Practical Case Studies in Hypertension Management
Series Editor: Giuliano Tocci

Agostino Virdis

Hypertension and Comorbidities

Springer

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The aim of the book series "Practical Case Studies in Hypertension Management" is to provide physicians who treat hypertensive patients having different cardiovascular risk profiles with an easy-to-access tool that will enhance their clinical practice, improve average blood pressure control, and reduce the incidence of major hypertension-related complications. To achieve these ambitious goals, each volume presents and discusses a set of paradigmatic clinical cases relating to different scenarios in hypertension. These cases will serve as a basis for analyzing best practice and highlight problems in implementing the recommendations contained in international guidelines regarding diagnosis and treatment.While the available guidelines have contributed significantly in improving the diagnostic process, cardiovascular risk stratification, and therapeutic management in patients with essential hypertension, they are of limited help to physicians in daily clinical practice when approaching individual patients with hypertension, and this is particularly true when choosing among different drug classes and molecules. By discussing exemplary clinical cases that may better represent clinical practice in a "real world" setting, this series will assist physicians in selecting the best diagnostic and therapeutic options.

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Foreword

Essential hypertension is a clinical condition in which established increase of blood pressure levels may promote development and progression of major cardiovascular, cerebrovascular, and renal complications, mostly including, myocardial atrial fibrillation, infarction, stroke, and congestive heart failure, as well as metabolic abnormalities, such as obesity and diabetes. All these comorbidities heavily impact the clinical management of hypertension, being often advocated to try to explain the relatively poor rates of blood pressure control recorded in very high-risk hypertensive patients.

Prompt assessment and diagnostic evaluation of these comorbidities represent a crucial aspect for the clinical management of patients with hypertension, not only in view of their influence on individual global cardiovascular risk stratification, but also in view of their potential implications for therapeutic choice among different classes and combination therapies of antihypertensive drugs. Compelling indications are, indeed, available to help physicians in choosing the most effective and better-tolerated antihypertensive drug therapy to be applied in these very high risk-hypertensive patients. Although the effective blood pressure reductions achieved throughout the implementation of the proper antihypertensive drug classes according to recommendations from international guidelines cannot impact the individual global cardiovascular risk profile in hypertensive patients with comorbidities (which is definitely very high-risk profile), it has demonstrated to reduce cardiovascular mortality and

hospitalization for cardiovascular causes, thus reducing the burden of hypertension-related disease.

In this volume of *Practical Case Studies in Hypertension Management*, the clinical management of paradigmatic cases of patients with hypertension and different comorbidities will be discussed, focusing on the different diagnostic criteria currently available for identifying the presence or the absence of these associated clinical conditions, as well as on the different therapeutic options currently recommended for achieving effective and sustained blood pressure control and reduce hypertension-related morbidity and mortality.

Rome, Italy Giuliano Tocci

Preface

This book is structured to assist physicians in the management of hypertensive patients, with a particular emphasis on a variety of clinical conditions often associated to hypertension. The clinical cases are selected according to the very frequent clinical conditions which everyday refer to a third-level Hypertension Center, thus reflecting the "real world". These clinical cases raise problematics, doubts, necessity of decision making which usually are not evidenced in the medicine textbooks. They provide examples of management according to current international guidelines. The importance of associated clinical conditions deals with the necessity to choose those antihypertensive agents, alone or in a right combination each other, which are necessarily different according to what condition together with hypertension occurs. In such scenario, the clinical case includes patients with diabetes mellitus, systolic dysfunction, obesity, renal impairment, or previous stroke of myocardial infarction. By representing clinical practice in a "real-life" setting, these cases hopefully will help the practitioner to select the more appropriate diagnostic and treatment tools to the individual patient and the particular, thereby ameliorating the cardiovascular risk profile and prognosis.

Pisa, Italy — Agostino Virdis

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Chapter 1
Clinical Case 1: Patient with Essential Hypertension and Systolic Dysfunction

1.1 Clinical Case Presentation

A 74-year-old, Caucasian male, retired (former employee), presented to the outpatient clinic for clinical assessment of uncontrolled essential hypertension.

History of essential hypertension by about 25 years. He was treated with a combination therapy based on beta-blocker (atenolol 50 mg) and diuretic (chlorthalidone 12.5 mg), obtaining a satisfactory blood pressure control and no important side effects. By about 5 years, he stopped to monitor home blood pressure and to undergo periodical medical visits. About 3 months ago, for incoming effort dyspnoea and lower limb oedema, he was moved to another diuretic (furosemide 25 mg) and maintained atenolol 50 mg/day. Unfortunately, his home blood pressure is uncontrolled (around 150/95 mmHg). The patient states persistent lower limb oedema and effort dyspnoea, shortness of breath. No chest pain is referred.

Family History

He has paternal history of diabetes mellitus and myocardial infarction, together with a maternal history of hypertension. He also has one sister with hypercholesterolaemia.

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Clinical History

He is currently a cigarette smoker (around 4–5 cigarettes daily, for >30 years). He has also mild hypercholesterolaemia, treated with simvastatin 10 mg daily. He has a history of alcohol abuse (he usually drinks around 700 mL of wine daily, corresponding to >70 g/day of alcohol intake). There are no additional known cardiovascular risk factors. Few days before the first visit in our outpatient clinic, the general practitioner prescribed him a standard chest radiography (see below).

