachidonic acid to 20-hydroxyeicosatetranoic

acid (20-HETE). This compound has a direct vasoconstrictor effect. However, in the kidney tubule it promotes natriuresis. CYP4A can therefore influence blood pressure in several, even opposite, ways, depending on its site of action. Inactivation of the CYP4a14 gene in the mouse, coding for a non-20-HETE-producing CYP4, induces severe hypertension in male animals; this is at least partly dependent on testicular function. The present study was undertaken to analyse the polymorphism of the CYP4504A genes in humans and the association of the genetic variations observed with hypertension. Among the two human CYP genes coding for putative 20-HETE-producing enzymes, CYP4A11 and CYP4A22, only CYP4A11 was found to be functional. A variant of the CYP4A11 gene was identified, bearing a serine instead of a phenylalanine at position 434 and displaying reduced (50%) catalytic activity *in vitro*. The allele frequency for this variant was 0.11 in white normotensive men. The variant was studied in a Tennessee cohort of 512 subjects, both normotensive and hypertensive, and a significant association with an increased prevalence of hypertension was observed in white subjects in this cohort. The CYP4A11 polymorphism was also tested in 1538 subjects of the Framingham Heart Study, and a trend towards association with hypertension was observed. The association became significant after exclusion of diabetic patients. In both studies, no gender effect was observed.

Interpretation. The study suggests that partial genetic deficiency in a 20-HETE-producing enzyme is relatively common in white populations and can lead to hypertension. The mechanism by which reduced 20-HETE can increase blood pressure is not established, but the loss of the intrarenal natriuretic effect of this compound may be involved, a hypothesis supported by previous studies in spontaneously hypertensive rats. The mutation decreases CYP4A11 activity by roughly 50% *in vitro*. Because of the relatively low frequency of the mutated allele in the populations tested, most subjects are heterozygous and probably have a modest level of deficiency. This may be confirmed by measurements of 20-HETE levels and may suggest a critical role of these levels in blood pressure regulation.

Comment

This study identifies a functional variant of a new candidate gene, expressed in both blood vessels and kidney tubules and coding for a powerful and pleiotropic compound, and suggests that this variant is associated with hypertension. It is therefore likely to generate interest in the fields of cardiovascular and renal genetics and to promote other studies testing replication of the genetic association observed.

Genetics of endothelial dysfunction

This field has been less explored than hypertension, in part because of the greater complexity of the experimental settings necessary for studying phenotypes. However, endothelial dysfunction occurs in subjects with essential hypertension, and may precede it as it has been observed in normotensive offspring of hypertensive subjects. In addition, endothelial dysfunction is a key feature of diabetes and is believed to play an important role in the development of vascular and renal complications of

this disease, including hypertension. There is a strong genetic determinism of these complications, and presumably of endothelial dysfunction in diabetes. The two studies below suggest new hypotheses concerning the genetic control of endothelial function and document new genetic variations with possible relevance to hypertension.

Impaired L-arginine transport and endothelial function in hypertensive and genetically predisposed normotensive subjects

Schlaich MP, Parnell MM, Ahlers BA, *et al*. *Circulation* 2005; **110**: 3680–6

BACKGROUND. L-arginine is the precursor of nitric oxide, which plays a key role in endothelium-mediated vasodilatation. The study tested the hypothesis that a heritable defect in the transmembrane transport of L-arginine is responsible for endothelial dysfunction and hypertension. L-arginine uptake, forearm blood flow and endothelium- and non-endothelium-mediated vasodilatations were studied in hypertensive subjects and in two groups of normotensive individuals with and without a family history of hypertension. L-arginine transport was significantly reduced in both the hypertensive and the normotensive subjects with a family history of hypertension, compared with normotensive subjects without a family history of hypertension. This observation was made in both the forearm circulation and isolated blood mononuclear cells. In addition, the normotensive subjects with a heredity of hypertension had, like the already hypertensive subjects, impaired endothelium-mediated vasodilatation compared with the other subjects.

INTERPRETATION. This study suggests that a defect in the transmembrane transport of L-arginine, leading to decreased L-arginine availability, decreased nitric oxide formation capacity and endothelial dysfunction, is a causal event in essential hypertension. This defect is heritable. Its molecular mechanism remains unknown, and the gene expression of the cationic amino acid transporter CAT-1 was found to be unaltered in the affected subjects.

Comment

This is an original and interesting hypothesis, worthy of further testing, even if no molecular mechanism for the L-arginine transport defect was identified in this study. A relatively limited number of subjects was studied (12–15 in each group), without a power calculation, but the difference observed in L-arginine transport between subjects with and without a family history of hypertension is large and its significance level is high, suggesting a strong effect of the unknown genetic variation(s) involved. However, although the impairment of L-arginine transport cannot be secondary to hypertension in this study, it may be a non-causal feature of endothelial dysfunction. Against this hypothesis are the results obtained in peripheral blood cells.

Arterial and renal consequences of partial genetic deficiency in tissue kallikrein activity in humans

Azizi M, Boutouyrie P, Bissery A, *et al*. *J Clin Invest* 2005; **115**: 780–7

See also: Vascular remodelling and the kallikrein–kinin system

Carretero OA. *J Clin Invest* 2005; **115**: 588–91

BACKGROUND. Tissue kallikrein (TK) is the major enzyme releasing the vasodilator peptides kinins. TK is synthesized in several organs, including the kidneys and arteries. Inactivation of the TK gene in the mouse induces endothelial and arterial dysfunction. In man there is strong genetic determinism of urinary kallikrein activity, recognized in family studies. A molecular basis for this heritability has been identified recently as a mis-sense mutation of the TK gene (R53H), which changes an arginine for a histidine at a substrate-binding subsite and is present, in the heterozygous state, in 5–7% of white subjects. This mutation strongly decreases TK catalytic activity *in vitro* and *in vivo*. As TK-deficient mice have arterial dysfunction, the present study tested whether the TK-deficient subjects also display endothelial and arterial dysfunction. While studying brachial artery flow in young normotensive volunteers in several different conditions, an increase in shear stress was consistently observed in R53H subjects, with a paradoxical inward remodelling of the artery. These haemodynamic features are suggestive of chronic endothelial dysfunction.

INTERPRETATION. This study shows the importance of TK and kinins in the physiology of human arteries. It also documents a new form of arterial dysfunction, present in 5–7% of white subjects, due to a partial (50%) genetic deficiency in TK activity. The relationship between the haemodynamic and trophic abnormalities remains unexplained, as increased shear stress would be expected to expand rather than narrow the arteries. The mechanism of endothelial dysfunction secondary to TK deficiency may be further studied in TK-deficient mice.

Comment

This study illustrates the interest of combining animal and human genetic studies in physiology. The number of subjects with the R53H mutation who were studied – ten – is relatively low because of the low frequency of the mutation in the population, but a pre-study power calculation was done. Moreover, the consistency between the animal and human data strongly suggests that the abnormal arterial phenotype of the 53H allele carriers is causally linked to kallikrein deficiency. The subjects studied were young normotensive males. The consequences in the long term of this arterial dysfunction are unknown. The R53H mutation was not found to be associated with hypertension in small populations, but this needs to be further investigated in larger cohorts and in selected subgroups of hypertensive subjects, such as salt-sensitive sub-

jects. Also, because TK-deficient mice have decreased protection against cardiac ischaemia, the mutation may increase the risk of myocardial infarction. This remains to be established in other clinical studies.

Conclusion

This survey certainly does not cover all aspects of the field, but has tried to illustrate the different conceptual and methodological approaches currently used for finding genes involved in blood pressure regulation and in human hypertension. Genetic studies in animals are also a powerful approach for describing the physiological role of genes in the cardiovascular system and in the kidney, and the roles of these genes in blood pressure regulation and hypertension |**9**|. Several important genes have already been identified in the past, especially in studies of monogenic forms of hypertension and in studies testing specific physiological hypotheses |**3**,**4**|. However, the genetics of hypertension are much more complex than initially thought, and still far from being completely understood. For this reason, this topic is still largely a subject for investigation, and not yet critical to daily practice and management of hypertensive patients. But because of the potential importance for cardiovascular medicine of discovering the genes involved in determining blood pressure level, an enormous effort is being pursued by researchers and will undoubtedly lead to more discoveries.

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12

New imaging techniques useful for optimal diagnostic work-up of hypertensive patients

JÖRG RADERMACHER, HERMANN HALLER

Introduction

Computed tomography angiography (CTA), magnetic resonance tomography (MRT), captopril-enhanced scintigraphy and colour Doppler sonography all compete in the diagnosis of renal artery stenosis and in experienced hands all perform equally well. These techniques have largely replaced captopril scanning for renal artery stenosis. CTA and MRT are more expensive than colour Doppler sonography, and CTA at present requires large amounts of potentially nephrotoxic radiocontrast agents.

However, not all patients with renal artery stenosis will benefit from angioplasty or surgery. For this reason it is not sufficient to diagnose the presence of renal artery stenosis—one also has to evaluate its functional significance |**1**|. Most studies that compared drug treatment with angioplasty for renal artery stenosis found only modest or no beneficial effects of angioplasty on renal function or blood pressure. Subgroups of patients with a high likelihood of a favourable response have yet to be identified.

We will therefore focus not only on the diagnostic value of ultrasonography to show the presence of renal artery stenosis but also on its diagnostic value regarding the functional significance of this condition. First, we will show how to diagnose and assess the anatomical severity of renal artery stenosis using ultrasound, and in the second part of the chapter we will show how ultrasonography might help to establish the functional severity of stenosis, i.e. establish the presence of renovascular hypertension or renovascular azotaemia.

Diagnosis of renal artery stenosis

There are two major ultrasonographic approaches to establishing the diagnosis of renal artery stenosis: the direct and the indirect approach. In the direct approach the flow acceleration at the site of stenosis is sought and in the indirect approach post-stenotic flow phenomena are sought. Different flow velocities have been used as

cut-off points to establish the diagnosis of stenosis, and the most accepted cut-off maximum systolic velocities are 180–200 cm/s (Table 12.1). Using this approach, stenoses in which the diameter is reduced by 50% or more can be found with good sensitivity and specificity. However, in about 10–20% of patients this approach does not work because the renal arteries cannot be visualized due to excessive meteorism, obesity, or the inability of the patient to stop breathing even for very a short time (Table 12.1). The indirect method makes use of flow characteristics in intrarenal arteries distal to the stenosis, which can be classified as tardus or parvus phenomena. A typical tardus phenomenon is a prolonged acceleration time (>70 ms) or a decreased acceleration index. A typical parvus phenomenon is the reduced resistance index at the site of stenosis. The latter indirect parameter works best in patients with two kidneys because there is no reliable absolute cut-off point which defines a low resistance index. The side-to-side difference in the resistance indices should be less than 5%, otherwise a significant renal artery stenosis may be suspected on the site with the lower resistance index value |**2,3**|. The indirect parameters can be measured in almost all patients but have the disadvantage that only severe degrees of stenosis – exceeding 60–70% diameter reduction – will lead to an alteration of the intrarenal Doppler signal (Table 12.1). The best approach seems to be to use a combination of the two principal methods and to use indirect signs of stenosis only if the renal artery cannot be sufficiently visualized using the direct approach.

Direct approach

Patients are scanned in the supine position with the upper body slightly elevated to make the patient more comfortable and to improve the visual field. Fasting for 8 h or application of carminatives may be performed but is not a prerequisite for a successful examination. Before examining the renal arteries a B-mode scan of the renal parenchyma is obligatory, including the kidney's size, form, parenchymal width and echogenicity |**16**|. A 2- to 4-MHz curved array transducer or a 2- to 3-MHz sector transducer are used to delineate the course of the renal artery. Routine examination of renal arteries in a time-saving way requires the use of colour-flow Doppler mode. This shortens examination time because a change in flow velocity within a stenosis is clearly noticeable, either as a lighter colour or, more frequently, as an aliasing phenomenon. Doppler spectra can be selectively obtained from these specific regions of interest, which reduces examination time. In addition, quantitative measurements of flow velocities in the renal arteries require angle-corrected measurements, and, since renal arteries cannot be routinely seen in B-mode, angle correction also requires the use of colour-flow Doppler. The proximal portion of the renal artery, where most atherosclerotic stenoses will be found, is usually sought from a subxiphoidal position. However, in B-mode it can be helpful to look at transverse sections of the right renal artery underneath the caval vein to find multiple right renal arteries. Direct visualization of the renal arteries will be successful in 84–100% of patients |**15,17**|, and is more easily done in women than in men and in patients with a body mass index below 30 kg/m^2 than with a higher index. Distal and medial parts of the renal arteries are best visualized through the kidney from a dorsolateral or, rarely, from a

Table 12.1 Stenosis criteria and the associated sensitivities and specificities in detecting angiographically controlled stenoses of the renal arteries using duplex and colour flow duplex sonography

	Patient number	Stenosis criteria	Technical (%) failure	Degree of stenosis (%)	Sensitivity/ specificity (%)
Direct criteria					
Hansen *et al*. (1990) |**4**|	74	RAR >3.5	8	≥60	93/98
Karasch *et al*. (1993) |**5**|	53	Vmax >180 cm/s	15	≥50	92/92
Olin *et al*. (1995) |**6**|	102	Vmax >200 cm/s or RAR >3.5	10	≥60	98/98
Postma *et al*. (1992) |**7**|	61	Doppler frequency >4 kHz and broadened Doppler spectrum	25	≥50	63/86
Schäberle *et al*. (1992) |**8**|	76	Vmax >140 cm/s	N/A	≥50	86/83
Indirect criteria (parvus–tardus)					
Baxter *et al*. (1996) |**9**|	73	AT >70 ms	16	≥70	89/97
Kliewer *et al*. (1993) |**10**|	57	AT ≥70 ms	0	≥50	82/20
Riehl *et al*. (1997) |**11**|	214	RI <0.45 or change in RI ≥8%	0	≥70	93/96
Schwerk *et al*. (1994) |**3**|	72	Change in RI ≥5%	0	≥50	82/92
						≥60	100/94
Speckamp *et al*. (1995) |**12**|	123	Change in AI ≥80%	N/A	≥70	100/94
Stavros *et al*. (1992) |**13**|	56	Loss of ESP	0	≥60	95/97
Strunk *et al*. (1995) |**14**|	50	AT ≥70 ms	4	≥50	77/46
Combination of direct and indirect criteria					
Krumme *et al*. (1996) |**2**|	135	Vmax >180 cm/s and/or change in RI ≥5%	0	≥50	89/92
Radermacher *et al*. (2000) |**15**|	226	Vmax >180 cm/s and RRR >4 and/or AT ≥70 ms	0	≥50	97/98

Only publications with more than 50 patients investigated were considered. All Doppler sonographic studies had to be performed prospectively and had to be compared with intra-arterial angiography as the established gold standard.
Technical failure: the renal artery or intrarenal arteries could not be analysed with Doppler ultrasonography.
Degree of stenosis: cut-off value of stenosis (% diameter reduction) for which the test has been evaluated.
N/A, data not available; AI, acceleration index; AT, acceleration time; RAR, renal–aortic ratio; RI, resistance index (Pourcelot index); ESP, early systolic peak; RRR, renal–renal ratio; Vmax, maximum velocity.

ventrolateral or dorsal approach. The dorsal approach also allows measurements of intrarenal velocity spectra, which are usually obtained from segmental renal arteries.

It is important to note that Doppler examinations have to be optimized and that reproducible measurements are only possible when the Doppler gate meets the vascular flow direction at the smallest possible incident angle. This means that transducer positions need to be selected that allow imaging of the target arterial segment of the renal arteries at the most acute angle possible between the vascular axis and the transducer. If colour-flow mode suggests a stenosis – in atherosclerotic stenoses usually in the ostial portion of the renal artery – this usually requires the transducer to be placed in either the left or right flank region to achieve an acute angle. Flow velocities from a Doppler spectrum are measured at the point of maximum aliasing, and an additional flow velocity can be measured either in the aorta proximal to the renal artery (renal–aortic ratio) or in a part of the renal artery itself that is located either proximal or far distal to the stenosis (renal–renal ratio). Calculating the renal–renal ratio, when technically possible, not only proves the presence of stenosis but also allows quantification (see below). The normal frequency spectrum from a main renal artery presents the typical form of a low-resistance artery. The normal maximum systolic velocity is given as 100–180 cm/s |**8,18–21**|. The normal end-diastolic flow velocity is 25–50 cm/s. Direct criteria of a renal artery stenosis are listed below.

- The angle-corrected maximum systolic flow velocity in the renal artery is locally greater than 140–180–198 cm/s |**8,22**|. The cut-off value of 180 cm/s has found the widest acceptance. One author also used a Doppler frequency above 4 MHz as a diagnostic criterion, but this method has not been used by others |**7**|.
- The angle-corrected flow velocity in the stenotic segment of the renal artery is more than 3.3–3.5 times faster than flow velocity in the aorta (renal–aortic ratio) |**22–24**|.
- The angle-corrected flow velocity in the stenotic segment of the renal artery is more than 4 times faster than flow velocity in the post- or pre-stenotic segment of the renal artery |**15,25**| (renal–renal ratio). This method also allows determination of the exact degree of stenosis using the formula: area of stenosis (%) = 100 * (1 – [post-stenotic velocity/intrastenotic velocity]). The correlation coefficient of Doppler-estimated degrees of stenoses compared with the gold standard (planimetric calculation using intravascular ultrasound) was 0.97 |**26**|.
- The end-diastolic flow velocity increases.
- Clear spectral broadening appears |**7**|.

Indirect approach

Intrarenal vessels – usually segmental renal arteries – are identified in colour Doppler mode. Doppler spectra from two or three vessels from the upper, medial and lower portions of the right and left kidneys are obtained and the values for each kidney are averaged. Care is taken to obtain a good signal quality, which means that only signals

that can be derived from vessels which run directly towards the scanner or at a maximum angle of 30° are used for analysis. Indirect criteria of renal artery stenosis are listed below.