Physical Examination

- Weight: 88 kg
- Height: 173 cm
- Body mass index (BMI): 29.4 kg/m^2
- Waist circumference: 104 cm
- Respiration: attenuated breath sounds; late-inspiratory fine bilateral basal crackles
- Heart sounds: distal cardiac sounds; pansystolic murmur, suggestive of mitral regurgitation; no adjunctive third or fourth sounds
- Resting pulse: regular rhythm with normal heart rate (80 beats/min)
- Lower limb pitting oedema
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive retinopathy

Haematological Profile

- Haemoglobin: 14.7 g/dL
- Haematocrit: 48.5 %
- Fasting plasma glucose: 94 mg/dL

- Fasting lipids: total cholesterol (TOT-C), 224 mg/dL; low-density lipoprotein cholesterol (LDL-C), 152 mg/dL; high-density lipoprotein cholesterol (HDL-C), 39 mg/dL; and triglycerides (TG), 164 mg/dL
- Electrolytes: sodium, 141 mEq/L, and potassium, 3.9 mEq/L
- Serum uric acid: 6.3 mg/dL
- Renal function: urea, 64 mg/dL; creatinine, 1.9 mg/dL; and estimated glomerular filtration rate (eGFR) (MDRD), 35 mL/min/1.73 m^2
- Urine analysis (dipstick): normal
- Urinary albumin/creatinine ratio (morning urine sample): 38 mg/g
- Liver function tests: AST 90 U/L; ALT 41 U/L; and γ-GT 58 U/L. Normal other liver function tests
- Thyroid function tests: normal

Blood Pressure Profile

- Home BP (average): 160/98 mmHg
- Sitting BP: 152/98 mmHg (right arm); 150/96 mmHg (left arm)
- Standing BP: 149/97 mmHg at 1 min

Chest Radiography

Enlargement of left cardiac sections. Pleural effusion mainly at the right lung base (Fig. 1.1).

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (66 bpm), left anterior fascicular block with right bundle branch block. No signs of LVH (Sokolow–Lyon 2.5 mV, Cornell voltage 2.0 mV) (illustrated in Fig. 1.2). Peripheral (**a**) and precordial (**b**) leads.

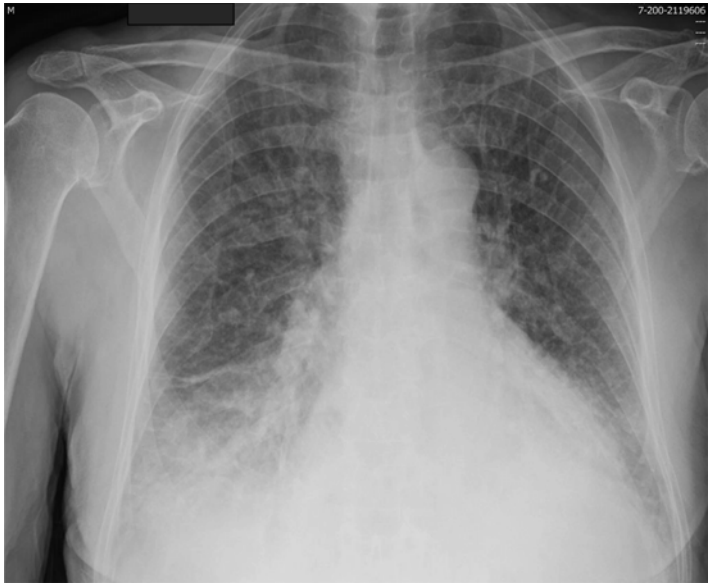

FIGURE 1.1 Standard postero-anterior chest radiograph showing enlargement of left cardiac sections. Pleural effusion mainly at the right lung base

Current Treatment

Atenolol 50 mg h 8:00; furosemide 25 mg h 8:00; and simvastatin 10 mg h 20:00

Diagnosis

Arterial hypertension with unsatisfactory blood pressure control. Radiographic enlargement of left cardiac sections and clinical signs of heart failure (NYHA III). Evidence of hypertension-related kidney damage (stage 3 chronic kidney disease). Additional modifiable cardiovascular risk factors (chronic cigarette smoking, hypercholesterolaemia, increased waist circumference). Abnormal plasma markers of liver disease and anamnesis of chronic alcohol abuse.

Which is the global cardiovascular risk profile in this patient?
Possible answers are:

1. Low
2. Medium
3. High
4. Very high

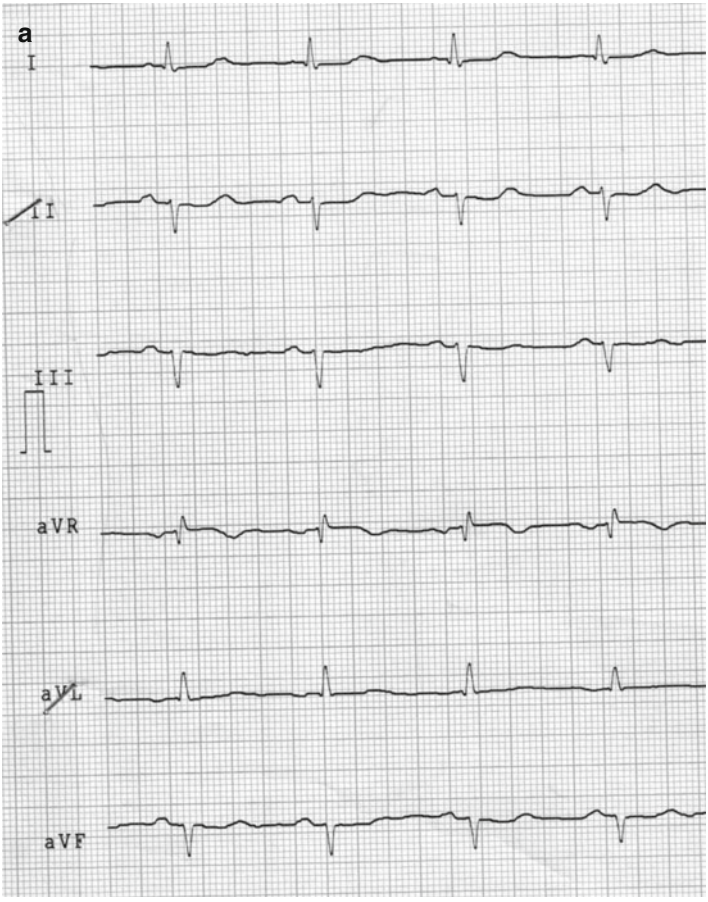

FIGURE 1.2 (**a**, **b**) Sinus rhythm with heart rate 66 bpm, left anterior fascicular block with right bundle branch block. No signs of LVH (Sokolow–Lyon 2.5 mV, Cornell voltage 2.0 mV)

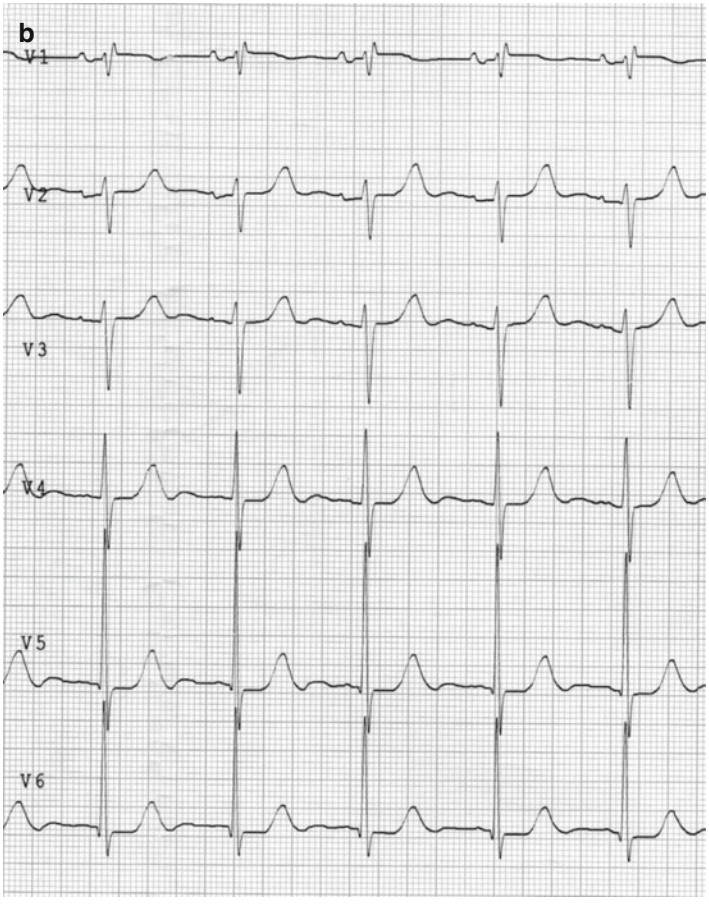

FIGURE 1.2 (continued)

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has high cardiovascular risk.

Which is the best therapeutic option in this patient?
Possible answers are:

1. Add another drug class (e.g. dihydropyridinic calcium antagonist).
2. Add another drug class (e.g. ACE-inhibitor).
3. Switch from atenolol to another beta-blocker.
4. Titrate the diuretic therapy.
5. Titrate the statin therapy.

Treatment Evaluation

- Stop atenolol and start bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00.
- Titrate furosemide to 25 mg 2 cp h 8:00 and 2 cp h 16:00.
- Titrate simvastatin to 20 mg 1 cp h 20:00.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Quit smoking.
- Dietary salt and caloric restriction.
- Reduce alcohol intake to no more than 20 g/day.
- Blood tests: serum creatinine, eGFR, potassium and carbohydrate-deficient transferrin.
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties).
- Abdominal echography with renal artery Doppler.
- Carotid ultrasound.

1.2 Follow-Up (Visit 1) at 2 Weeks

At follow-up visit, the patient refers an improvement of general clinical conditions. In particular, an amelioration of the lower limb oedema and of effort dyspnoea occurred. No

more shortness of breath. He does not stop smoking, but he reduced the alcohol intake. He also reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels remained substantially uncontrolled.