Parvus phenomenon

- The flow velocity and the resistance index decrease in distal arterial segments and intrarenally. (Either absolute resistance index value less than 0.45–0.5 |**11**| or difference between left and right kidney greater than 5–10%) |**2,3,27–29**|.

Tardus phenomenon |**30**|

- The acceleration time increases in post-stenotic distal arterial segments and intrarenally (acceleration time >70 ms |**9,10,14,15,17**|).
- The acceleration index decreases below 3.78 m/s |**17**| or the ratio of acceleration indices between the stenosed and non-stenosed kidney is greater than 1.8 |**12**|.
- The early systolic peak is lost |**13**|.

Other

- Renal cortical perforating vessels with flow towards the kidney |**31**|.

As can be seen from Table 12.1, the indirect criteria perform poorly when any stenosis from 50% onwards had been included and the results were much better when only stenoses of greater than 60–70% were included. The direct criteria, on the other hand, had good sensitivity and specificity for lower degrees of stenosis but could not be obtained in 8–25% of patients.

The combination of the two techniques allowed the detection of stenoses of lesser severity with good accuracy and a diagnosis could be made in all patients (Table 12.1). Whether the use of ultrasound contrast agents will further improve diagnostic accuracy without adding substantially to the investigation cost remains to be shown |**32,33**|.

Diagnosis of renovascular hypertension and azotaemia

Only 60–80% of patients will benefit from correction of renal artery stenosis by experiencing a lowering of blood pressure or an improvement or at least stabilization of renal function. The reason could be underlying nephrosclerosis due to long-standing hypertension or underlying diabetic glomerulosclerosis. Both diseases have been associated with increased vascular resistance, which can be estimated ultrasonographically by measuring the renal resistance index. This resistance index can be calculated from the maximum systolic velocity (Vmax) and minimum diastolic velocity (Vmin) from a Doppler spectrum. Resistance index = (1 – [Vmin/Vmax]).

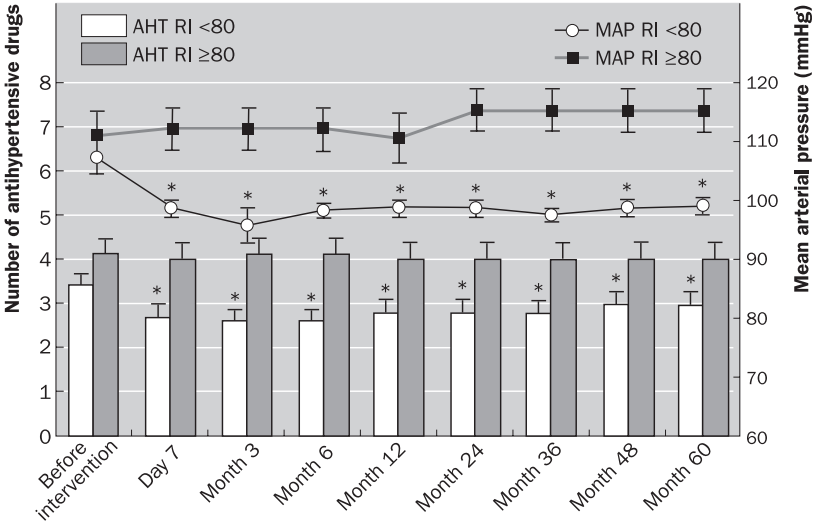

Fig. 12.1 Mean change in mean arterial blood pressure (MAP, *line graph*) and the amount of antihypertensive drugs taken (AHT, *bar graph*) in patients before and after correction of renal artery stenosis. The results are shown for 34 patients with segmental renal artery resistance index (RI) values <80 and for 16 patients with RI values ≥80 who had at least 5 years of follow-up after correction of renal artery stenosis. *P <0.05 as tested by an unpaired t-test (Bonferroni adjustment). In RI <80, blood pressure decreased from baseline 150/89 ± 22/12 mmHg to 135/80 ± 14/10 at the last follow-up visit (P <0.001), in RI ≥80 it changed from 164/83 ± 21/16 to 163/86 ± 19/10 mmHg (not significant). The number of antihypertensive drugs denotes the number of different drug classes taken, not the absolute number of pills. Antihypertensive drug classes: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium antagonist, α-blockers, direct vasodilators, diuretics and nitrates. Error bars are SEM.

The prognostic significance of the pre-interventional resistance index as a predictor of clinical success of percutaneous transluminal angioplasties or operations for renal artery stenosis is a topic of intense debate. Frauchiger *et al.* |**34**| investigated 32 patients who subsequently underwent correction of renal artery stenosis with Doppler ultrasound. They found a cortical diastolic to systolic (d/s) ratio of below 0.30 (corresponding to a resistance index above 0.70) to be prognostic of treatment failure. None of 11 clinically successful procedures had a d/s ratio of less than 0.30 (resistance index >0.70) compared with seven of 24 patients with treatment failure. Cohn *et al.*, using the same cut-off value of d/s ratio, had similar findings in 23 patients |**35**|. In all patients who improved, blood pressure and renal function d/s ratio was above 0.30 (resistance index <0.70), whereas all patients who failed to improve blood pressure or renal function had decreased d/s ratio. More recently we published a paper using a more strict cut-off value of 0.80 for the resistance index |**36**|. The resistance index was measured prospectively in proximal segmental arteries

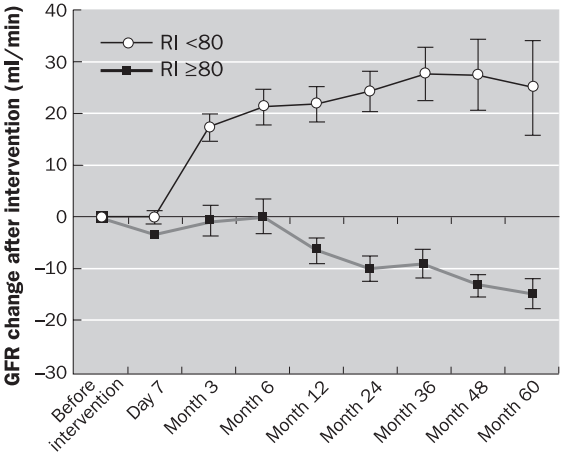

Fig. 12.2 Mean change in creatinine clearance in patients before and after correction of renal artery stenosis. The results are shown for 96 patients with segmental renal artery resistance index (RI) values <80 and for 35 patients with RI values ≥ 80. *P value <0.05 as tested by an unpaired t-test (Bonferroni adjustment).

of both kidneys. A resistance index value of greater than 0.80 in either kidney was considered prognostic of treatment failure. Among the 35 patients with resistance index values of at least 0.80 before revascularization, mean ambulatory blood pressure failed to decrease in 34 and renal function declined in 28. Among the 96 patients with resistance index values below 0.80, mean blood pressure decreased in all but six and renal function worsened in only three (Figs. 12.1 and 12.2). A resistance index of 0.80 or greater was superior to all other tested parameters in predicting worsening renal function (Fig. 12.3).

The resistance index, as measured by Doppler ultrasonography, is influenced by a variety of physiological factors. The resistance index decreases from the main renal artery to the segmental renal artery, the interlobar, the arcuate and finally the interlobular artery |**37**|. The resistance index in the renal arteries increases during inspiration, and increases even more during the Valsalva manoeuvre |**38,39**|. Pulse rate has an influence on the resistance index, with bradycardia leading to lower end-diastolic flow and a higher resistance index and tachycardia causing the opposite. Schwerk *et al.* suggested a corrective formula to account for different pulse rates |**40**|; however, for pulse rates in the range of 50–70 beats per minute, there is little change in resistance index. The resistance index increases with age |**40,41**|; more so in patients with hypertension.

In addition to physiological factors, some renal diseases are also associated with increased resistance index values (Table 12.2). This means that a resistance index above 0.80 is a reliable sign of irreversible chronic renal disease when it is measured

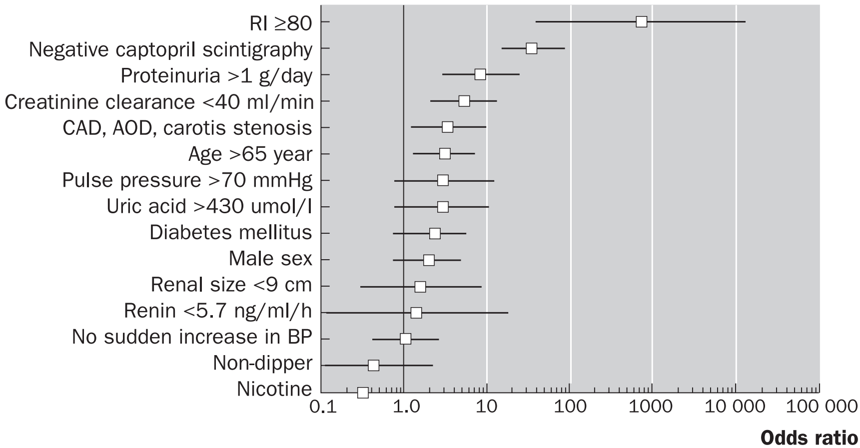

Fig. 12.3 Unadjusted odds ratios for different factors regarding worsening of renal function. The *squares* give the odds ratio and the *lines* give the 95% confidence interval. RI, resistance index; CAD, coronary artery disease; AOD, arterial occlusive disease of the legs; CVD, cerebrovascular disease; non-dipper, no nocturnal decrease in blood pressure as determined from ambulatory 24-hour blood pressure measurements. § Odds ratio for a negative captopril scintigraphy which was calculated from published data |**16,34**|.

Table 12.2 Diseases with increased resistance index values

Diabetic glomerulosclerosis	Increased renal volume Normal echogenicity of parenchyma |**25,42–44**| Resistance index correlates with impaired renal function |**45**|
Hypertensive nephrosclerosis	Decreased renal volume Normal or increased echogenicity of renal parenchyma |**25**|
Haemolytic uraemic syndrome	|**46–49**|
Hepatorenal syndrome	|**50,51**|
Acute renal failure	Increased renal volume |**52**|
Urinary tract obstruction, hydronephrosis	|**53–57**|
High-grade reflux	|**58**|
Acute vascular rejection in renal transplantation	|**59,60**|
Lupus nephritis with high chronicity index and bad prognosis	|**61**|
Renal vein thrombosis	|**62–64**|

in segmental renal arteries, when the Valsalva manoeuvre is avoided during the determination, when extreme bradycardia is excluded and when acute reversible renal diseases, such as acute renal failure, the haemolytic uraemic syndrome, urinary tract obstruction and renal vein thrombosis, can be excluded.

Conclusion

In all patients, to diagnose stenoses with a diameter reduction greater than 50% a combination of Doppler parameters making use of both direct and indirect signs of stenosis should be used. In our hands, a renal–renal ratio greater than 4 and – if this parameter is not measurable – an acceleration time longer than 70 ms is the best combination. The reversibility of hypertension or impaired renal function after successful correction of renal artery stenosis can be assessed by measuring segmental artery resistance indices. A resistance index value greater than 0.80 makes a treatment effect highly unlikely and these patients should not undergo angioplasty or surgery of their stenosis. Confirmatory studies regarding the last statement have yet to be performed.

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Part IV

Pharmacological

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13

Women's health: hormone replacement therapy

SUZANNE OPARIL

Introduction

The past year has seen a major reassessment of the role of menopausal hormone therapy in women's health. Publication of the oestrogen plus progestin clinical trial component of the Women's Health Initiative (WHI) |**1,2**|, reviewed in *The Year in Hypertension 2004*, initially sounded a death knell for hormone use in post-menopausal women. This placebo-controlled trial of hormone replacement therapy (HRT; conjugated equine oestrogen [CEE] 0.625 mg/day plus medroxyprogesterone acetate [MPA] 2.5 mg/day) in 16 608 post-menopausal women found significant increases in the risk of coronary heart disease (CHD), stroke, venous thromboemboli and invasive breast cancer in the HRT group. The reductions in colorectal cancer and hip fractures seen with HRT did not balance these increased cardiovascular disease (CVD) and cancer risks, and publication of the WHI results stimulated consensus panels to recommend against the use of HRT for chronic disease prevention in post-menopausal women |**3**|. Based on the widely publicized findings of harm in the oestrogen plus progestin trial of the WHI and a major secondary prevention study that used the same hormone regimen, the Heart and Estrogen/Progestin Replacement Study (HERS) |**4,5**|, the promotion and prescribing of HRT fell drastically. Prescriptions for the fixed-dose combination of CEE plus MPA declined by 66%, and those for CEE alone fell by 33%, within 1 year (Fig. 13.1) |**6,7**|. Transdermal hormone preparations were less affected, and transvaginal and low-dose preparations gained somewhat, reflecting caution in the use of the full-dose oral regimens that had been used in WHI and HERS.

Extensive discussion regarding the reasons for the unanticipated deleterious effects of HRT ensued, consideration being given to whether the formulation, dose and route of administration of HRT might play a role |**8–10**|. In particular, the progestin MPA was identified as having potential deleterious effects on the vasculature. Pre-clinical studies had shown that MPA negates the vasoprotective and anti-inflammatory effects of 17β-oestradiol in the setting of acute vascular injury |**11–14**|, and recent *in vitro* studies found that MPA signals differently from native progesterone in endothelial cells |**15**|. The surprising outcomes of the oestrogen-alone component of WHI

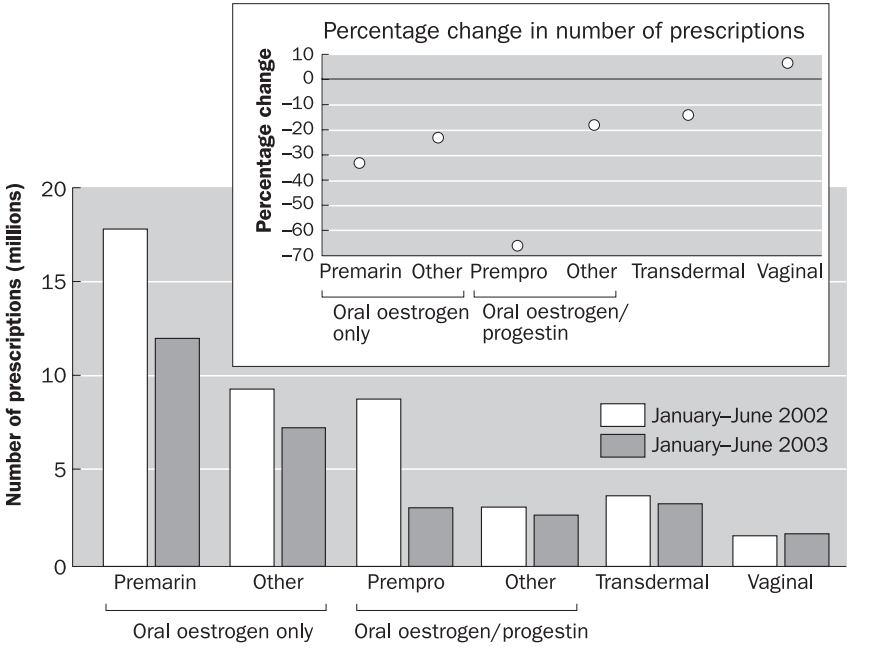

Fig. 13.1 Number of and percentage change in US prescriptions for hormone therapy between January–June 2002 and January–June 2003 by formulation. Source: Hersh *et al*. (2004) |**6**|.

|**16**|, discussed in detail in this review, added further evidence that MPA might be a problem and that unopposed oestrogen benefits younger post-menopausal women. This trial, which was stopped early, showed no significant effect of unopposed CEE on the primary CHD outcome and a surprising tendency for benefit in the primary safety (invasive breast cancer) outcome.

The advanced age (63 years in WHI, 67 years in HERS) and long period of hormone deprivation prior to starting HRT have been adduced as an explanation for deleterious outcomes of hormone treatment in WHI and HERS. Based on a review of pre-clinical studies, as well as observational studies and clinical trials in women, including those with intermediate end-points and CVD outcomes, a 'unified hypothesis' that emphasizes the timing of initiation of HRT has been constructed |**10**|. This hypothesis attributes the complex CHD responses to HRT in recent human trials to a combination of early erosion/rupture of 'vulnerable' coronary plaque, which is made worse by HRT; long-term reduction in plaque formation, which is improved by HRT; and modulation of the vasoprotective actions of oestrogens by systemic progestins. The hypothesis predicts that HRT initiated at the time of menopause should produce a decrease in CHD over time, while HRT begun years after menopause should produce an increase in CHD events shortly after therapy is begun, followed

later by benefit. Evidence from human trials that initiate HRT in perimenopausal women is currently lacking, but the ongoing Kronos Early Estrogen Prevention Study (KEEPS) |**17**| and Early versus Late Intervention Trial with Estradiol (ELITE) |**18**|, discussed in detail in this review, are designed to provide this information.

In addition, cellular and molecular studies are urgently needed to elucidate the differential effects of HRT and its components on young, healthy arteries and on older, diseased arteries. Emerging evidence suggests that HRT administered to young, healthy women has anti-inflammatory and vasodilator effects that tend to lower blood pressure and slow the progression of atherosclerotic lesions, while the same HRT preparation administered to older women, particularly those with established vascular disease, has a proinflammatory effect, perhaps leading to atherosclerotic plaque instability and neovascularization |**19,20**|. The mechanisms of these altered vascular responses are not understood, but may relate to age-related deterioration in oestrogen receptor (ER) expression and signalling. Recent studies of the effects of HRT on blood pressure and vascular function, summarized in key papers published over the last year, support the age-dependence of the action of HRT on the vasculature. Beneficial effects of HRT appear to be realized only in younger, perimenopausal women in whom hormone response systems remain intact.