Physical Examination

- Respiration: attenuated but still present fine bilateral basal crackles
- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 145/95 mmHg
- Sitting BP: 150/94 mmHg (right arm)
- Standing BP: 146/96 mmHg

Current Treatment

Bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00; furosemide 25 mg 2 cp h 8:00 and 2 cp h 16:00; and simvastatin 20 mg 1 cp h 20:00

Haematological Profile

- Electrolytes: potassium, 3.2 mEq/L
- Creatinine, 2.0 mg/dL, and eGFR (MDRD), 34 mL/min/1.73 m^2
- Carbohydrate-deficient transferrin: 1.9 % (normal values, 0.0–1.3 %)

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Normal dimension of aortic root. Left atrium dilated (46 mm). Left ventricle (LV) with abnormal chamber dimension (LV end-diastolic diameter 71 mm), impaired LV relaxation at both conventional (E/A ratio <1) and tissue Doppler evaluations, and global ventricular hypokinesia with reduced ejection fraction (LV ejection fraction 32 %). Indexed LV mass increased, 193 g/m^2; relative wall thickness, 0.28. Type 1 diastolic dysfunction. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Aortic (+) and mitral (+) regurgitations at Doppler ultrasound examination. PAPs 32 mmHg.

Abdominal Echography with Renal Artery Doppler

Marked liver steatosis. No signs of portal hypertension. Biliary tree not dilated. Normal spleen dimensions. Adrenal glands without signs of abnormal lesions. Abdominal aorta with normal dimension and atherosclerotic plaques.

Kidneys with normal dimensions and cortical thickness. Renal arteries without signs of haemodynamically significantly stenosis. Intrarenal index resistance bilaterally increased (right, 0.79; left, 0.81).

Carotid Ultrasound

Calcific atherosclerotic plaques at both carotid levels, without signs of haemodynamically significantly stenosis.

Diagnosis

Essential hypertension with unsatisfactory blood pressure control and associated heart failure (nature to be determined) with left ventricular systolic dysfunction (AHA clas-

sification stage C, NYHA II). Vascular (carotid and aortic atherosclerosis) and renal (stage 3 chronic kidney disease) organ damages. Additional modifiable cardiovascular risk factors (cigarette smoking, hypercholesterolaemia, increased waist circumference). Liver steatosis.

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The echocardiographic evidence of dilated cardiomyopathy and systolic dysfunction modifies the individual global cardiovascular risk profile. On the basis of this assessment, this patient has moved from high to very high cardiovascular risk, according to 2013 ESH/ESC global cardiovascular risk stratification [1].

Which is the best therapeutic option in this patient?

Possible answers are:

1. Add another drug class (e.g. ACE-inhibitor).
2. Add another drug class (e.g. aldosterone antagonist).
3. Modify the diuretic therapy.
4. Titrate the beta-blocker therapy.

Treatment Evaluation

- Start lisinopril 20 mg 1 cp h 8:00.
- Start spironolactone 25 mg 1 cp h 8:00.

- Maintain bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00 and simvastatin 20 mg 1 cp h 20:00.
- Down-step furosemide 25 mg to 2 cp h 8:00.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Quit smoking.
- Dietary salt and caloric restriction.
- Reduce alcohol intake to no more than 20 g/day.
- Blood tests: creatinine, potassium and lipid profile.
- Chest radiography.
- Coronary angiography.

1.3 Follow-Up (Visit 2) at 2 Months

At follow-up visit, the patient is in quite stable clinical conditions. The lower limb oedema and effort dyspnoea are reduced. He carries out ordinary physical activity without symptoms. He stopped smoking and maintained low alcohol intake. He also reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure is well controlled.

Physical Examination

- Respiration: attenuated fine bilateral basal crackles
- Quite disappearance of lower limb pitting oedema
- Resting pulse: regular rhythm with normal heart rate (66 beats/min)
- Other parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 134/85 mmHg
- Sitting BP: 132/84 mmHg (right arm)
- Standing BP: 128/86 mmHg

Haematological Profile

- Fasting lipids: TOT-C, 211 mg/dL; LDL-C, 139 mg/dL; HDL-C, 40 mg/dL; and TG, 157 mg/dL
- Electrolytes: potassium, 3.7 mEq/L
- Creatinine, 1.81 mg/dL, and eGFR (MDRD), 37 mL/min/1.73 m^2

Current Treatment

Lisinopril 20 mg 1 cp h 8:00; spironolactone 25 mg 1 cp h 8:00; bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00; furosemide 25 mg 2 cp h 8:00; and simvastatin 20 mg 1 cp h 20:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Chest Radiography

As compared to the previous one, the present radiography shows a significant reduction of left cardiac sections. The pleural effusion has disappeared (Fig. 1.3).

Coronary Angiography

Epicardial coronary arteries free of significant atherosclerotic lesions. Diffuse left ventricular dysfunction.

Diagnosis

Essential hypertension well controlled and associated heart failure (likely alcoholic dilated cardiomyopathy) with left ventricular systolic and diastolic dysfunction (AHA

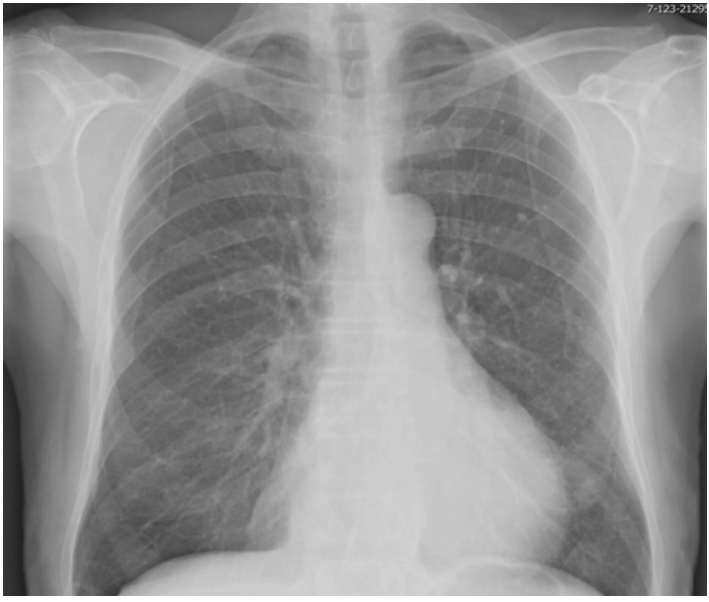

Figure 1.3 Standard postero-anterior chest radiograph showing a reduction of left cardiac sections. Pleural effusion no more evident

classification stage C, NYHA II). Vascular (carotid and aortic atherosclerosis) and renal (stage 3 chronic kidney disease) organ damages. Additional modifiable cardiovascular risk factors (cigarette smoking, hypercholesterolaemia, increased waist circumference). Liver steatosis.

Treatment Evaluation

- Maintain lisinopril 20 mg 1 cp h 8:00; spironolactone 25 mg 1 cp h 8:00; bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00; and furosemide 25 mg 2 cp h 8:00.
- Stop simvastatin 20 mg 1 cp h 20:00.
- Start atorvastatin 20 mg 1 cp h 20:00.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Dietary salt and caloric restriction.
- Reduce alcohol intake to no more than 20 g/day.
- Blood tests: creatinine, potassium, fasting plasma glucose, lipid profile and liver function tests.
- Repeat 12-lead electrocardiogram.
- Repeat echocardiogram aimed at evaluating left ventricular function.

1.4 Follow-Up (Visit 2) at 6 Months

At follow-up visit, the patient refers a stability of his general clinical conditions. In particular, he carries out ordinary physical activity without symptoms. He maintains low alcohol intake and dietary salt and caloric restrictions and has good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels remained substantially well controlled.

Physical Examination

- Weight: 85 kg
- Body mass index (BMI): 28.4 kg/m^2
- Waist circumference: 102 cm
- Other parameters unchanged

Blood Pressure Profile

- Home BP (average): 130/82 mmHg
- Sitting BP: 134/84 mmHg (right arm)
- Standing BP: 130/84 mmHg

Haematological Profile

- Creatinine, 1.78 mg/dL, and eGFR (MDRD), 38 mL/min/1.73 m^2
- Potassium, 3.65 mEq/L
- Fasting plasma glucose, 92 mg/dL
- TOT-C, 171 mg/dL; LDL-C, 99 mg/dL; HDL-C, 42 mg/dL; and TG, 147 mg/dL
- Liver function tests: AST 54 U/L; ALT 32 U/L; and γ-GT 49 U/L

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (65 bpm), left anterior fascicular block with right bundle branch block. No signs of LVH (Sokolow–Lyon 2.4 mV, Cornell voltage 1.8 mV). Identical to the previous one (illustrated in Fig. 1.4). Peripheral (**a**) and precordial (**b**) leads.

Echocardiogram with Doppler Ultrasound

Normal dimension of aortic root. Left atrium dilated (46 mm). Left ventricle (LV) with abnormal chamber dimension (LV end-diastolic diameter 67 mm), impaired LV relaxation at both conventional (E/A ratio <1) and tissue Doppler evaluations, and global ventricular hypokinesia with reduced ejection fraction (LV ejection fraction 35 %). Indexed LV mass increased, 186 g/m^2; relative wall thickness, 0.28. Type 1 diastolic dysfunction. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Aortic (+) and mitral (+) regurgitations at Doppler ultrasound examination. PAPs 32 mmHg.

Current Treatment

Lisinopril 20 mg 1 cp h 8:00; spironolactone 25 mg 1 cp h 8:00; bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00; furosemide 25 mg 2 cp h 8:00; and atorvastatin 20 mg 1 cp h 20:00