Clinical trials

Effects of conjugated equine estrogen in post-menopausal women with hysterectomy: the Women's Health Initiative Randomized Controlled Trial

Women's Health Initiative Steering Committee. *JAMA* 2004; **291**: 1701–12

Background. Despite decades of use and considerable research, the role of unopposed oestrogen in preventing chronic diseases, including CVD, in post-menopausal women remains uncertain. The oestrogen-alone component of the WHI was a double-blind, placebo-controlled trial designed to assess the effects on major disease incidence rates of conjugated equine oestrogen CEE (0.625 mg/day), the most commonly used menopausal hormone therapy (HRT) used in the US. Participants included 10 739 post-menopausal women, aged 50–79 years, with prior hysterectomy, including 23% of minority race/ethnicity. The primary outcome was CHD incidence (non-fatal myocardial infarction or CHD death); the primary safety outcome was invasive breast cancer incidence. After a mean follow-up of 6.8 years, the National Institutes of Health stopped the intervention phase of the trial because of an increased risk of stroke in the CEE arm and the futility of finding a significant effect on either the primary outcome (CHD) or the primary safety outcome (breast cancer) with CEE treatment. In contrast to the previously reported oestrogen plus progestin trial of WHI |1,2|, there was no excess of CHD or invasive breast cancer with CEE treatment (Fig. 13.2). CEE was associated with increased risk of stroke,

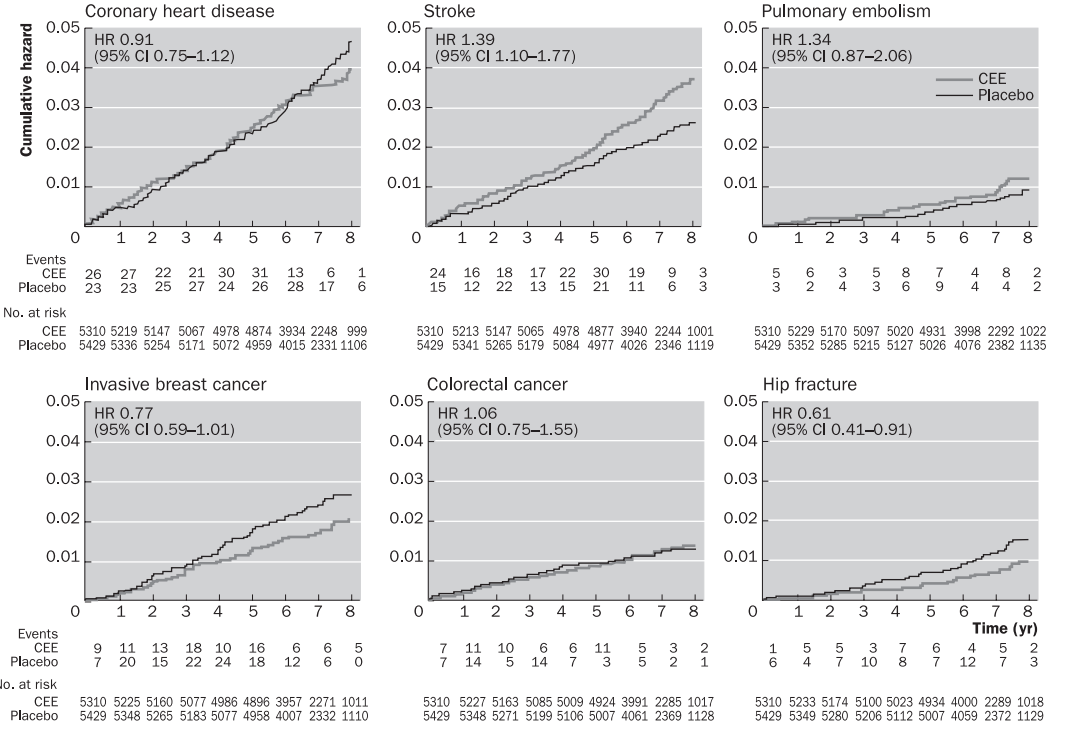

Fig. 13.2 Kaplan–Meier estimates of cumulative hazards for selected clinical outcomes. CEE, conjugated equine oestrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals up to and beyond year 8. Source: The Women's Health Initiative Steering Committee (2004).

pulmonary embolism, and total CVD and decreased risk of fractures. There was no effect on overall mortality. Blood pressure was measured by mercury sphygmomanometer in the clinic but was not a primary or secondary outcome. Systolic blood pressure (SBP) at year 1 was 1.1 mmHg higher in the CEE group than in the placebo group ($P = 0.003$) and remained similarly elevated throughout follow-up. Diastolic blood pressure (DBP) did not differ between groups.

Interpretation. Use of CEE increases the risk of stroke, decreases the risk of hip fracture and does not affect the incidence of CHD in post-menopausal women with prior hysterectomy over an average of 6.8 years. The apparent reduction in breast cancer risk requires further investigation. Since there was no overall benefit of CEE treatment, CEE should not be recommended for chronic disease prevention in post-menopausal women.

Comment

In contrast to the previously reported randomized trials of oestrogen plus progestin (HRT) in WHI |**1,2**| and in HERS |**4,5**|, the oestrogen replacement therapy (ERT) trial in WHI showed no effect of unopposed CEE on CHD risk overall. There was a statistically significant time trend in CHD occurrence, with a statistically insignificant increase in risk in the first year of CEE exposure that diminished over time, such that a possible modest benefit with long-term use was suggested. Results of the WHI–HRT and HERS trials, in contrast, demonstrated significant increases in CHD risk in the first year of HRT (CEE plus MPA) treatment and no benefit in subsequent years. Possible explanations for the discrepancy in effects of the two hormone regimens include the deleterious effects of the progestin, which has been shown in pre-clinical studies to negate the anti-inflammatory and vasoprotective effects of 17β-oestradiol in the setting of acute vascular injury |**11–14**|, as well as differences in the study populations and baseline risk factors |**21**|, the duration of intervention and follow-up time, and the play of chance.

As in the previous oestrogen plus progestin trials, the risk of stroke increased significantly (by 39%) with unopposed CEE treatment. The small but persistent increase in SBP may have contributed to the excess stroke, but formal statistical analysis of the magnitude of the putative blood pressure effect was not presented.

Subgroup analysis of results by participant age at enrolment revealed an intriguing trend: estimated hazard ratios for CEE for several outcomes, including CHD, were lower for women in the sixth decade of life than for older women. Although the differences in hazard ratios across age groups were not statistically significant, the results suggest that CEE may have more favourable effects in younger than older women. This is consistent with the concept, suggested by both human and animal studies, that ageing and hormone deprivation may attenuate neurohormonal and vascular responses to oestrogen. The ongoing KEEPS |**17**| and ELITE |**18**| studies are testing the hypothesis that early initiation of hormone therapy in women who are at the inception of their menopause will delay the onset of subclinical CVD. The rationale for KEEPS and ELITE is that intervention carried out earlier than that in WHI and HERS will provide cardiovascular benefit to women. KEEPS will evaluate the effectiveness

of CEE (0.45 mg/day) or transdermal oestradiol (50 μg/wk) in combination with cyclic oral micronized progesterone and placebo in preventing the progression of carotid intimal–medial thickness by ultrasound and coronary artery calcification by electron beam tomography in women aged 42–58 years who are within 36 months of their final menstrual period. ELITE is randomizing women according to their number of years since menopause (<6 vs ≥ 10) to receive either oral 17β-oestradiol (1 mg/day) or placebo; women with a uterus also receive vaginal progesterone gel (or placebo gel) for the last 10 days of each month. Carotid artery thickness by ultrasound is the primary end-point of the trial. Surrogate end-points for vascular disease will be measured in both trials in place of morbid and mortal CVD events, which are rare in the perimenopausal age group.

Major caveats that influence interpretation of the oestrogen-alone component of WHI are the incompleteness of the data presented in the initial report, the high rates of discontinuation of study medications and of crossover from placebo to active hormone use, and the fact that the trial was stopped early. All of these considerations decrease the precision of the estimated effects, both positive and negative, of CEE treatment. In particular, as the authors point out, a longer intervention period may have provided stronger evidence for effects on CHD, for which some evidence of a time trend was observed (Fig. 13.3), and for breast cancer. Extended follow-up data for these women, as planned by WHI, should be informative.

Pulse pressure and coronary atherosclerosis progression in post-menopausal women

Nair GV, Waters G, Rogers W, *et al*. *Hypertension* 2005; **45**: 53–7

Background. Pulse pressure, an index of large artery stiffness, has been associated with CHD events, but the mechanisms responsible are unclear. Increased pulse pressure has been reported in the setting of progressive atherosclerosis in the aorta and carotid arteries, but not in the coronary arteries of humans. This study examined the relationship between pulse pressure and the progression of coronary atherosclerosis, as well as the effects of HRT on pulse pressure in post-menopausal women with angiographically confirmed CHD who were followed for 3.2 years in the Estrogen Replacement in Atherosclerosis (ERA) trial |22|. Participants ($n = 309$; mean age 66 years) were randomized to CEE (0.625 mg/day), CEE plus MPA (0.625 + 2.5 mg/day) or placebo. CHD progression was assessed by quantitative coronary angiography. There was a significant graded increase in the progression of coronary stenosis, as reflected in change in mean minimum diameter adjusted for baseline mean minimum diameter, with increasing quartiles of baseline pulse pressure such that the progression rate for women in the highest quartile was 5-fold higher than for those in the lowest quartile. Pulse pressure increased in all three treatment arms in the course of the trial, and there was no significant association between HRT and pulse pressure.

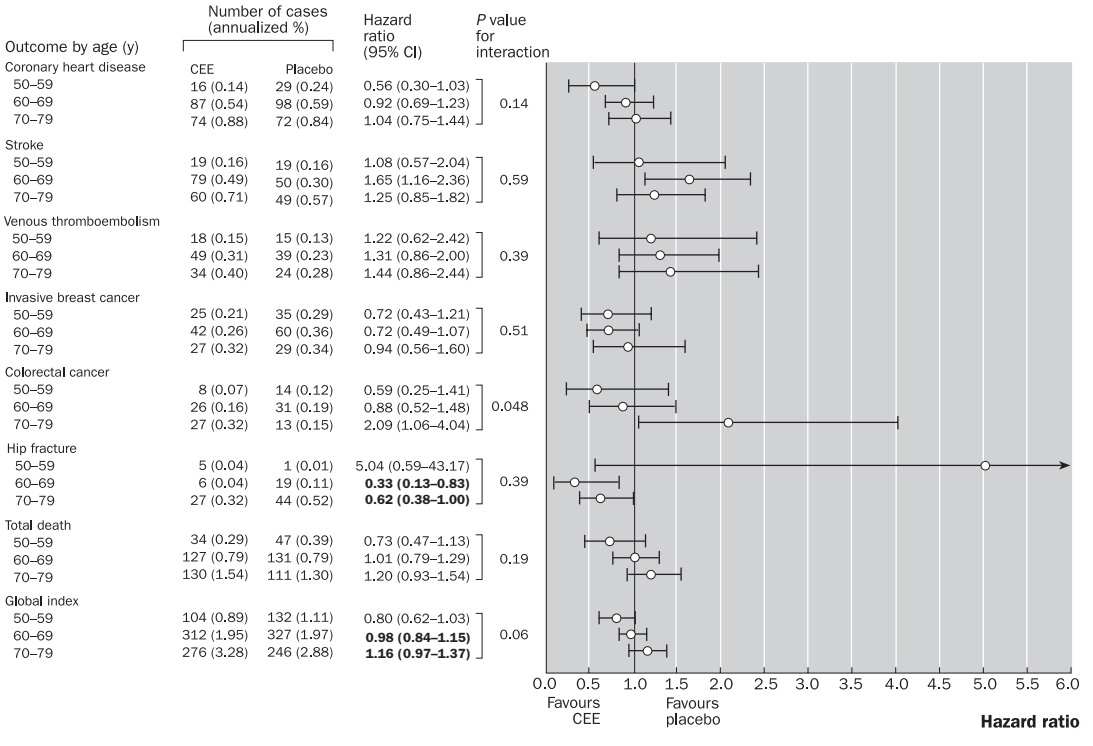

Fig. 13.3 Selected clinical outcomes by participant age and randomization assignment. CEE, conjugated equine oestrogen; CI, confidence interval. Data are plotted as hazard ratios with error bars showing 95% confidence intervals. Source: The Women's Health Initiative Steering Committee (2004).

Interpretation. In post-menopausal women with established CHD, progression of coronary atherosclerosis is positively associated with baseline pulse pressure, but is unaffected by HRT or ERT.

Comment

The negative findings of the ERA trial regarding the effects of HRT and ERT on pulse pressure and the progression of coronary atherosclerosis (reported previously |**22**|) contrast with observations of favourable effects of HRT on large artery compliance and the progression of atherosclerosis in healthy post-menopausal women. This confirms previous observations that ageing, established atherosclerosis and concomitant progestin use attenuate the favourable effects of oestrogen on the vasculature |**22–25**|, perhaps accounting for the lack of benefit seen with HRT and ERT in WHI and other randomized controlled trials. A limitation of ERA, acknowledged by the authors, is that blood pressure was not a primary outcome of the trial and that the annual measurements of cuff brachial blood pressure used to calculate pulse pressure may not reflect an individual's usual blood pressure. Further, brachial pulse pressure is an insensitive index of aortic stiffness and tends to overestimate central pulse pressure due to pressure amplification. Further studies with more sensitive and specific measures of large-vessel compliance are needed to assess the effects of ERT and HRT on vascular function and on subsequent CVD morbidity and mortality.

Pulse pressure and cardiovascular events in post-menopausal women with coronary heart disease

Nair GV, Chaput LA, Vittinghoff E, Herrington DM; for the Heart and Estrogen/progestin Replacement Study Investigators. *Chest* 2005; **127**: 1498–506

Background. This *post hoc* analysis of the HERS study examined the relationship between pulse pressure and the risk of CVD events, as well as the effect of HRT on pulse pressure in the HERS cohort, which included 2763 post-menopausal women (mean age 66 years) with documented CHD. Average follow-up was 4.1 years. Women in the highest quartile of pulse pressure at baseline had a more than 2-fold increase in the risk of stroke, transient ischaemic attack (TIA) or hospitalization for congestive heart failure (CHF) and a 47% increase in the risk of acute myocardial infarction or CHF death. After adjustment for blood pressure and other CVD risk factors, pulse pressure remained significantly associated with stroke, TIA and hospitalization for CHF, but not with fatal and non-fatal CHD events. Importantly, pulse pressure was 1–2 mmHg higher in women randomized to HRT (CEE 0.625 mg/day + MPA 2.5 mg/day) versus those randomized to placebo ($P < 0.01$).

Interpretation. Pulse pressure had predictive value for CHF and stroke or TIA, but not myocardial infarction or CHD death in this cohort of elderly post-menopausal women with established CHD. The use of HRT produced a small but statistically significant increase in

pulse pressure. The authors concluded that further research is needed to determine the clinical utility of pulse pressure as a potential therapeutic target.

Comment

The finding of a small but statistically significant 1–2 mmHg increase in pulse pressure, driven by an increase in SBP, in the HRT arm of HERS is consistent with results of previous studies of HRT in elderly post-menopausal women, e.g. WHI. The beneficial effects of HRT on vascular stiffness and pulse wave velocity reported in young, healthy menopausal women were not seen in HERS. This finding adds to the growing body of evidence that the beneficial effects of HRT and ERT on blood pressure, arterial mechanics and other aspects of vascular function are attenuated with increasing age and time after the menopause. The mechanisms by which HRT increases vascular stiffness and the associated risk of stroke and CHF in elderly women with underlying vascular disease are unknown and merit further study in animal models, as well as humans. These mechanisms may account for the unfavourable effects of HRT on CVD outcomes in the large randomized trials published to date.

Cardiovascular effects of 6 months of hormone replacement therapy versus placebo: differences associated with years since menopause

Brownley KA, Hinderliter AL, West SG, *et al*. *Am J Obstet Gynecol* 2004; **190**: 1052–8

BACKGROUND. In response to the issue, raised by WHI and discussed above, that the length of time between menopause and initiation of HRT may affect treatment outcomes, these investigators re-examined data from their previously reported 6-month randomized, double-blind, placebo-controlled trial of HRT in post-menopausal women |26|. They grouped their participants according to time since menopause in order to test the hypothesis that the cardiovascular effects of HRT would be greater in women who entered the study within 5 years of menopause than in those who were post-menopausal for 5 or more years. Sixty-nine healthy post-menopausal women were studied; haemodynamic measures included SBP, DBP, cardiac output and heart rate by impedance cardiography at rest and during behavioural stress. Impedance-derived variables included systematic vascular resistance index. Plasma norepinephrine was assessed as an index of sympathetic activity. Women who were less than 5 years after the menopause were more responsive to HRT than those who were 5 or more years after the menopause; the latter did not differ from the placebo group. Blood pressure fell significantly and systemic vascular resistance and plasma norepinephrine trended downward in response to HRT only in the group that was less than 5 years after the menopause.

INTERPRETATION. Blood pressure and sympathetic tone are reduced in HRT-treated women in their early post-menopausal years only. Thus, time since menopause may be an important consideration in making individualized patient treatment decisions.

Comment

This mechanistic study is consistent with previous reports of greater cardiovascular benefits of HRT in younger than in older post-menopausal cohorts. Interestingly, the magnitude of HRT-related blood pressure reduction (~8.5 mmHg) in the group less than 5 years after menopause was nearly twice that previously reported in the overall sample |**26**|; there was no blood pressure reduction in the older group. Possible vascular mechanisms responsible for the differential effects of HRT in the two groups with different age/time since menopause, e.g. altered ER expression/responsiveness and development of vascular lesions, were not examined and strongly merit future study. These findings may provide the basis for a more tailored approach to the prescription of HRT based on individual risk–benefit profiles rather that simple extrapolation from epidemiological findings.

Hormone replacement therapy and arterial blood pressure in post-menopausal women with hypertension

Karalis I, Beevers G, Beevers M, Lip G. *Blood Press* 2005; **14**: 38–44

BACKGROUND. Data on the effects of HRT on blood pressure in hypertensive post-menopausal women are limited. This study examined the association between HRT and longitudinal change in blood pressure in 161 hypertensive post-menopausal women (mean age 52 years) who required HRT to attenuate menopausal symptoms. SBP was unaffected throughout the 36-month follow-up period; DBP was slightly reduced. There was an increased need for antihypertensive medication throughout the follow-up period, during which time body weight increased.

INTERPRETATION. The use of HRT does not have a major adverse effect on blood pressure in younger hypertensive post-menopausal women who are taking it to relieve menopausal symptoms, although there may be an increased need for antihypertensive therapy over time.

Comment

The main finding of this study, that HRT has only very subtle effects on blood pressure control in treated hypertensive post-menopausal women, is consistent with the results of a number of small studies that have appeared in the past year |**27,28**|. While additional, controlled, longer-term studies of this issue carried out in older post-menopausal women may yield useful information, it is clear that HRT does not have a major pressor effect in post-menopausal women with treated and controlled hypertension, and that the presence of hypertension is not a contraindication to HRT use.

Effect of hormone therapy on BP in normotensive and hypertensive post-menopausal women

Mueck AO, Seeger H. *Maturitas* 2004; **49**: 189–203

BACKGROUND. These authors reviewed papers published since 1960 and listed in the Medline, EMBASE and Biosis databases describing studies that monitored the effects of HRT on blood pressure. The risk of an increase in blood pressure during HRT was very low in both normotensive and hypertensive post-menopausal women.In fact, HRT often lowered blood pressure, as in these authors' own study of 1397 hypertensive post-menopausal women, in whom various transdermal HRT regimens lowered blood pressure by an average of 7/9 mmHg; there were no significant changes in blood pressure in response to HRT in the 12 394 normotensive women included in the study. Only 30 patients (0.22%) developed increased blood pressure, which was recorded as an adverse event, but not with serious clinical sequelae. Of the nineteen 24-hour ambulatory blood pressure studies (13 placebo-controlled and ten crossover) reviewed, 14, including eleven of 13 studies with transdermal oestradiol and four of eleven with oral oestrogen, demonstrated blood pressure reductions and five found no effect on blood pressure. Effects on day- versus night-time blood pressure were not consistent. The authors acknowledged the paucity of data on at-risk populations, e.g. on progestin effects in women with atherosclerosis and/or hypertension, and that some high-risk women have exaggerated blood pressure responses to HRT.

INTERPRETATION. The risk of developing *de novo* hypertension during HRT (all forms) is very low but, as in women taking oral contraceptives, blood pressure in women receiving HRT, particularly those at high risk of CVD, should be monitored closely.

Comment

This very comprehensive literature review of the effects of HRT on blood pressure failed to find a signal that any form of HRT elevates blood pressure in the general population of post-menopausal women. However, the limitations of the data, including the small size and short duration of most of the studies described and the heterogeneity in the hormone preparations used, make it impossible to rule out a substantial pressor effect of some hormones, e.g. CEE and some progestins, in a small percentage of sensitive post-menopausal women. The authors remark that their finding that HRT induced small decreases in blood pressure in most studies of the effects of HRT on blood pressure contrasts with the HRT-induced increases in blood pressure seen in randomized controlled outcome trials of HRT and ERT, e.g. WHI. They query whether a subset of women with larger HRT-induced increases in blood pressure may have contributed to the high incidence of HRT- and ERT-related stroke seen in these trials. The authors reach the reasonable conclusion that, if HRT is to be given to hypertensive post-menopausal women, the lowest possible dose should be used, particularly with regard to the progestin, and 17β-oestradiol should be the preferred

oestrogen. The data available do not justify considering hypertension as a contraindication to HRT.

Association between cardiovascular outcomes and antihypertensive drug treatment in older women

Wassertheil-Smoller S, Psaty B, Greenland P, *et al*. *JAMA* 2004; **292**: 2849–59

BACKGROUND. The WHI Observational Study (WHI-OS), with 93 676 participants, is the largest prospective study to follow a multiethnic cohort of post-menopausal women with rigorously ascertained end-points. At baseline in 1994–1998, WHI-OS identified 35 920 women, aged 50–79 years, with hypertension, of whom 30 219 had no history of CVD and 18 969 were receiving pharmacological treatment for hypertension with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, diuretics, or a combination of two classes of these drugs. This report tested prospectively over a mean follow-up period of 5.9 years whether there are differences in CVD (CHD and stroke) morbidity and mortality among women treated with different classes of antihypertensive agents, singly or in combination. CVD death occurred in 58 of 3096 women on calcium channel blocker monotherapy versus 39 of 3169 on diuretic monotherapy (hazard ratio [HR] 1.55; 95% confidence interval [CI] 1.02–2.35) and in 31 of 1223 on calcium channel blocker plus diuretic versus 18 of 1380 on β-blocker plus diuretic therapy (HR 1.85; 95% CI 1.02–3.36). One hundred and seventy-five CHD events and 74 strokes occurred in women on calcium channel blocker monotherapy versus 149 and 61 events, respectively, in women on diuretics (for CHD, HR 1.19; 95% CI 0.94–1.51; for stroke, HR 1.32; 95% CI 0.92–1.89). There were no significant differences in hazard ratios for CVD morbidity, including CHD events or stroke, between the ACE inhibitor or β-blocker group versus the diuretic group, between women receiving dihydropyridine versus non-dihydropyridine calcium channel blockers, or between the diuretic plus calcium channel blocker or diuretic plus ACE inhibitor versus the diuretic plus β-blocker groups.

INTERPRETATION. The major conclusion of this WHI-OS report is that, among post-menopausal women with hypertension but no history of CVD, a regimen of calcium channel blocker plus diuretic is associated with a higher risk of CVD mortality than is a regimen of β-blocker plus diuretic, while risks are similar for ACE inhibitor plus diuretic and β-blocker plus diuretic, and monotherapy with a diuretic is equal or superior to monotherapy with the other three drug classes in preventing the CVD complications of high blood pressure.

Comment

This analysis of the WHI-OS provides a wealth of information about community treatment of hypertension in a large multiethnic cohort of generally healthy post-menopausal women. Since the theme of this analysis was the differential effects of various classes of drugs used for the treatment of hypertension, some of which are also indicated for other CVD conditions (e.g. angina, heart failure, post-myocardial

infarction), the authors attempted to minimize confounding by indication by eliminating women with a history of CVD. Potential confounding by indication was also addressed by obtaining a propensity score from a multinomial logistic regression to predict baseline medication usage from baseline risk factors, i.e. age, race/ethnicity, smoking, dyslipidaemia requiring medication, prior use of hormone therapy, diabetes, DBP and SBP, and all pairwise interactions, using stepwise regression. The logistic regressions used pairwise comparisons of the drug class combinations, with diuretic as the reference for monotherapy and diuretic plus β-blocker as the reference for combined therapy. Baseline characteristics of the different medication groups differed in ways that might have influenced the outcomes: baseline SBP was lowest in the diuretic group (135.5 mmHg) and highest in the calcium channel blocker group (139.2 mmHg), and more of those receiving channel blockers or diuretics were black (16.2 and 17.1%, respectively) compared with those receiving ACE inhibitors (7.4%) or β-blockers (4.9%). Further, the duration of drug use at baseline differed among classes: 7.5 years for diuretics, 4.0 years for ACE inhibitors, and 3.6 years for calcium channel blockers. However, the authors stated that when the data were fitted to models that adjusted for baseline blood pressure, duration of receiving baseline medication, and propensity to be receiving a particular drug or drug combination based on the covariates, the results were not changed significantly.

The most important limitation of this study is its observational design. In the absence of randomized treatment assignments, it is not possible to control fully for confounding by indication, i.e. to rule out unmeasurable factors that would lead physicians to prescribe one class of antihypertensive drugs rather than another for first-line or combination therapy. Another limitation is the absence of data on blood pressure responses and treatment modifications/persistence in the course of the observation period. For example, the calcium channel blocker scare of 1995 may have resulted in discontinuation of these drugs in many women who had been taking them at baseline in WHI-OS. Persistent undertreatment of these patients and resulting poorer blood pressure control could conceivably explain some of the unfavourable results in the calcium channel blocker group. Lack of information about the sequence in which drug classes were initiated (e.g. whether diuretics were used first in most patients and other classes were substituted only in those who were not controlled on a diuretic) is another limitation that obfuscates the interpretation of the findings.

The findings of WHI-OS are in striking contrast to those of the major recent randomized controlled outcome trials of antihypertensive therapy, including the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) |**29**|, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) |**30**| trial, and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) |**31**|. ALLHAT found no difference between calcium channel blocker-based and diuretic-based treatment with respect to fatal and non-fatal CHD end-points, stroke, combined CVD and CVD and all-cause mortality. CHF was the only outcome for which calcium channel blocker-based treatment was inferior. VALUE found a significant reduction in acute myocardial infarction and a statistically non-significant reduction in stroke with treatment based on calcium channel blocker compared with treatment based on

angiotensin receptor blocker, although interpretation of the results is clouded by significant differences in blood pressure between the treatment arms that favour the calcium channel blocker. CHD morbidity and mortality and all-cause death did not differ between treatment groups. ASCOT was stopped prematurely because of an excess of events in the β-blocker plus diuretic arm compared with the calcium channel blocker plus ACE inhibitor arm. Preliminary analysis of the results has revealed significant reductions in all-cause mortality, CHD events, stroke, CVD mortality and new-onset diabetes, as well as a non-significant reduction in the primary end-point of non-fatal myocardial infarction and fatal CHD, in the calcium channel blocker plus ACE inhibitor arm. While data specific to post-menopausal women without clinical CVD at baseline were not reported for these large trials, most of the women included must have been post-menopausal, since the minimum age for entry was 55 years. Data concerning possible effects of HRT on blood pressure or interactions between HRT and antihypertensive drug treatment were not reported.

The main take-home message from WHI-OS is the inadequacy of blood pressure treatment and control in post-menopausal women in the US: only 36% of women with hypertension and no history of CVD were treated and controlled to <140/90 mmHg, and 24% were controlled to <130/80 mmHg. Among diabetic women, blood pressures of <130/80 mmHg were achieved in only 21%. Despite these poor control rates, 70% of women were receiving monotherapy; only 30% were receiving two or more drugs. Rather than focus on which drug class is best (or worst) for preventing CVD outcomes, a more productive approach is to attempt to achieve blood pressure control with multiple agents. All recent randomized controlled trials have shown that multidrug therapy is needed for the older, relatively high-risk hypertensive patient, including the post-menopausal woman.

Effects of drospirenone/17-β estradiol on blood pressure and potassium balance in hypertensive post-menopausal women

Preston RA, White WB, Pitt B, Bakris G, Norris PM, Hanes V. *Am J Hypertens* 2005; **18**: 797–804

BACKGROUND. Drospirenone (DRSP) is a novel progestin with mineralocorticoid receptor antagonist activity that was developed for use as HRT in combination with 17β-oestradiol (DRSP/E2). This study examined the effects of DRSP/E2 on blood pressure and serum K^+ in hypertensive post-menopausal women with (*n* = 82) or without (*n* = 148) type 2 diabetes and using an ACE inhibitor or angiotensin receptor blocker. To further increase the likelihood of unmasking hyperkalaemia, the non-diabetic group was given a 5-day course of ibuprofen.

INTERPRETATION. In hypertensive post-menopausal women with or without type 2 diabetes and concomitant use of ACE inhibitors, angiotensin receptor blockers or ibuprofen, DRSP/E2 had a significant antihypertensive effect (–8.6/–5.8 mmHg) compared with placebo (–3.7/–2.9 mmHg; *P* <0.01), but did not increase the incidence of hyperkalaemia. *Post hoc*

analysis of changes in serum K^+ over time in patients particularly prone to the development of hyperkalaemia, i.e. those with renal impairment or older than 60 years, revealed no significant tendency to develop hyperkalaemia with DRSP/E2.

Comment

DRSP/E2 represents a novel form of HRT with mineralocorticoid receptor antagonist and antihypertensive effects that could reduce cardiovascular risk in postmenopausal women. As pointed out in the accompanying editorial by Rosendorff |**32**|, there are some lingering concerns about hyperkalaemia with the agent: incidence of serum K^+ greater than 5.5 mEq/l was 7.9 and 6.9%, respectively, in diabetics and non-diabetics on the drug versus 4.5 and 1.4% in diabetics and non-diabetics on placebo, a statistically non-significant but numerically impressive difference. Further study of the safety and potential target organ protection and outcome benefits of this interesting new agent is warranted.

Mechanisms of hormone-induced blood pressure effects in humans

Renin–angiotensin–aldosterone system

Estradiol induces discordant angiotensin and blood pressure responses to orthostasis in healthy menopausal women

Harvey PJ, Morris BL, Miller JA, Floras JS. *Hypertension* 2005; **45**: 399–405

BACKGROUND. Oestrogen has been shown to perturb the renin–angiotensin–aldosterone system (RAAS) at a number of sites: increases in hepatic expression and circulating levels of angiotensinogen and circulating levels of angiotensin II with either no change or a decrease in plasma renin and a concurrent decrease in ACE activity have been reported during administration of ERT to post-menopausal women. Conversely, oestrogen deficiency has been associated with increased ACE synthesis and activity and upregulation of the angiotensin II type 1 (AT_1) receptor. This study examined the effects of ERT-induced increases in circulating angiotensin II on cardiovascular function during simulated orthostasis with lower body negative pressure (LBNP) in 13 normotensive post-menopausal women before and after 1 month of oral 17β-oestradiol (2 mg/day) and in 14 pre-menopausal women. The specific hypothesis tested was that oestrogen-induced activation of the RAAS would result in increased blood pressure before and during LBNP. Major findings of the study were that oestradiol treatment of post-menopausal women increased resting angiotensinogen, renin activity and

angiotensin II levels, but not renin content or aldosterone, and that the oestrogen-induced increase in angiotensin II did not result in higher blood pressure, either at rest or with LBNP, thus refuting the authors' hypothesis. Further, LBNP increased active renin, angiotensin II and aldosterone levels in pre-menopausal but not post-menopausal women, indicating that reflex activation of both haemodynamic events and the RAAS was impaired in the latter group. Oestradiol treatment of post-menopausal women reduced both resting and LBNP-stimulated blood pressure in the presence of increased circulating angiotensin II levels.

Interpretation. When administered to healthy post-menopausal women, oral oestradiol induces RAAS activation characterized by an increase in circulating angiotensin II, but the pressor actions of the peptide may be counteracted by downregulation of vasoconstrictor, autonomic or adrenocortical responsiveness to it. This may occur at the level of the AT_1 receptor or via counter-regulatory post-receptor hypotensive mechanisms. These protective mechanisms may be lost as a result of ageing or concomitant conditions such as hypertension or atherosclerosis, perhaps contributing to the higher CVD event rates seen in the elderly women enrolled in recent ERT trials.

Comment

This well-done study demonstrates a disassociation between the humoral and haemodynamic effects of exogenous 17β-oestradiol in healthy, relatively young post-menopausal women. The observation that aldosterone levels and blood pressure did not increase in response to elevated angiotensin II levels in these women suggests downregulation of the AT_1 receptor, as demonstrated by previous studies in animal models. As pointed out by the authors, there is ample evidence of both direct and indirect (by increasing nitric oxide [NO] bioavailability and angiotensin II levels) inhibition of AT_1 receptor expression by oestrogen. Physiological consequences of this effect may include decreased sympathetic nervous system outflow, as has been noted in post-menopausal women receiving ERT and in pre-menopausal women during the high-oestrogen phase of the cycle. It should be noted that the experimental subjects in this study were relatively young (average age 54 years) and healthy, and thus may have responded to ERT differently from patients enrolled in major outcome trials of menopausal hormone therapy, who were on average much older and had been free of hormones for many years. As the authors pointed out, ageing *per se* may alter both the expression of and responsiveness to the components of the RAAS in a way that may predispose to the development of CVD. Likewise, ageing and hormone deprivation may attenuate neurohormonal and vascular responses to oestrogen. A study similar to this in older post-menopausal women would be of great interest and could help to resolve the discordance between the results of outcome trials with ERT and mechanistic studies carried out in younger women and animal models.

Effects of conjugated oestrogen and droloxifene on the renin–angiotensin system, blood pressure, and renal blood flow in post-menopausal women

Seely EW, Brosnihan KB, Jeunemaitre X, *et al*. *Clin Endocrinol (Oxf)* 2004; **60**: 315–21

BACKGROUND. This study examined the effects of ERT (CEE 0.625 mg/day) or the selective oestrogen receptor modulator (SERM) droloxifene (60 mg/day) on components of the RAAS and blood pressure in 21 normotensive and ten hypertensive post-menopausal women. Ambulatory blood pressure was monitored and renal blood flow was measured by para aminohippurate (PAH) clearance at baseline and after angiotensin II infusion in a subset of patients. CEE and the SERM had differential effects on some components of the RAAS: CEE increased angiotensinogen but reduced active renin and ACE compared with baseline, while droloxifene had no effect. Both interventions increased circulating angiotensin II levels in normotensive and hypertensive participants without altering levels of the parent peptide, angiotensin I, and neither had a significant effect on blood pressure during the 6-week active treatment period. Further, both CEE and droloxifene reduced renal blood flow to below baseline levels and blunted the decrement in renal blood flow seen with angiotensin II infusion, supporting the functional significance of the hormone-induced increase in angiotensin II, the major endogenous regulator of renal blood flow.

INTERPRETATION. The main finding of this study is that both CEE and droloxifene cause circulating angiotensin II levels to increase without altering blood pressure or aldosterone levels.