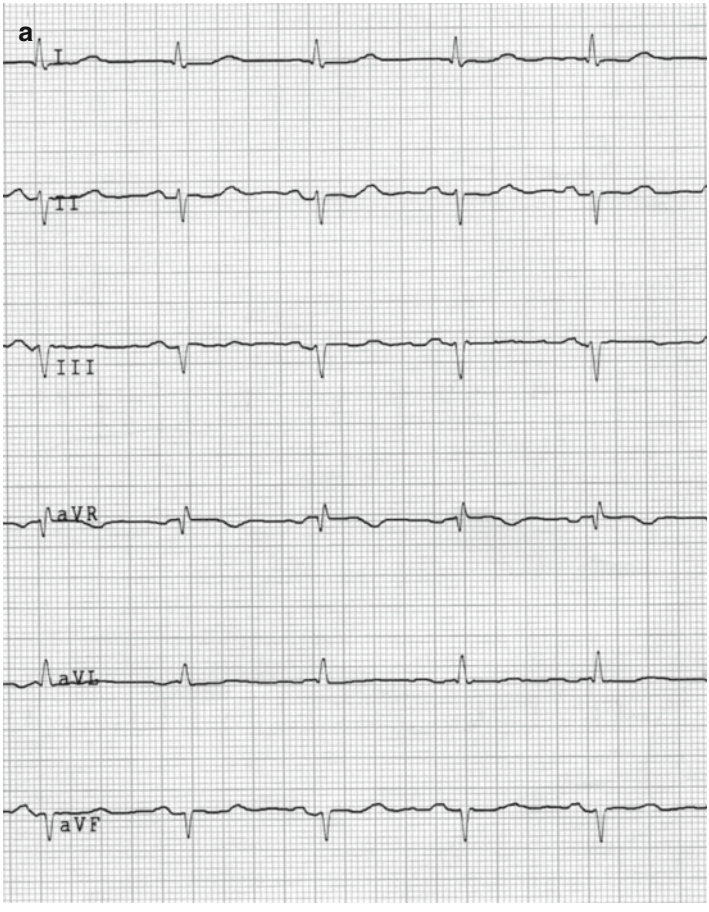

FIGURE 1.4 (**a**, **b**) Sinus rhythm with heart rate 65 bpm, left anterior fascicular block with right bundle branch block. No signs of LVH

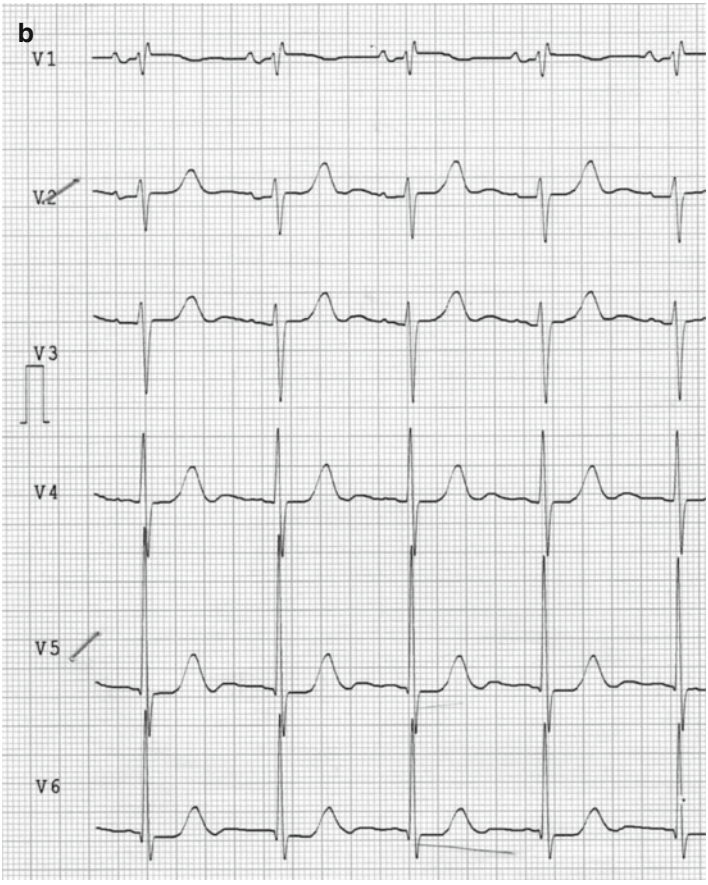

FIGURE 1.4 (continued)

Treatment Evaluation

No change for current pharmacological therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary low-salt and caloric intake (continued)

- Maintain alcohol intake to no more than 20 g/day
- Daily slow walk

1.5 Discussion

Arterial hypertension is a major cardiovascular risk factor, which promotes the development and progression of asymptomatic organ damages at cardiac, renal and vascular levels [1]. At the first two visits, this patient showed signs of vascular atherosclerotic damage (carotid and abdominal aorta) serum signs of chronic kidney disease (stage 3, eGFR 30–60 mL/min). The evidence of enhanced bilateral intrarenal index resistances likely indicates a condition of hypertensive nephropathy. All these subclinical organ damages are a likely consequence of a long history of hypertension, with an insufficient blood pressure control. The chronic cigarette smoking habit further accelerates and amplifies such alterations. The patients also show clinical symptoms and signs and then instrumental evidence of heart failure with left ventricular dysfunction, as associate clinical condition. The coronary angiography excluded an ischaemic coronary artery disease. The anamnesis of chronic alcohol intake, together with echocardiographic parameters and elevated serum levels of carbohydrate-deficient transferrin, indicates the presence of a dilated cardiomyopathy secondary to alcohol abuse. Chronic alcoholism is one of the most important causes of dilated cardiomyopathy. The clinical diagnosis is suspected when biventricular dysfunction and dilatation are persistently observed in a heavy drinker in the absence of other known causes for myocardial disease. Alcoholic cardiomyopathy most commonly occurs in men 30–55 years of age who have been heavy consumers of alcohol for >10 years. Women represent approximately 14 % of the alcoholic cardiomyopathy cases but may be more vulnerable with less lifetime alcohol consumption [2]. The risk of asymptomatic alcoholic cardiomyopathy is increased in those consuming >90 g of alcohol per day (approximately 7–8 standard drinks per day) for