Comment

The findings with the SERM are novel, while those with CEE generally confirm previous reports. The mismatch between the increased angiotensin II levels and absent blood pressure response with hormone treatment is unexplained, although oestrogen-induced suppression of AT_1 receptor expression, as previously described, may play a role. The fall in renal blood flow and increase in angiotensin II induced by both agents are potentially deleterious by mechanisms independent of blood pressure elevation. The authors end their discussion with a call for further study of the effects of SERMs on the RAAS and on the renal and systemic vasculature. This information is urgently needed before these agents are administered to large numbers of high-risk post-menopausal women.

Aortic stiffness

Menopause is an independent factor augmenting the age-related increase in arterial stiffness in the early post-menopausal phase

Zaydun G, Tomiyama H, Hashimoto H, *et al*. *Atherosclerosis* 2005 May 21; [Epub ahead of print]

BACKGROUND. This cross-sectional study, carried out in 3149 women (age 21–94 years) who underwent annual health screening examinations at an affiliated institute of Tokyo Medical University, tested whether menopause augments the age-related increase in brachial–ankle pulse wave velocity (PWV). Brachial–ankle PWV was measured using a volume–plethysmographic apparatus previously validated and described by the authors. The slope of the quadratic curve describing the relationship between brachial–ankle PWV and age was steeper in post- than in pre-menopausal participants (Fig. 13.4) and data from those aged 45–56 years demonstrated that women who had undergone menopause at least 6 years earlier had double the risk of belonging to the highest PWV tertile, independently of age and other CVD risk factors. Importantly, women with a history of HRT use were excluded from the study.

INTERPRETATION. The age-related increase in arterial stiffness appears to be augmented during the early post-menopausal period and is probably related to oestrogen deficiency. The contribution of the menopause-related increase in arterial stiffness to the risk of CVD in menopausal women requires further evaluation.

Comment

The issue of whether menopause *per se* augments the age-related increase in arterial stiffness and, if so, whether this effect is a consequence of oestrogen deficiency remains controversial. This large cross-sectional study, carried out in a Japanese population, provides evidence that naturally occurring menopause is associated with increased brachial–ankle PWV, a surrogate for aortic stiffness. Limitations of the study include reliance on self-identification for timing the menopause. As acknowledged by the authors, oestrogen deficiency in perimenopausal women has been reported to progress gradually, until nearly 60 years of age |**33**|, making it difficult to distinguish the effects of menopause from those of ageing with the associated increases in CVD risk factors. The cross-sectional design of the study is an additional limitation, as is the use of brachial–ankle PWV measurements, which assess both central and peripheral arterial stiffness, and have not been validated as a marker of CVD risk. As explained by the authors, the brachial–ankle measurement was chosen for convenience in screening thousands of participants in the course of a routine health check. These provocative findings point to the need for an outcome

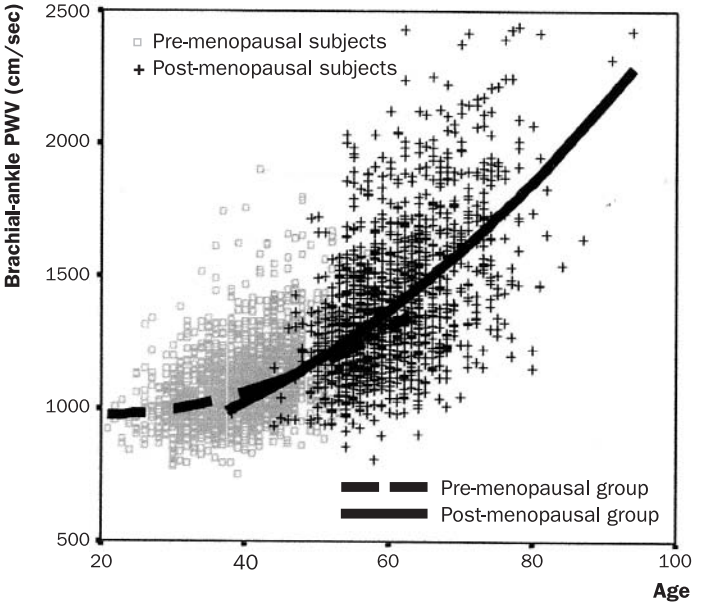

Fig. 13.4 Association between age and brachial–ankle pulse wave velocity. The *empty light grey squares* represent the residual plots of pre-menopausal subjects and the *dark + symbols* represent the residual plots of post-menopausal subjects. The curve for the pre-menopausal women is steeper than that for the post-menopausal women. PWV, pulse wave velocity. Source: Zaydun *et al*. (2005).

study to assess the contribution of the menopause-related increase in PWV and its potential modulation by HRT to CVD morbidity and mortality in post-menopausal women.

Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study

Mitchell GF, Parise H, Benjamin EJ, *et al*. *Hypertension* 2004; **43**: 1239–45

Background. This cross-sectional study dissected various components of central (carotid–femoral) and peripheral (carotid–brachial) pulse waves (PWV, amplitudes of forward and reflected pressure waves, and augmentation index) (Fig. 13.5) in 188 men and 333 women in the Framingham Heart Study offspring cohort who were free of clinical CVD and major risk factors. Arterial tonometry with simultaneous ECG was obtained from brachial, radial, femoral and carotid arteries using a commercially available tonometer, and pulse wave parameters were calculated using published

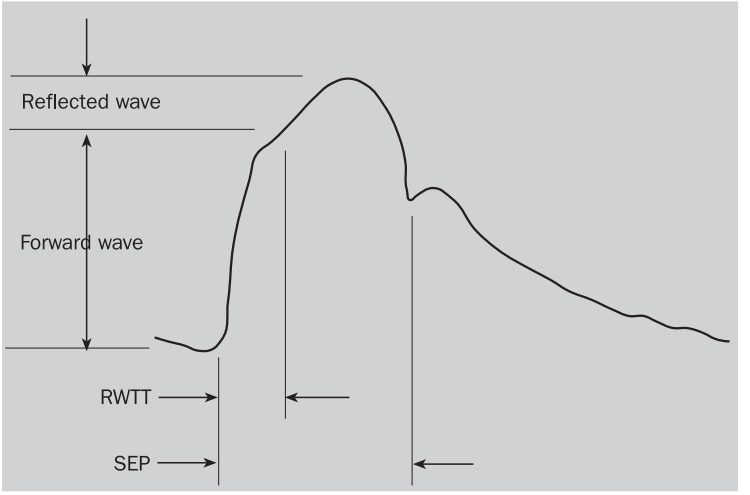

Fig. 13.5 Carotid pressure landmarks. Reflected wave transit time (RWTT) was identified by the first occurrence of an inflection point on the carotid pressure waveform. If the inflection point occurred before peak pressure (an augmented waveform), pressure at the inflection point minus foot pressure was the forward wave pressure and systolic pressure minus pressure at the inflection point was the reflected wave pressure. If the inflection point occurred after peak pressure (no augmentation), reflected wave pressure was zero and systolic pressure minus pressure at the foot was forward wave pressure. Systolic rejection period (SEP) was measured from the foot of the waveform to the dicrotic notch.
Source: Mitchell *et al*. (2004).

methods. There was a strong, non-linear increase in carotid–femoral PWV with advancing age; in comparison, the age-related increase in carotid–brachial PWV was markedly attenuated. Forward wave amplitude and reflected wave pressure were higher in women than men. Carotid–femoral PWV, a measure of central arterial stiffness, was lower than carotid–brachial PWV, a measure of peripheral arterial stiffness, before age 50 but exceeded it thereafter. Before age 60, the increase in carotid–femoral PWV was accompanied by a reciprocal decrease in reflected wave transit time, no change in location of major reflecting sites and an increase in augmentation index, while after age 60 forward wave amplitude continued to increase but the relative amplitude of the reflected wave (augmentation index) reached a plateau in men and fell in women, in relation to a shift of reflecting sites to more distal locations.

Interpretation. In a healthy cohort with no evidence of CVD and a low burden of risk factors, there was a marked age-related increase in aortic stiffness and forward pulse wave amplitude, with little change in peripheral arterial stiffness or reflected pulse wave amplitude. These findings suggest that increased central aortic stiffness, rather than reflected wave amplitude, is mainly responsible for the increased central and peripheral SBP and pulse pressure that can occur with advancing age. The authors hypothesize that increased forward

transmission of a larger forward wave may expose the peripheral vasculature to potentially damaging levels of pressure pulsatility and may contribute to the development of microvascular disorders in the elderly.

Comment

This study uses rigorous non-invasive methods to delineate the effects of ageing on the mechanical properties of central and peripheral arteries in a well-characterized cohort of apparently healthy persons (average age 57 years). While sex differences in the findings are presented and discussed, the menopausal status of female participants and their use of HRT are not mentioned. Prospective controlled studies using this rigorous method are needed to delineate the effects of menopause and HRT on arterial stiffness in ageing women.

Ascorbic acid selectively improves large elastic artery compliance in post-menopausal women

Moreau KL, Gavin KM, Plum AE, Seals DE. *Hypertension* 2005; **45**: 1–6

BACKGROUND. The previous findings that markers of oxidative stress are higher and endogenous antioxidant defences lower in some oestrogen-deficient post-menopausal women compared with pre-menopausal controls led the authors to test the hypothesis that oxidative stress contributes mechanistically to reduced large elastic artery compliance in post-menopausal women. Carotid artery compliance and beta stiffness index were determined using high-resolution ultrasound imaging and applanation tonometry in ten pre-menopausal and 21 post-menopausal women who were at least 1 year after menses and had not taken HRT for at least 6 months. Measurements were made before and after acute intravenous infusion of supraphysiological doses of the antioxidant vitamin ascorbic acid. Baseline carotid artery compliance was 56% lower in pre-menopausal than in post-menopausal women; ascorbic acid infusion increased compliance by 26% in the post-menopausal group without affecting blood pressure or heart rate, but had no effect in the pre-menopausal women (Fig. 13.6). Ascorbic acid-induced changes in arterial compliance correlated with plasma norepinephrine, low-density lipoprotein cholesterol and waist-to-hip ratio.

INTERPRETATION. Oxidative stress appears to contribute to the reduced large artery compliance of oestrogen-deficient post-menopausal women, and this modulatory influence is related to sympathetic nervous system activity, circulating low-density lipoprotein cholesterol and abdominal fat storage. These mechanisms may contribute to the development of oxidative stress, thus indirectly inhibiting large elastic artery compliance in post-menopausal women.

Comment

The authors make a compelling case that oxidative stress contributes to the reduced large artery compliance seen in post-menopausal women who are not receiving ERT.

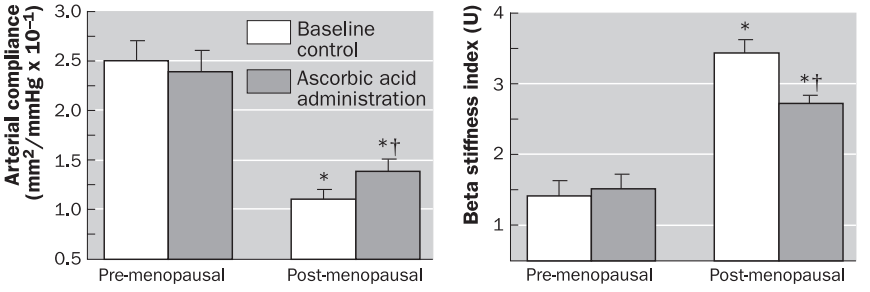

Fig. 13.6 Carotid artery compliance and beta stiffness index during acute saline (baseline control, *white bars*) and ascorbic acid administration (*grey bars*). * $P < 0.001$ vs pre-menopausal; † $P < 0.001$ vs saline of the same group. Source: Moreau *et al*. (2005).

Interestingly, the same group has shown that the dramatic improvement in carotid artery compliance in response to ascorbic acid infusion seen in post-menopausal women without HRT is not seen in men |**34**|. They speculate that the reason for this differential arterial sensitivity to antioxidants may be that the loss of circulating oestrogen with menopause results in an antioxidant deficit, leading to an increase in vascular responsiveness to exogenous antioxidants, e.g. ascorbic acid. A rigorous test of this hypothesis would require examination of the effects of acute and chronic oestrogen administration on indices of oxidative stress and large artery compliance in these women.

Non-dipping status does not attenuate the conjugated estrogen-induced improvement in aortic stiffness in post-menopausal women with untreated hypertension

Tsioufis C, Tzioumis K, Dimitriadis K, *et al*. *Am J Hypertens* 2005; **18**: 607–11

Background. ERT has significant positive effects on vascular structure and function, including improvement in endothelial function and large artery compliance, in post-menopausal women. This study tested whether blunted nocturnal fall in blood pressure (non-dipper status), a condition that is associated with increased target organ damage and CVD risk, attenuates the beneficial effects of ERT on arterial elastic properties in hypertensive post-menopausal women. A total of 66 post-menopausal women (21 non-dippers, 45 dippers) with untreated essential hypertension underwent carotid–femoral PWV measurement at baseline and after 12 weeks of ERT with 0.625 mg CEE/day. ERT reduced PWV significantly in both non-dippers and dippers (by 1.28 and 1.50 cm/s, respectively, $P < 0.05$ for both) without affecting office SBP or DBP. Patient age and 24-hour SBP were significant determinants of ERT-induced aortic PWV reduction ($P < 0.05$).

INTERPRETATION. A blunted nocturnal fall in blood pressure does not attenuate the favourable effects of ERT on the elastic properties of large arteries in hypertensive post-menopausal women.

Comment

This study adds to the body of evidence suggesting that post-menopausal hormone therapy (combined progestin plus oestrogen as well as oestrogen alone) may improve arterial compliance in hypertensive post-menopausal women, and further suggests that similar benefit occurs in women who lack the normal diurnal variation in blood pressure and therefore may have more severe target organ damage. The strengths of the study incorporate inclusion of relatively young, recently post-menopausal (average age 53.5 years, average time after menopause 3.4 years) women with untreated stage 1 hypertension diagnosed in the previous 2 years. Menopausal status was documented with measurements of plasma follicle-stimulating hormone and oestradiol, and adherence to ERT, with follow-up plasma oestradiol measurements. Weaknesses include the absence of a control group, the lack of PWV measurements after ERT withdrawal, and failure to specify the instrumentation used to measure PWV. A limitation of the clinical relevance of the study is the use of ERT only, a therapy unsuitable for post-menopausal women with intact uteri. As acknowledged by the authors, this study points out the need for larger randomized controlled trials of HRT in a population of young post-menopausal women with aortic stiffness as an intermediate end-point and CVD morbidity and mortality as outcomes.

Effects of hormone replacement therapy or raloxifene on ambulatory blood pressure and arterial stiffness in treated hypertensive post-menopausal women

da Costa LS, de Oliviera MA, Rubim VS, *et al*. *Am J Cardiol* 2004; **94**: 1453–6

BACKGROUND. This randomized, single-blind crossover design study examined the effects of transdermal HRT (oestradiol 50 μg plus norethisterone 250 μg/day) or the SERM raloxifene (60 mg/day) on arterial rigidity using PWV analysis and on office and 24-hour ambulatory blood pressure in 30 hypertensive post-menopausal (≥60 years old, ≥2 years after physiological menopause with intact uteri) women. Women with a history of CVD, positive stress tests or major CVD risk factors were excluded by careful screening. All participants were treated with hydrocholorthiazide (12.5 or 25 mg/day) only. Right carotid–femoral PWV was recorded using an automatic computerized system and analysed using the Complior® device. HRT produced significantly greater reductions in office SBP and 24-hour and daytime ambulatory SBP and DBP than raloxifene; blood pressure levels seen with raloxifene did not differ from those with placebo. In contrast, PWV was reduced significantly and to similar values by both HRT and raloxifene, and PWV changes did not correlate with SBP changes, demonstrating independence of improvement in vascular compliance

from blood pressure reduction. In a subgroup of participants treated with blinded placebo in a run-out period following the active treatment phase, both PWV and blood pressure returned to baseline values, demonstrating the reversibility of the HRT and SERM effects.

INTERPRETATION. HRT and SERM treatment produced equivalent reductions in carotid–femoral PWV, while HRT reduced blood pressure to a greater extent than the SERM. The effect of raloxifene on vascular compliance was independent of its effects on blood pressure.

Comment

This well-designed controlled study demonstrates that the SERM raloxifene provides reductions in carotid–femoral PWV equivalent to standard HRT, while reducing blood pressure to a much lesser extent. This brings up the intriguing possibility that different hormone preparations may have differential effects on the structural and functional properties of the vasculature. The cardiovascular effects of the SERMs, which are used clinically for osteoporosis treatment and breast cancer prevention, are just beginning to be explored. The Raloxifene Use for The Heart (RUTH) study, soon to be completed, should be informative in this regard |**35**|.

Sympathetic nervous system

Gender-selective interaction between aging, blood pressure, and sympathetic nerve activity

Narkiewicz K, Phillips BG, Kato M, Hering D, Bieniaszewski L, Somers VK. *Hypertension* 2005; **45**: 522–5

BACKGROUND. Traditional risk factors are thought to account for only about half of the age-related increase in CVD morbidity and mortality in women, which is greater than in men. The contribution of the menopause *per se* to this phenomenon is controversial. This study tested the hypothesis that ageing has greater impact on sympathetic nerve traffic in women than in men and evaluated the relative influences of age and menopause on sympathetic activity in 216 healthy normotensive white persons (130 men, 96 women). No participant was using menopausal hormone therapy. The main finding of this large cross-sectional study is that ageing has a greater stimulating effect on sympathetic nerve traffic, assessed by measurement of muscle sympathetic nerve activity (MSNA) in the peroneal nerve, in women than in men, such that the rate of increase in MSNA per decade is 2.5-fold higher (Fig. 13.7), and the contribution of age to MSNA variance is 6-fold greater in women than in men. Interestingly, changes in body mass index and waist-to-hip ratio did not appear to contribute to the ageing effect. There was a significant positive interaction between sympathetic nerve traffic and blood pressure only in participants over 40 years

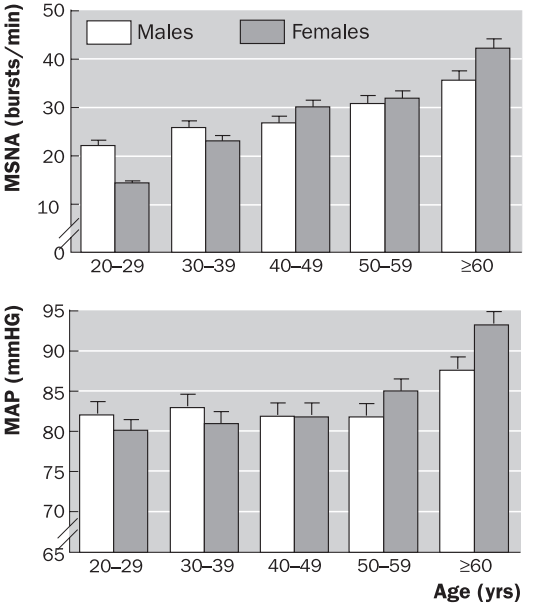

Fig. 13.7 Muscle sympathetic nerve activity (MSNA) and mean arterial pressure (MAP) per decade in male and female subjects. Two-way ANOVA revealed that age influenced both MSNA ($P < 0.0001$) and MAP ($P = 0.005$). Gender had no significant effect on MSNA ($P = 0.52$) or MAP ($P = 0.59$). Gender and age had an interactive effect on MSNA ($P = 0.01$), but not on MAP ($P = 0.50$). In subjects aged 20–29, MSNA was lower in females than males ($P < 0.01$ by pairwise comparison with the use of the Scheffé test). Source: Narkiewicz *et al*. (2005).

of age, and the correlation was more striking in women than in men (Fig. 13.8). Menopause, as documented by menstrual history only, did not appear to contribute to the age-related increase in sympathetic traffic in women.

INTERPRETATION. Ageing is accompanied by a greater increase in sympathetic nerve traffic in women than in men, independently of body mass and menopausal status. The finding of a strong interaction between blood pressure and MSNA in women over age 40 suggests that sympathetic neural mechanisms may contribute importantly to the more marked influence of age on blood pressure and CVD in women.

Comment

The strengths of this study are the large size and wide age range of the study population, restriction of the study to apparently healthy normotensive persons taking no medications, including HRT and oral contraceptives, and the expertise of the groups making the MSNA measurements. The major limitations are the cross-sectional design, which makes it impossible to link ageing, sympathetic drive and the

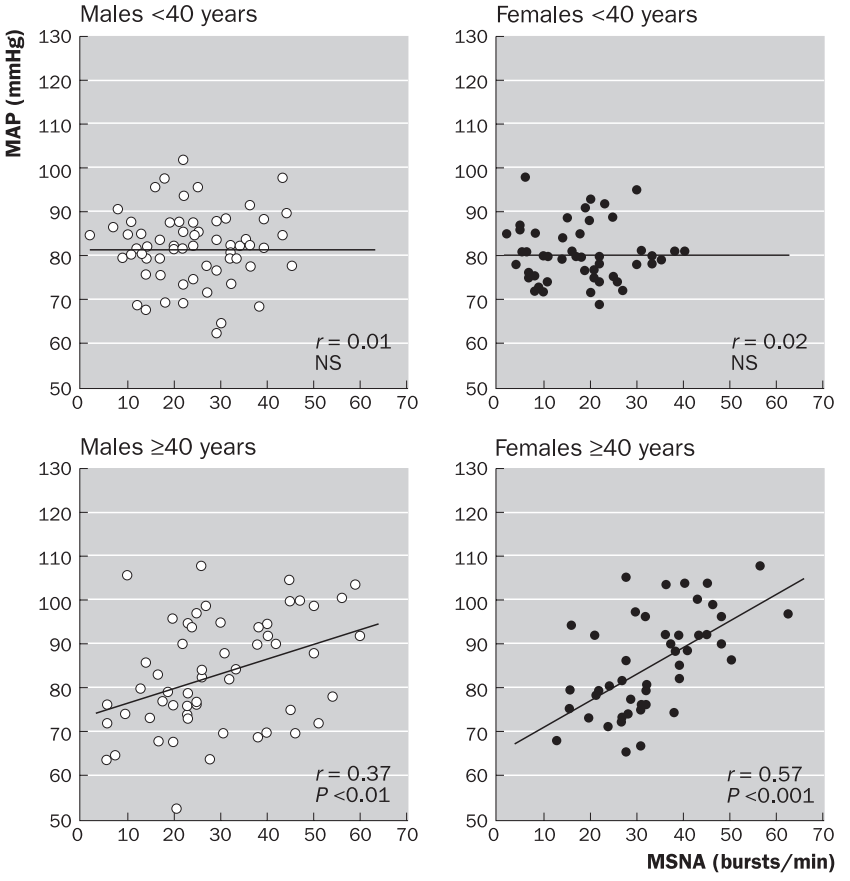

Fig. 13.8 Relationship between muscle sympathetic nerve activity (MSNA) and MAP according to gender and age. MSNA correlated with MAP in older subjects, and especially in females. Source: Narkiewicz *et al*. (2005).

development of hypertension, and the lack of documentation of the hormonal status of the female participants. Menopausal status was documented by history only, and the conclusion that menopause does not explain the age-related increase in sympathetic traffic was based on a comparison of 16 women aged 40–56 years who classified themselves as post-menopausal versus 19 women in the same age group who were self-identified as pre-menopausal. The data would have been stronger if circulating oestrogen and follicle-stimulating hormone levels had been measured and if pre- and post-menopausal women had been age-matched to eliminate the confounding variable of age-related increases in MSNA. Clearly, natural menopause is not an abrupt event, and there was probably a gradient rather than a dichotomy in circulating oestrogen levels between pre- and post-menopausal women, making it more difficult

to assess the impact of menopause on MSNA. It is clear from other studies that the relatively small fluctuations in circulating oestradiol levels that occur in the course of the normal menstrual cycle affect sympathetic nerve activity, so it would be important to document menopause with hormone measurements and to analyse the MSNA data with respect to hormone levels and time since menopause before drawing firm conclusions on the effects of menopause on sympathetic traffic and the sympathetic neural control of blood pressure. Prospective studies and studies including women treated with ERT and HRT would be useful in this regard. Finally, the intriguing finding that MSNA is related to blood pressure only in persons over age 40 years is totally unexplained by the data and merits further investigation.

Transdermal versus oral estrogen therapy in post-menopausal smokers: hemodynamic and endothelial effects

Girdler SS, Hinderliter AL, Wells EC, Sherwood A, Grewen KM, Light KC. *Obstet Gynecol* 2004; **103**: 169–80

BACKGROUND. Previous studies have shown that cigarette smoking is anti-oestrogenic. Compared with non-smokers, smokers have lower levels of circulating oestrogen after oral HRT, fail to show significant reduction in the risk of hip fracture, and experience less improvement in bone density, lipids, blood pressure and vascular resistance in response to HRT |36,37|. There is evidence that the mechanism of this anti-oestrogenic effect involves smoking-induced alterations in the hepatic metabolism of oestrogen, shifting the metabolic pathways of oestrogen to inactive metabolites |38|. Transdermal oestrogen does not undergo hepatic metabolism, so would be expected to retain its blood pressure-reducing, vasodilator and sympatholytic properties in post-menopausal smokers. This randomized, double-blind, placebo-controlled study tested this hypothesis in 82 healthy post-menopausal smokers who were treated with either transdermal 17β-oestradiol (0.05 mg/day) plus MPA (2.5 mg/day), oral CEE (0.625 mg/day) plus MPA (2.5 mg/day) or placebo. Blood pressure, cardiac performance (by impedance cardiography), isoproterenol sensitivity, brachial artery reactivity and plasma norepinephrine were measured at rest and during behavioural stress. Treatment-related reductions in blood pressure, total peripheral resistance and circulating norepinephrine levels and increases in endothelial-dependent vasodilation and vascular β_2-adrenoreceptor responsiveness were much more consistent and pronounced in the transdermal oestrogen group (Fig. 13.9), and serum oestradiol and oestrone concentrations were lower and more reflective of pre-menopausal values during transdermal oestrogen treatment compared with CEE.

INTERPRETATION. Transdermal oestrogen treatment is associated with greater reductions in indices of vascular sympathetic tone than is oral conjugated oestrogen in healthy post-menopausal smokers, a group at high risk of CVD and osteoporosis. Thus, transdermal oestrogen may have a more favourable risk/benefit ratio for this patient group.

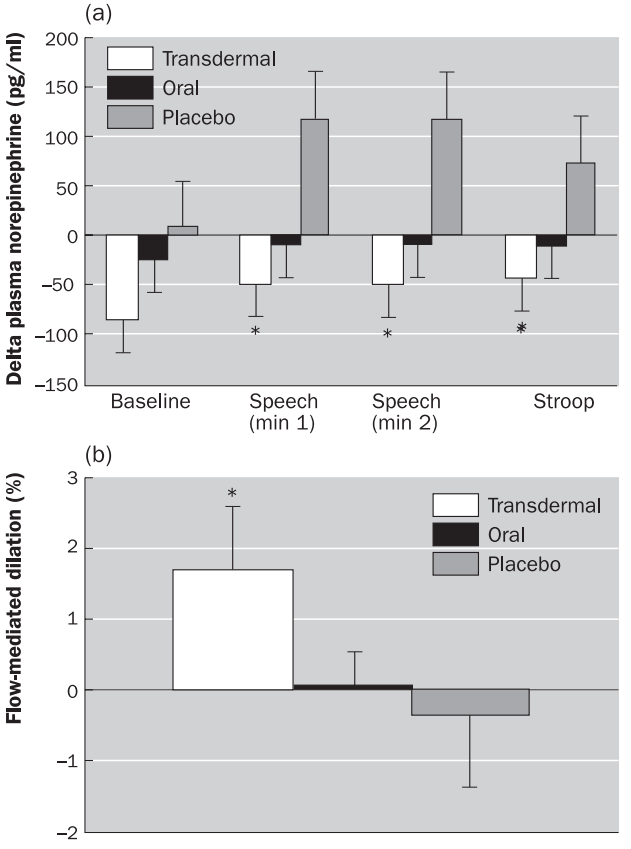

Fig. 13.9 Change from pre-treatment levels (post-treatment–pre-treatment) in plasma norepinephrine (a) and flow-mediated dilation of the brachial artery (b) in women randomly assigned to transdermal oestrogen, oral CEE or placebo. Source: Girdler *et al*. (2004).

Comment

This study documents consistent reductions in blood pressure, peripheral vascular resistance and stress-induced plasma norepinephrine levels, along with endothelium-dependent vasodilation and vascular β_2-receptor reaction in response to transdermal 17β-oestradiol, but not oral CEE. These alterations in sympathetic tone and vascular reactivity in response to stress may have long-term clinical significance in that vascular responses to laboratory stressors have been shown to predict future development of hypertension, CHD and left ventricular hypertrophy and dysfunction. Importantly, the haemodynamic benefits of transdermal oestradiol were realized in a relatively young (average age 53, 10 years younger than women in WHI at enrolment) cohort of women in whom plasma oestrogen levels were minimally elevated (two times

pre-treatment levels) and in a profile similar to pre-menopausal women. Oral CEE resulted in 4-fold elevations in plasma oestriol and oestrone levels and was not associated with haemodynamic benefit. Limitations of this study include small patient numbers and a short duration of treatment (6 months). Clearly, longer-term studies with CVD outcomes, or at least surrogate measures of vascular structure and function, as in the KEEPS and ELITE trials |**17,18**|, are needed to test the benefits of transdermal oestradiol in younger post-menopausal women.

Renal mechanisms

Female sex hormones, salt, and blood pressure regulation

Pechère-Bertschi A, Burnier M. *Am J Hypertens* 2004; **17**: 994–1001

Background. This article reviews evidence that effects of sex hormones on the kidney contribute to gender differences in blood pressure regulation in humans and in animal models. It focuses on differences in responses to dietary salt in pre- versus post-menopausal women and on the influence of endogenous and exogenous female sex hormones on renal haemodynamics and tubular segmental sodium handling. The authors' original data demonstrate that blood pressure in young normotensive women is insensitive to dietary salt, even in the presence of oral contraceptives (Fig. 13.10).

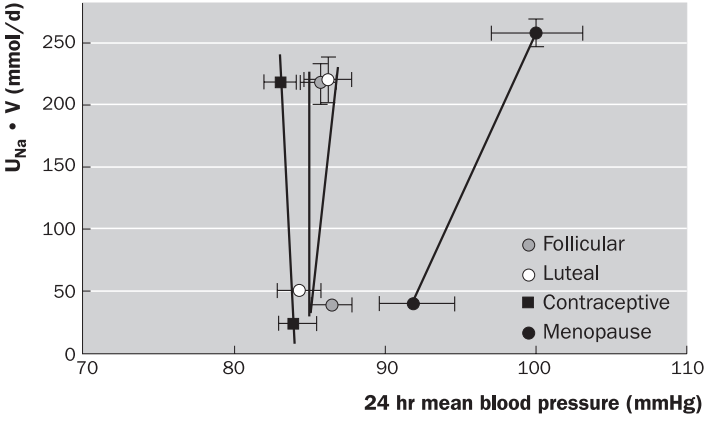

Fig. 13.10 Pressure–natriuresis relationship in normotensive women during the normal menstrual cycle, during use of oral contraceptives, and after menopause. All women randomly received a diet low in sodium (40 mmol Na/day) and high sodium (250 mmol Na/day) for 1 week. Blood pressure was measured over 24 h using ambulatory blood pressure monitoring. Source: Pechère-Bertschi and Burnier (2004).

Thus, the pressure–natriuresis curve is steep in young women during all phases of the menstrual cycle and during oral contraceptive use. In contrast, the pressure–natriuresis curve of post-menopausal women is shifted to the right, indicating that blood pressure becomes salt-sensitive after the menopause. The inability of the kidney of post-menopausal women to handle a salt load is reflected in exaggerated weight gain when going from low to high salt intake. The mechanism of the post-menopausal increase in salt sensitivity is unclear.

Interpretation. The emergence of salt sensitivity of blood pressure after the menopause, so elegantly demonstrated in this study, could be related to ageing changes in the kidney as well as to modification of the sex hormone profile and response mechanisms, i.e. ER expression and signalling.

Comment

Salt-sensitive hypertension in post-menopausal women is highly prevalent and probably contributes to increased CVD and chronic kidney disease in older women. Further study is needed to assess the impact of ERT and HRT on renal salt handling and the salt sensitivity of blood pressure in post-menopausal women. In any event, this mechanism supports the use of diuretics in the treatment of hypertension in post-menopausal women, as recommended by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) of the United States |**39**|.

Endothelial function

The effect of hormone replacement therapy on endothelial function in post-menopausal women with hypertension

Czarnecka D, Kawecka-Jaszcz K, Olszanecka A, *et al*. *Med Sci Monit* 2004; **10**: CR55–61

Background. Endothelial dysfunction has been implicated in the pathophysiology of CVD and hypertension. Previous studies have shown that transdermal ERT restores plasma NO to pre-menopausal levels and improves endothelial function in healthy normotensive post-menopausal women. This study assessed endothelial function, indexed by plasma nitrate and nitrite (NOx) levels, in women with natural menopause and stage 1 hypertension receiving antihypertensive treatment plus HRT with transdermal 17β-oestradiol plus norethisterone acetate ($n = 40$) or no treatment ($n = 36$). Treatment assignment was by patient preference. There were marked individual differences in NOx levels in response to HRT: approximately 50% of the HRT group had significantly increased levels at 3 and 12 months of treatment compared with baseline; NOx did not change over time in the untreated group. The

increased NOx levels in responders were associated with decreased low-density lipoprotein cholesterol. The 24-hour ambulatory blood pressure did not differ from baseline in either group.

INTERPRETATION. Improvement in endothelial function, reflected in increased circulating NOx levels, occurred in only half of the post-menopausal women receiving HRT. This variable response rate suggests that beneficial cardiovascular effects of HRT are not uniformly realized in hypertensive post-menopausal women on treatment for their blood pressure.

Comment

Despite its obvious design flaws (unblinded, non-randomized, lacking haemodynamic assessment of endothelial function, uncontrolled for variations in dietary NOx, reliance on plasma NOx as the measure of endogenous NO generation), this study makes the important point that blood pressure in post-menopausal women with essential hypertension on conventional antihypertensive therapy is not affected by HRT. The variable responses of the marker of oxidative stress (NOx) to HRT in this population remain unexplained. The authors' speculation that this may be due to senescence of ERs and their post-receptor signalling pathways in the absence of endogenous oestrogen is intriguing and deserves experimental testing.

C-reactive protein

Distribution and correlates of C-reactive protein concentrations among adult US women

Ford ES, Giles WH, Mokdad AH, Myers GL. *Clin Chem* 2004; **50**: 574–81

BACKGROUND. Plasma C-reactive protein (CRP) is accepted as an independent risk factor for CVD in women. This study used data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 to determine the distribution of CRP concentration among adult women representative of the US population; to estimate proportions and numbers of adult women at high risk of CVD based on their CRP concentrations; and to examine correlates of CRP concentrations among women. Mean CRP concentration was increased significantly among current HRT users compared with never users ($P < 0.001$). CRP was also significantly related to a variety of CVD risk factors, including SBP, total cholesterol, triglycerides and waist circumference.

INTERPRETATION. This study, using data from 2205 adult women examined in NHANES 1999–2000, confirmed previous observations that HRT use is associated with increased CRP levels.

Comment

Although not discussed in this paper, the form of HRT used by women surveyed in NHANES 1999–2000 was undoubtedly oral CEE ± MPA, the same as the active

treatment used in the WHI and HERS trials. Other forms of HRT, e.g. transdermal 17β-oestradiol, appear not to elevate CRP levels. Whether this correlates with a reduction in CVD risk remains to be determined. Further, whether HRT-related increases in CRP play a pathogenic role in the excess CVD events seen in the outcome trials is also unknown. This question, as well as the more fundamental question of whether CRP is a cause or just a biomarker of increased CVD risk, is in urgent need of further investigation.