>5 years. Interestingly, in the general population, mild to moderate alcohol consumption has been reported to be protective against development of heart failure [3]. These paradoxical findings suggest that duration of exposure and individual genetic susceptibility play an important role in pathogenesis. Recovery of left ventricular function after drinking cessation has been reported.

The carbohydrate-deficient transferrin serum parameter deserves a further comment. Indeed, various forms of transferrin exist, with differing levels of sialylation. The most common form is tetrasialotransferrin, with four sialic acid chains. In persons who consume significant quantities of alcohol (usually more than four or five alcoholic beverages a day or more), the proportion of transferrin with zero, one or two sialic acid chains is increased [4]. These are referred to as *carbohydrate-deficient transferrins*. These carbohydrate-deficient transferrins can be measured in the bloodstream. Used with other tests, such as gamma glutamyl transferase, aspartate aminotransferase and alanine aminotransferase, carbohydrate-deficient transferrin can be a useful tool and an important marker for alcohol abuse.

With respect to heart failure with impaired left ventricular function, the physical signs (attenuated breath sounds, inspiratory bilateral basal crackles and lower limb pitting oedema) and the symptoms reported by the patient at the first visit, together with the echocardiographic conclusions, strongly indicate the presence of a heart failure condition at stage C (heart failure ACCF/AHA classification) [5]. This indicates the presence of structural heart disease with prior or current symptoms of heart failure. Accordingly, the patient was moved to an ACE-inhibitor, high dose of furosemide, while atenolol was switched to bisoprolol, in order to reduce the excess fluid accumulation (dyspnoea) and ameliorate the cardiac output (fatigue, weakness). In particular, the choice of bisoprolol is because this selective type β_1 adrenergic receptor blocker, besides being effective in treatment for hypertension, also showed beneficial effect in congestive heart failure, as documented by the CIBIS II trial [6]. With respect to

atenolol, bisoprolol does not show significant metabolic adverse effects. In this patient spironolactone was also added. Indeed, as stated by the ACCF/AHA guidelines [5], clinicians should strongly consider the addition of the aldosterone receptor antagonists spironolactone (or eplerenone) for all patients with HFrEF at stage C who are already on ACE-inhibitors (or sartans) and beta-blockers, excluding patients with a creatinine >2.5 mg/dL, and monitoring of kalaemia.

Take-Home Messages

- Systolic dysfunction is a condition in those hypertensive patients at high cardiovascular risk profile, referring to sudden shortness of breath, effort dyspnoea or fatigue.
- In hypertensive patients with left ventricular systolic dysfunction, the target blood pressure is <140/90 mmHg.
- The main cardiovascular agents include ACE-inhibitors, or sartans if not tolerated, III generation beta-blockers and diuretics. In selected patients, consider the utilization of aldosterone antagonist.

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Chapter 2
Clinical Case 2: Patient with Essential Hypertension and Myocardial Infarction

2.1 Clinical Case Presentation

A 64-year-old, Caucasian male, postal employee presented to the outpatient clinic for clinical assessment of uncontrolled essential hypertension.

He has a history of essential hypertension by about 10 years, treated with a dihydropyridine-type calcium channel blocker (nifedipine 30 mg), with good blood pressure control and no side effects. Five years ago he was diagnosed an inferior STEMI, treated by percutaneous coronary angioplasty with drug-eluting stent at the level of right coronary artery. At that time, the therapy was shifted to a beta-blocker (bisoprolol 2.5 mg 1 cp), ACE-inhibitor (ramipril 5 mg), Ca-antagonist (amlodipine 10 mg daily), diuretic (furosemide, 25 mg 1 cp), dual-antiplatelet therapy (clopidogrel 75 mg plus acetylsalicylic acid 100 mg) and atorvastatin 80–40 mg. He referred a good home blood pressure control (130/80 mmHg) and a general wellbeing. One year later acetylsalicylic acid was stopped. Since about 1 year, he refers inhomogeneous blood pressure values. Usually, a marked sensation of fatigue and weakness at noon or postprandial occurs. Once, he reported a fainting sensation, without the loss of consciousness. No chest pain is referred.

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Family History

He has paternal history of hypertension and a maternal history of type 1 diabetes mellitus. He also has one brother with hypertension.

Clinical History

He has a long history of cigarette smoking (more than 20 cigarettes daily) until the age of 58 years, when the myocardial infarction was diagnosed. Among his lifestyles, he has always played a sedentary lifestyle, with an overweight condition. He has no history of alcohol intake. Since 2 years he started a dietary caloric restriction, together with a moderate physical activity, resulting in a significantly reduction of body weight (around 10 kg). There are no additional known cardiovascular risk factors.