Plasma C-reactive protein is not elevated in physically active post-menopausal women taking hormone replacement therapy

Stauffer BL, Hoetzer GL, Smith DT, DeSouza CA. *J Appl Physiol* 2004; **96**: 143–8

Background. Favourable effects of high levels of physical activity on plasma CRP concentration have been demonstrated in healthy middle-aged and older adults. This cross-sectional study examined the effect of habitual physical activity on the HRT-associated elevation of CRP in healthy post-menopausal women (65 HRT users, 22 endurance-trained and 43 sedentary; 49 non-users, 17 endurance-trained and 32 sedentary). While CRP levels were ~75% higher in sedentary HRT users versus sedentary non-users ($P < 0.01$), they were ~65% lower in both physically active groups, regardless of HRT use.

Interpretation. Physically active post-menopausal women have lower plasma CRP concentrations than sedentary women, and the HRT-related elevation in plasma CRP levels seen in sedentary women is not seen in physically active women. Regular physical activity can prevent the HRT-induced elevation in CRP.

Comment

HRT in this study consisted of oral CEE (0.25–2.5 mg/day) alone or combined with MPA (2.5 mg/day). Both regimens produced similar effects on plasma CRP, so the data were pooled. These HRT regimens had no effect on plasma concentrations of interleukin-6 (IL-6), a proinflammatory cytokine that is a powerful stimulant of hepatic production of CRP. Uncoupling of IL-6 and CRP expression in the setting of HRT administration suggests that HRT causes CRP elevation through a non-inflammatory mechanism, i.e. via a direct effect on the liver. WHI has shown us that CRP levels independently predict subsequent CHD events irrespective of HRT use |**40**|, but has left the clinical significance of HRT-related elevation in CRP unclear. This cross-sectional study, with its small numbers of physically active women, cannot answer questions about the ability of increased physical activity to counter the putative adverse effects of HRT on vascular health. Larger, prospective trials are needed for this purpose.

Natriuretic peptides

Effects of estrogen replacement therapy on natriuretic peptides and blood pressure

Karjalainen AH, Ruskoaho H, Vuolteenaho O, *et al*. *Maturitas* 2004; **47**: 201–8

Background. The natriuretic peptides have natriuretic and vasodilator activity and inhibit components of the RAAS. This study tested the hypothesis that ERT-induced changes in blood pressure may be mediated via activation of the natriuretic peptide system. Post-menopausal women (*n* = 79) aged 42–68 years with prior hysterectomy seeking HRT to relieve climacteric symptoms were randomized to receive either oestradiol valerate 2 mg/day orally or transdermal oestradiol 1 mg/day for 6 months. Both regimens resulted in reductions in blood pressure and increases in circulating immunoreactive N-terminal fragment of pro-atrial natriuretic peptide (NT-proANP) without altering plasma atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), aldosterone or renin levels.

Interpretation. Both oral and transdermal ERT activate the natriuretic peptide system, elevating circulating levels of NT-pro ANP. This could contribute to the lowering of blood pressure during ERT.

Comment

The novelty of this study is that it measured the N-terminal fragment of pro-atrial natriuretic peptide, which circulates at higher concentrations and with a longer half-life than ANP or BNP, and therefore is a more reliable index of natriuretic peptide activation, at the same time as components of the RAAS in healthy women after hysterectomy who were receiving oral or transdermal ERT. Blood pressure decreased significantly in response to both forms of ERT by mechanisms that are unclear, but may involve the natriuretic peptide system and its natriuretic/RAAS-suppressing effects. The authors raise the intriguing possibility that the absence of the uterus may contribute to the results observed, since hysterectomized women with ovarian preservation have been shown in at least one prior study to have higher blood pressure than age-matched women with intact uteri |**41**|. On the other hand, blood pressures during placebo treatment and blood pressure responses to ERT did not differ between women with and without intact uteri in WHI, ruling against the uterus as a determinant of blood pressure in post-menopausal women.

Mechanisms of hormone-induced blood pressure effects in animals

Animal models of post-menopausal hypertension

Age-related reduction in estrogen receptor-mediated mechanisms of vascular relaxation in female spontaneously hypertensive rats

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BACKGROUND. This study tested whether age-related increases in blood pressure in female spontaneously hypertensive rats are associated with reduced levels of oestrogen and ER expression and related attenuation of the vasorelaxant effects of endogenous oestrogen. Blood pressure and plasma oestradiol levels were reduced, but ERα and ERβ expression levels were only slightly lower in ageing (16-month-old) compared with young adult (12-week-old) rats. Phenylephrine caused greater contraction in endothelium-intact vascular strips from ageing rats than in strips from young adult rats, and oestrogen-induced relaxation of phenylephrine-contracted arteries and stimulation of vascular NOx production were attenuated in vessels from ageing rats. KCl-stimulated Ca^{2+} influx produced greater constriction in vascular strips from young adult rats; these effects were reduced in ageing rats.

INTERPRETATION. Ageing in female spontaneously hypertensive rats is associated with attenuation of ER-mediated NO production from endothelial cells and in the inhibitory effects of oestrogen on Ca^{2+} entry into vascular smooth muscle cells and the resulting vasoconstriction. The age-related decrease in ER-mediated vascular relaxation may help to explain the increase in blood pressure associated with ageing in female rats (and by extrapolation, in women).

Comment

This well-designed study demonstrates that both endothelium-dependent and endothelium-independent vascular relaxation in response to oestrogen treatment is attenuated in ageing female spontaneously hypertensive rats compared with young adult females. The former effect is related to a decrease in oestrogen-mediated activation of the endothelial NO–cGMP pathway; the latter is related to a reduction in the inhibitory effects of oestrogen on Ca^{2+} entry into vascular smooth muscle. The absence of a significant difference in ERα and ERβ expression in aged versus young adult rats suggests that the attenuated effects of oestrogen on vascular relaxation in aged animals are due to decreased activation of post-receptor mechanisms. Similar inactivation of ER signalling in post-menopausal women could explain the observed

increase in blood pressure and refractiveness of the vasculature to the vasorelaxant (and possibly vasoprotective) effects of ERT. As acknowledged by the authors, more detailed mechanistic studies of ER expression and signalling, as well as oestrogen-induced endothelial nitric oxide synthase (eNOS) activation and signalling, and of oestrogen effects on membrane Ca^{2+} and K^{+} channels in ageing cells and intact organisms (including women), are needed to evaluate the molecular/cellular basis of the ageing-related increases in vasoconstriction and blood pressure in females.

Conclusion

In the past year, publication of findings from the oestrogen-only arm of the WHI has stimulated a new round of discussion about the role of menopausal hormones in women's health. In contrast to the previously reported oestrogen plus progestin trial of WHI, there was no excess of CHD or invasive breast cancer with CEE treatment. In fact, there was an apparent reduction in breast cancer risk and a time trend in CHD occurrence that suggested a modest benefit with long-term CEE use. These findings point to a potential deleterious effect of the progestin MPA on the vasculature, as previously suggested by pre-clinical studies of hormonal modulation of the response to acute vascular injury. Subgroup analysis of results of the oestrogen-only arm of WHI by participant age at enrolment revealed a trend for more favourable effects of CEE on a variety of outcomes, including CHD, in younger women. This is consistent with the concept, suggested by both human and animal studies, that ageing and prolonged hormone deprivation may attenuate neurohormonal and vascular responses to oestrogen. Mechanistic studies of the effects of oestrogen on the RAAS, arterial stiffness, renal sodium handling, sympathetic nervous system activity and blood pressure/peripheral vascular resistance published in the past year have provided further evidence for this concept: favourable neurohormonal and vascular responses to exogenous oestrogen were observed in healthy women studied within a few years of menopause, but not in older women, particularly those with established vascular disease. The ongoing ELITE and KEEPS trials of ERT in younger perimenopausal women will provide valuable new information about the ability of oestrogen to provide vasoprotection to women with intact hormone response systems. Coupled with examination of the cellular and molecular effects of ageing on oestrogen receptors and their downstream signalling cascades, these studies will inform clinical decisions about the use of HRT in the growing population of older post-menopausal women, as well as enhance our fundamental understanding of the vascular biology of ageing in women.

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14

Stroke in patients with diabetes and hypertension

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Introduction

Stroke is a major public health problem and leads to increased morbidity and mortality. Modifiable risk factors for stroke include hypertension, diabetes, atrial fibrillation, dyslipidaemia, smoking and alcohol abuse. There are rapidly growing epidemics of diabetes and hypertension in the world, leading to substantial increases in cardiovascular disease and stroke. In this review we discuss the risk factors for stroke with emphasis on the diabetic and hypertensive population, highlighting the interventions that have been shown to decrease the risk of stroke in this patient population.

Stroke is the third most important cause of death in the US and is the leading cause of disability |**1–4**|. Epidemiological data indicate that there has recently been a levelling off of previous declines in stroke-related mortality and possibly an increase in the incidence of stroke |**1,4**|. Indeed, between 1988 and 1998 the total number of stroke deaths in the US rose by 5.3% |**1,2**|. These recent increases are most probably related to the increased amount of diabetes and the ageing of the US population |**1–4**|. These data suggest that better preventative measures need to be applied. Hypertension and diabetes are independent, modifiable stroke risk factors that are of increasing significance as our population ages and the prevalence of diabetes increases. This article reviews the issue of stroke in patients with diabetes and hypertension.

Modifiable stroke risk factors (hypertension and diabetes)

Hypertension, diabetes mellitus, smoking, dyslipidaemia, atrial fibrillation and sickle cell disease are well-documented risk factors for stroke |**1**| (Table 14.1). Although factors such as atrial fibrillation, hypercoagulability and hormone replacement therapy are relatively powerful risk factors for stroke, these risk factors will be discussed briefly since this review will focus on strategies to lessen the burden of stroke associated with hypertension and diabetes.

Table 14.1 Non-modifiable, potentially modifiable and modifiable risk factors for stroke

Non-modifiable	Modifiable
Age	Hypertension
Sex	Diabetes mellitus
Race/ethnicity	Smoking
Potentially modifiable	Atrial fibrillation
Poor nutrition	Hyperlipidaemia
Obesity	Alcohol abuse
Inactivity	Drug abuse (i.e. Is 'i.e.' (= that is) correct or should it be 'e.g.' (= for example)? cocaine)
Hyperhomocysteinaemia	Hormone replacement therapy
Hypercoagulability	
Increases in inflammation and oxidative stress	

Hypertension and stroke

Hypertension is a major risk factor for ischaemic stroke and intracerebral haemorrhage |**1–4**|. Elevated systolic pressure is a direct, continuous and independent risk factor for stroke |**1–4**|. Isolated systolic hypertension is a particularly strong risk factor for stroke in the elderly and in those with type 2 diabetes |**5–8**|. Control of high blood pressure, especially systolic hypertension, has been clearly shown to reduce the risk of stroke in several prospective controlled trials |**8–14**|. A target blood pressure blood pressure of 130/80 mmHg is currently advocated for hypertensive diabetic patients with an increased risk of primary stroke |**15**|. Available data do not support a specific drug class for the prevention of primary stroke in hypertensive diabetic patients |**13,14**|; rather, tight control of blood pressure is emphasized. This generally entails multidrug therapy. Clinical trial findings support the use of any of a number of drug classes (or combinations of them), including thiazide-type diuretics and/or β-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers, as components of a treatment plan |**12**|.

Diabetes and stroke

The crude incidence of stroke among patients with diabetes is three times greater than that in the general population |**16–22**|, with especially high-risk rates reported in Sweden |**16**| and the south-eastern US |**22**|. In the Framingham Heart Study, patients with glucose intolerance had double the risk of brain infarction compared with non-diabetics, and the relative risk is greater in diabetic women compared with men |**20**|. The relative risk of stroke in persons with type 2 diabetes reaches a maximum in the 40- to 60-year-old group. Diabetic women constitute a greater proportion of patients with stroke than non-diabetic women |**21,22**|.

Patients presenting with stroke are more likely to have undiagnosed type 2 diabetes |**23,24**|. Furthermore, patients with glucose intolerance, elevated glucose following

oral glucose tolerance testing performed before the stroke or 3 months after the stroke, also have a higher prevalence of stroke |**24**|. In the prospective Honolulu Heart Study, the prevalence of thromboembolic but not haemorrhagic stroke was increased in individuals with serum glucose levels above 120 mg/dl 1 h after a 50 g glucose load |**19**|. Proteinuria appears to be a risk factor for stroke in people with impaired glucose tolerance as well as those with diabetes |**19**|. Finally, African-Americans have an almost 2.4-fold increased incidence and Caribbean Hispanics have an almost 2-fold increased incidence of stroke, perhaps reflecting the greater propensity to both diabetes and hypertension in these groups |**1,4**|.

Increased morbidity, mortality and disability from stroke in diabetic patients

There is an increase in both short-term and long-term mortality in the diabetic patient who has had a stroke |**23,26**|. A Finnish study evaluated the survival of diabetic patients compared with a group of randomly selected non-diabetic patients and a group of age and sex-matched non-diabetic controls with a stroke |**27**|. After 5 years, only 20% of the diabetic persons were alive compared with 40% of the control groups. Twenty per cent of the diabetic patients who had a stroke were first diagnosed when they presented with their stroke |**27**|. In part, the increased mortality following stroke in diabetic patients is related to glucose levels at the time of hospital admission. In several studies the cutoff glycaemic level is 120 mg/dl |**26–29**|. A study from England showed that only in those patients with a persisting blood glucose concentration below 120 mg/dl did complete recovery from hemiparesis occur within the first month |**29**|. Another group |**26**| reported that, in diabetic patients less than 65 years of age, 70% of those with a presenting glucose level of 120 mg/dl or less but only 30% with a glucose concentration greater than 120 mg/dl were able to return to work eventually.

Management of stroke risk factors in diabetic patients

Hyperglycaemia

As noted, acute hyperglycaemia has been shown to affect stroke outcome adversely in both diabetic and non-diabetic patients |**30,31**|. Hyperglycaemia increases lactate production by the brain and facilitates conversion of hypoperfused at-risk tissue into areas of infarction |**31**|. Furthermore, hyperglycaemia, defined as a glucose level above 140 mg/dl, reduces the beneficial effect of early restoration of blood flow, leading to a worse outcome despite plasminogen activator-induced recanalization |**32**|. These findings, however, support the need for randomized controlled trials of aggressive glycaemic control in acute stroke. Intensive glycaemic control has not yet been

shown to have a significant effect on stroke reduction in the diabetic population |**33**|. However, in both type 1 and type 2 diabetic patients intensive glycaemic control is recommended in order to reduce the risk of microvascular complications of the disease.

Insulin resistance may be an independent risk factor for stroke in type 2 diabetic patients, particularly those with lacunar and atherothrombotic infarcts. This has been shown in a study of 94 stroke cases on the basis of brain imaging findings |**34**|. On the other hand, another study, of 304 Japanese subjects, showed no association between insulin resistance and the risk of stroke |**35**|. Therefore, further studies are needed to confirm insulin resistance as a risk factor for stroke.

Hypertension associated with diabetes

Randomized controlled trials with large diabetic populations |**13,37–42**| include the UK Prospective Diabetes Study (UKPDS) |**13**|, the Systolic Hypertension in Europe (Syst-Eur) |**37**|, Hypertension Optimal Treatment (HOT) trial |**38**|, the MICRO-HOPE substudy of the Heart Outcome prevention Evaluation (HOPE) study |**39**|, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) |**40**|, the International Verapamil SR-Trandopril study (INVEST) |**41**| and the Valsartan Antihypertensive Long-Term Use Evaluation randomized trial (VALUE) |**42**|. These trials have demonstrated that adequate blood pressure control in patients with diabetes reduces the risk of cardiovascular disease (CVD), particularly stroke. For example, in the UKPDS, for combined fatal and non-fatal stroke, tight blood pressure control (mean achieved, 144/82 mmHg) resulted in a reduction of 44% in relative risk compared with less aggressive control (mean blood pressure achieved, 154/87 mmHg) |**12**|. In the Syst-Eur trial, 492 patients randomized to treatment with a nitrendipine-based antihypertensive regimen were diabetic. Those with diabetes achieved a 26.6% reduction in stroke compared with 12.3% in the non-diabetic cohort. Blood pressure reduction was similar in the two groups |**36**|. The ALLHAT, VALUE and INVEST trials underscored the importance of adequate control of systolic blood pressure: groups that achieved better blood pressure control had a decreased risk of stroke |**39–41**|.

In the MICRO-HOPE subanalysis of the HOPE study, involving 3577 diabetic patients, the risk of stroke was reduced by 33% with the use of a regimen based on the ACE inhibitor ramipril compared with other therapy |**39**|. However, it is important to note that in this study there has been better control of blood pressure in the ramipril arm compared with placebo |**38**|. ACE-inhibitor-based therapy has also been shown to be effective in the secondary prevention of stroke in both hypertensive and non-hypertensive subjects. In the Perindopril Protection Against Stroke Study (PROGRESS), combination therapy with perindopril and indapamide reduced blood pressure by 12/5 mmHg and stroke risk by 43% |**43**|. Again in this study with ACE-inhibitor-based therapy, the contribution of indapamide to blood pressure reduction should be considered. Nevertheless, these data on ACE inhibitors underscore the importance of treatment strategies targeting the renin–angiotensin–aldosterone system, which plays a role in the aetiology of CVD and stroke |**43**|. The incidence of

stroke in the ALLHAT study was 15% greater with the ACE inhibitor lisinopril than with a thiazide diuretic. In a comparison of lisinopril with chlorthalidone, lisinopril had higher 6-year rates of stroke (6.3 vs 5.6%; relative risk 1.15, 95% confidence interval 1.02–1.30) |**39**|. However, blood pressure reduction in the lisinopril group was less than with chlorthalidone or amlodipine, especially in African-American patients |**39**|. Observations made in the VALUE trial indicate that more strokes occurred early because of poorer control of systolic blood pressure with the angiotensin receptor blocker valsartan than with amlodipine |**41**|. The amlodipine group had blood pressures that were 4.0/2.1 mmHg lower at 1 month, 2.0/1.5 mmHg lower at 1 year and 1.8/1.5 mmHg lower at the conclusion of the study compared with valsartan group |**41**|.

The role of angiotensin receptor blockers in the prevention of stroke in patients with diabetes, however, is not clear. In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study |**11**| there was a 25% reduction in stroke in patients treated with a regimen based on the angiotensin receptor blocker losartan compared with β-blocker therapy with atenolol plus other treatment. However, in the subanalysis of the 1195 diabetic patients with hypertension included in the study, losartan reduced the combined CVD mortality by 24% but stroke and myocardial infarctions occurred in small numbers that did not reach statistical significance |**11**|.

These data on hypertension support the recent guidelines of the American Diabetes Association (ADA) |**15**| and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) |**44**|, recommending a blood pressure goal of $<$130/80 mmHg in diabetic patients. These guidelines also involve lifestyle modifications, such as stopping smoking and the avoidance of excess alcohol and exercise. Such interventions may be beneficial in reducing the risk of stroke in diabetic patients |**37,45**|.

Dyslipidaemia and lipid-lowering therapy

Most of the data on cholesterol-lowering and cerebrovascular events in patients with diabetes have been derived from studies of patients with documented coronary heart disease |**46–48**|. The Scandinavian Simvastatin Survival Study (4S) was the first to show exclusively that lowering lipids with statins reduces the incidence of stroke |**46**|. Significant reduction of the incidence of stroke with lipid-lowering therapy has been shown only in trials using statins or gemfibrozil, and the degree of cholesterol reduction is related to the absolute reduction in the risk of stroke. However, lipid-lowering therapy with statins has also been shown to be effective in stroke prevention in patients with impaired fasting glucose |**49**|. A recent analysis of 1077 diabetic patients and 940 patients with impaired fasting glucose among 9014 with coronary heart disease in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID trial) showed that lipid-lowering therapy with statins prevents CVD, including stroke, in patients with diabetes or impaired fasting glucose and established coronary heart disease |**50**|.

Statins have also been shown to be effective in the primary prevention of stroke in people with diabetes |**51**|. In a study of 2838 diabetic patients without evidence of

CVD who were randomized to receive atorvastatin 10 mg per day versus placebo, with a stroke as a primary end-point (together with coronary events and coronary revascularizations), statin therapy was effective in the primary prevention of stroke. Stroke was decreased by 48% in the atorvastatin group compared with placebo |**50**|. The study was terminated 2 years early because of the substantial benefits of statins with respect to CVD events |**51**|. The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) is another trial designed to examine the effects of statin on the primary prevention of CVD in hypertensive patients, and has also showed a substantial decrease (27%) in fatal and non-fatal strokes in the treatment arm |**52**|. This study was also terminated prematurely, with a median follow up of 3.3 years, because of the substantial benefits with atorvastatin in reducing CVD events and stroke |**52**|. Diabetes in this study was pre-specified for subgroup analysis. However, statin therapy in the diabetic subgroup in this trial did not show significant benefits |**52**|. Although these results were surprising, careful examination of the trial design may explain these unexpected results, which are probably due to inadequate power, early termination of the trial and the higher rate of statin drop-ins in the diabetic cohort. In fact, 14% of the diabetic patients on placebo received statin therapy compared with only 8% of the non-diabetic population |**52**|.

Accumulating evidence also indicates that lowering the level of low-density lipoprotein (LDL) cholesterol even within the normal range, i.e. less than 100 mg/dl, provides protection against CVD and stroke |**50,52**|. The Heart Protection Study (HPS), a randomized placebo-controlled trial with simvastatin in 5963 people with diabetes, provided direct evidence that, in diabetic patients, lowering of LDL-cholesterol is beneficial, even in the absence of high cholesterol, in preventing CVD, including stroke |**53**|. The authors of this study concluded that statin therapy should be considered routinely for all diabetic patients, irrespective of their initial cholesterol concentrations |**53**|. This highlights the beneficial effects of statins, above and beyond lipid-lowering, which include anti-inflammatory and anti-thrombotic effects and the positive effects of statins on endothelial function |**53**|.

In the HPS, diabetic patients with CVD, including stroke, were at a very high risk of future CVD events |**52**|. These patients had the greatest benefit in terms of absolute risk reduction with statin therapy, regardless of their baseline LDL levels. On the basis of these results and the results from other recently published randomized controlled trials, the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII), which recommends lowering LDL-cholesterol below 100 mg/dl in people with diabetes (Table 14.2) |**55**|, has recently revised its recommendations to an optional therapeutic goal of LDL-cholesterol below 70 mg/dl for patients with diabetes and prior stroke |**55**|. On the other hand, for diabetic patients without prior stroke or other evidence of CVD, the revised NCEP-ATPIII recommended goal is LDL-cholesterol less than 100 mg/dl.

Furthermore, non-high-density lipoprotein (HDL) cholesterol is a secondary target of therapy, with a goal 30 mg/dl higher than the identified LDL-cholesterol goal, in patients with triglycerides above 200 mg/dl |**54,55**|.

Table 14.2 Modifiable risk factors for stroke in diabetic patients and treatment recommendations

Modifiable risk factors	Evidence	Recommendations
Hypertension (especially systolic elevation)	RCT in diabetic patients	Blood pressure control to <130/80 mmHg
Dyslipidaemia	Subanalysis of diabetic cohort in RCT	LDL-cholesterol <100 mg/dl
In diabetic patients without prior stroke		
LDL-cholesterol <70 mg/dl, in diabetic patients with prior stroke*		
Dysglycaemia	Inconclusive	Glycaemic control to A1c <7.0%
Hypercoagulability and increased platelet aggregation	Inconclusive	Antiplatelet therapy
Atrial fibrillation	RCT in diabetic patients and meta-analysis of RCTs that included diabetics	Anticoagulation
Smoking	Epidemiological and observational data in RCT; smoking was not a significant risk factor in diabetic patients	Smoking cessation
Excessive alcohol intake	Inconclusive; moderate intake might be protective	Moderation to <2 drinks/day
Asymptomatic carotid artery disease	Not well established for diabetic patients	
Diabetes might be a risk factor for CEA	CEA, reduction of IMT (ACE inhibitors, statins)	

LDL, low-density lipoprotein; ACE I, angiotensin-converting enzyme inhibitors; HMG-CoA, hydroxymethyl glutaryl Co-A; CEA, carotid endarterectomy; RCT, randomized controlled trials; IMT, intima–media thickness; A1c, haemoglobin A1c.
*As recommended in the revised National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII) |**54,55**|.

Antiplatelet therapy

The Antithrombotic Trialist's Collaboration, analysing the results of 278 studies involving 135 000 patients, including diabetics, has shown that aspirin (or another oral antiplatelet drug) is protective in ischaemic stroke |**57**|. However, in the sub-analysis of the diabetic patients in the HOT trial |**38**| there was no effect on the incidence of stroke with the use of aspirin, although aspirin in this trial reduced major cardiovascular events by 15% ($P = 0.03$) and all myocardial infarction by 36% ($P = 0.002$) |**38**|. The ADA recommends aspirin therapy for adults with diabetes unless contraindicated |**57**|.

Atrial fibrillation

Atrial fibrillation is a powerful risk factor for stroke, particularly in patients with diabetes |**58**|. In the UKPDS cohort, the risk of stroke was eight times higher in patients with atrial fibrillation than in those with normal rhythms |**6,7**|. In a multivariate analysis of six major clinical trials of patients with atrial fibrillation, diabetes was found to be an independent risk factor for stroke, together with hypertension, increased age and a previous history of transient ischaemic attacks. Any of these risk factors conferred an annual risk of stroke of 4% |**58**|. This meta-analysis revealed a 64% risk reduction of stroke risk with warfarin, compared with placebo |**58**|. Furthermore, diabetic patients with atrial fibrillation have additional risk factors for stroke or embolism, and treatment with oral anticoagulation is therefore recommended |**57**|.

Smoking

Smoking causes reduced compliance and distensibility of the blood vessels and increases fibrinogen, haematocrit and platelet aggregation |**45**|. Epidemiological and observational data indicate that smoking is an independent risk factor for stroke. For example, a meta-analysis of 22 studies indicates that there is a doubling of the risk of stroke associated with smoking |**60**|. Prospective data from the Framingham Heart Study confirm the substantial increase in stroke among smokers compared with non-smokers after adjusting for age, sex, blood pressure, diabetes and heart disease |**61**|. Furthermore, the study also showed that the risk of stroke decreased significantly after 2 years and was at the level of non-smokers 5 years after cessation of cigarette smoking |**60**|. However, it is important to note that in the UKPDS |**6,7**| smoking was not a risk factor for stroke in the diabetic cohort. Furthermore, there are no studies on smoking cessation and the reduction in the risk of stroke in the diabetic population. Both the ADA |**61**| and the American Heart Association |**2**| recommend complete cessation of smoking in order to decrease the risk of stroke.

Asymptomatic carotid artery disease

The beneficial effects of carotid endarterectomy for selected patients with high-grade stenosis (reduction in diameter by >60%) of the external carotid artery have been shown in several randomized controlled trials |**1**|. Small reports in diabetic patients indicate that the procedure can be performed in diabetic patients, with excellent peri-

operative morbidity and mortality rates and late stroke-free survival rates comparable to those in non-diabetics. However, other studies have documented higher 30-day and 1-year mortality rates after carotid endarterectomy in patients with diabetes compared with non-diabetic persons. This is mainly due to increased cardiac complications |**62–64**|.

Finally, it is important to note that the benefit of carotid endarterectomy in the setting of asymptomatic carotid artery stenosis is highly dependent on the surgical risk. The American Heart Association recommends that carotid endarterectomy be considered in patients with high-grade stenosis performed by a surgeon with $<3\%$ morbidity/mortality rate |**1**|. There are no specific guidelines on the use of carotid endarterectomy in diabetic patients. Medications that have been shown to reduce atherosclerosis and intima–media thickness, such as ACE inhibitors |**38,43**| and statins |**54**|. might be particularly beneficial in diabetic patients who are also high-risk surgical candidates |**65**|.

Conclusion

Stroke is a major public health problem and is a leading cause of morbidity and mortality. In the US, stroke is the third most important cause of death. Hypertensive diabetic patients are at a substantially increased risk of primary and secondary strokes. There are non-modifiable, potentially modifiable and modifiable risk factors for stroke. In the diabetic hypertensive population, among the most important modifiable risk factors is elevated blood pressure, particularly systolic elevation. Lowering the blood pressure to a target below 130/80 mmHg is strongly recommended for the primary and secondary prevention of strokes. Lowering LDL-cholesterol below 100 mg/dl in diabetic patients without prior stroke and below 70 mg/dl in stroke patients with diabetes is also currently recommended. These measures are also important for the control of cardiovascular risk in these highly susceptible populations. For primary stroke prevention in this population, randomized controlled trials have also shown benefit in also treating atrial fibrillation and asymptomatic carotid disease. Observational and case–control studies have supported the treatment of hyperglycaemia, the use of anticoagulation and smoking cessation for the primary prevention of stroke. Further studies are needed to ascertain the role of intensive glycaemic control and the use of anti-inflammatory agents, anticoagulation treatment and smoking cessation in reducing stroke in patients with diabetes.

Acknowledgement

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List of abbreviations

AASK	African-American Study of Kidney Disease and Hypertension
ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACTION	Actinomycin eluting stent improves outcomes by reducing neointimal hyperplasia: a coronary disease trial investigating outcome with nifedipine GITS
AER	albumin excretion rate
AIPRI	Angiotensin-converting enzyme Inhibition in Progressive Renal Insufficiency
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMAZE	A multicentre trial using Atacand®-Zestril®* versus Zestril to evaluate the effects on lowering blood pressure [*Atacand as add-on therapy with Zestril]
ANBP2	Second Australian National Blood Pressure study
ANP	atrial natriuretic peptide
ARB	angiotensin receptor blocker
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
AT_1	angiotensin II type 1
ATP3	Adult Treatment Panel III
baPWV	brachial–ankle pulse wave velocity
BENEDICT	Bergamo Nephrologic Diabetes Complications Trial
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CALM	candesartan and lisinopril microalbuminuria
CAPPP	Captopril Prevention Project
CCB	calcium channel blocker
CEE	conjugated equine oestrogen
cGMP	N1-hydroxy-N2-[(4-methoxyphenyl)sulfonyl]-N2-(pyridin-3-ylmethyl)-D-valinamide
CHARM	Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity program
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CL	confidence limit
cM	centimorgan
CONVINCE	Controlled ONset Verapamil INvestigation of Cardiovascular End-points
COOPERATE	Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease
CRP	C-reactive protein
CTA	computed tomographic angiography
CVD	cardiovascular disease
CYMA3	cardiomyopathy associated 3 gene
DCA	dihidropyridine calcium antagonist
DETAIL	Diabetics Exposed to

DETAIL	Diabetics Exposed to Telmisartan and Enalapril trial
DBP	diastolic blood pressure
DREAM	Diabetes REduction Approaches with ramipril and rosiglitazone Medications
DRSP	drospirenone
DRSP/E2	drospirenone with 17-oestradiol
d/s	diastolic/systolic
ECG	electrocardiography
eGFR	estimated glomerular filtration rate
ELITE	Early versus Late Intervention Trial with Estradiol
ELVERA	Effects of amlodipine and lisinopril on left ventricular mass and diastolic function (E/A Ratio)
eNOS	endothelial nitric oxide synthase
ER	oestrogen receptor
ERA	Estrogen Replacement and Atherosclerosis
ERT	oestrogen replacement therapy
ESH/ESC	European Society of Hypertension/European Society of Cardiology
ESRD	end-stage renal disease
EUROPA	EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease
FMD	flow-mediated dilatation
GenNet	Genealogy Network
GENOA	Genetic Epidemiology Network of Atherosclerosis
GFR	glomerular filtration rate
GITS	gastrointestinal therapeutic system
HDL	high-density lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HERS	Heart and Estrogen/Progestin Replacement Study
20-HETE	20-hydrosyeicosatetranoic acid
HOMA	Homeostasis Model Assessment
HOPE	Heart Outcomes Prevention Evaluation
HPLC	high-performance liquid chromatography
HR	hazard ratio
HRT	hormone replacement therapy
hs-CRP	high sensitivity C-reactive protein
HyperGEN	Hypertension Genetic Epidemiology Network
IDNT	Irbesartan Diabetic Neuropathy Trial
IL-6	interleukin-6
INSIGHT	International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment
INVEST	International Verapamil SR/Trandolapril
IRMA	IRbesartan MicroAlbuminuria trial
JNC	Joint National Committee
K/DOQI	Kidney Disease Quality Initiative
KEEPS	Kronos Early Estrogen Prevention Study
LBNP	lower body negative pressure
LDL	low-density lipoprotein
LIFE	Losartan Intervention For End-point reduction in hypertension (study)
L-NMMA	*NG*-monomethyl-*L*-arginine
lod	log of the odds
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
MAP	mean arterial pressure
MICRO-HOPE	Microvascular Heart Outcomes Prevention Evaluation
MMD	mean minimum diameter
MPA	medroxyprogesterone acetate

MRT	magnetic resonance tomography
MSNA	muscle sympathetic nerve activity
NCCT	NaCl cotransporter
NCEP	National Cholesterol Education Panel
NDCA	non-dihidropyridine calcium antagonist
NHANES	National Health and Nutrition Examination Survey
NHLBI-FBPP	National Heart, Lung and Blood Institute–Family Blood Pressure Program
NIDDM	non-insulin dependent diabetes mellitus
NO	nitric oxide
NOx	nitrate and nitrite
NT-proANP	N-terminal fragment of pro-ANP
OBP	office blood pressure
PAH	para aminohippurate
PEACE	Prevention of Events with Angtiotensin-Converting Enzyme Inhibition
PHAII	pseudohypoaldosteronism type II
PHYLLIS	Plaque Hypertension Lipid-Lowering Italian Study
PREVEND	Prevention of Renal and Vascular End-stage Disease
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PWV	pulse-wave velocity
RAAS	renin–angiotensin–aldosterone system
REIN	Ramipril Efficacy In Nephropathy
RENAAL	Reduction of End-points in NIDDM with the Angiotensin II Antagonist Losartan
RI	resistance index
ROMK	rectifying-K^+ channel
RUTH	Raloxifene Use for the Heart study
RWTT	reflected wave transit time
SAGE	serial analysis of the gene expression
SAP	systolic arterial pressure
SAPPHIRe	Stanford Asian Pacific Program In Hypertension and Insulin Resistance
SBP	systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SDB	sleep-disordered breathing
SEP	systolic ejection period
SERM	selective oestrogen receptor modulator
SHEP	Systolic Hypertension in the Elderly Program
SHR	spontaneous hypertensive rate
SOLVD	Studies of Left Ventricular Dysfunction
STOP-2	Swedish Trial in Old Patients with hypertension-2
TIA	transient ischaemic attack
TK	tissue kallikrein
TOMHS	Treatment of Mild Hypertension Study
TRACE	Trandolapril Cardiac Evaluation Study
UACR	urinary albumin/creatinine ratio
UKPDS	United Kingdom Prospective Diabetes Study
VALUE	Valsartan Antihypertensive Long-term Use Evaluation Trial of Cardiovascular Events in Hypertension
VEGF	vascular endothelial growth factor
Vmax	maximum velocity
Vmin	minimum velocity
WHI	Women's Health Initiative
WHI-OS	Women's Health Initiative–Observational Study
WHO	World Health Organization

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Index of papers reviewed

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General index

B

E