Physical Examination

- Weight: 78 kg
- Height: 169 cm
- Body mass index (BMI): 27.3 kg/m^2
- Waist circumference: 100 cm
- Respiration: normal
- Heart sounds: S1–S2 regular, normal and no murmurs
- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Lower limb oedema
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive retinopathy

Haematological Profile

- Haemoglobin: 14.1 g/dL
- Haematocrit: 47.5 %

- Fasting plasma glucose: 87 mg/dL
- Fasting lipids: total cholesterol (TOT-C), 156 mg/dL; low-density lipoprotein cholesterol (LDL-C), 87 mg/dL; high-density lipoprotein cholesterol (HDL-C), 40 mg/dL; and triglycerides (TG), 145 mg/dL
- Electrolytes: sodium, 136 mEq/L, and potassium, 3.5 mEq/L
- Serum uric acid: 6.9 mg/dL
- Renal function: urea, 44 mg/dL; creatinine, 1.04 mg/dL; and estimated glomerular filtration rate (eGFR) (MDRD), 72 mL/min/1.73 m^2
- Urine analysis (dipstick): normal
- Urinary albumin/creatinine ratio (morning urine sample): 14 mg/g
- Liver function tests: normal
- Thyroid function tests: normal

Blood Pressure Profile

- Home BP (average): 150/95 mmHg
- Sitting BP: 124/78 mmHg (left arm); 122/76 mmHg (right arm)
- Standing BP: 120/78 mmHg at 1 min
- 24-h BP, 116/76 mmHg, and HR, 74 bpm
- Daytime BP: 125/84 mmHg; HR 81 bpm—lowest values: h 10:16, 90/40 mmHg, and h 12:15, 65/49 mmHg
- Night-time BP, 130/78 mmHg; HR, 56 bpm

A 24-h ambulatory blood pressure profile is illustrated in Fig. 2.1.

Chest Radiography

Normal cardiac sections. No pleural or lung parenchymal lesions (Fig. 2.2).

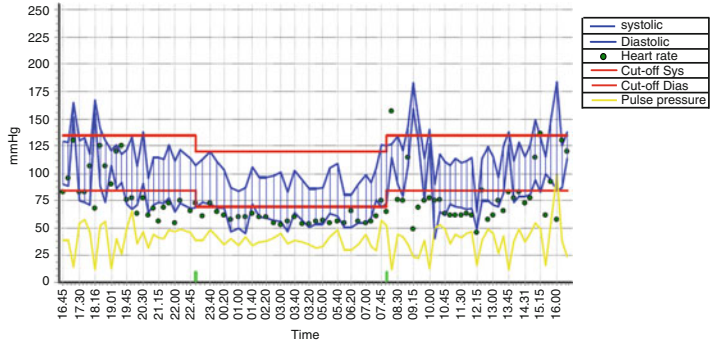

FIGURE 2.1 A 24-h ambulatory blood pressure profile

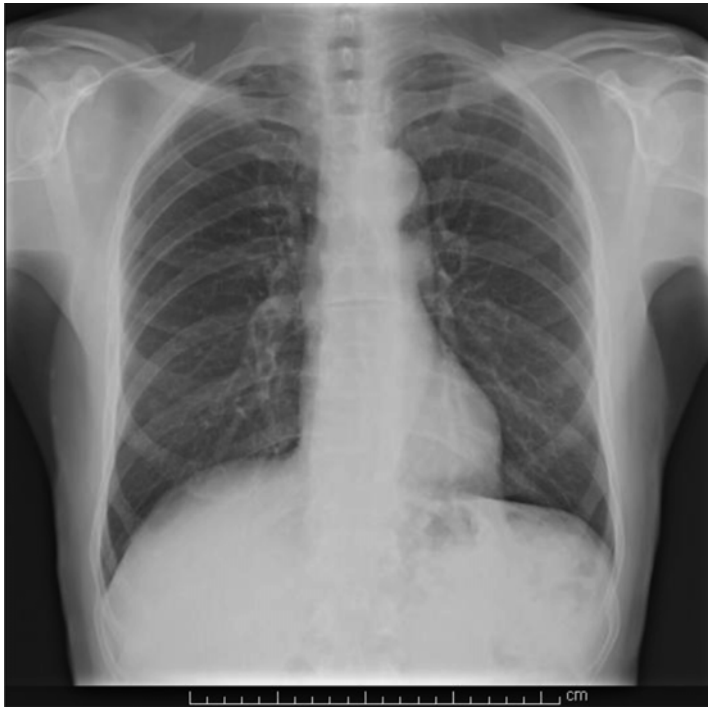

FIGURE 2.2 Standard postero-anterior chest radiograph showing normal cardiac sections. No acute pleural or lung parenchymal lesions

12-Lead Electrocardiogram

Sinus rhythm with heart rate 84 bpm, normal atrioventricular and intraventricular conduction. Q wave in DII, DIII and aVF leads. ST-segment abnormalities. No signs of LVH (Sokolow–Lyon 1.8 mV, Cornell voltage 2.4 mV) (Fig. 2.3). Peripheral (**a**) and precordial (**b**) leads.

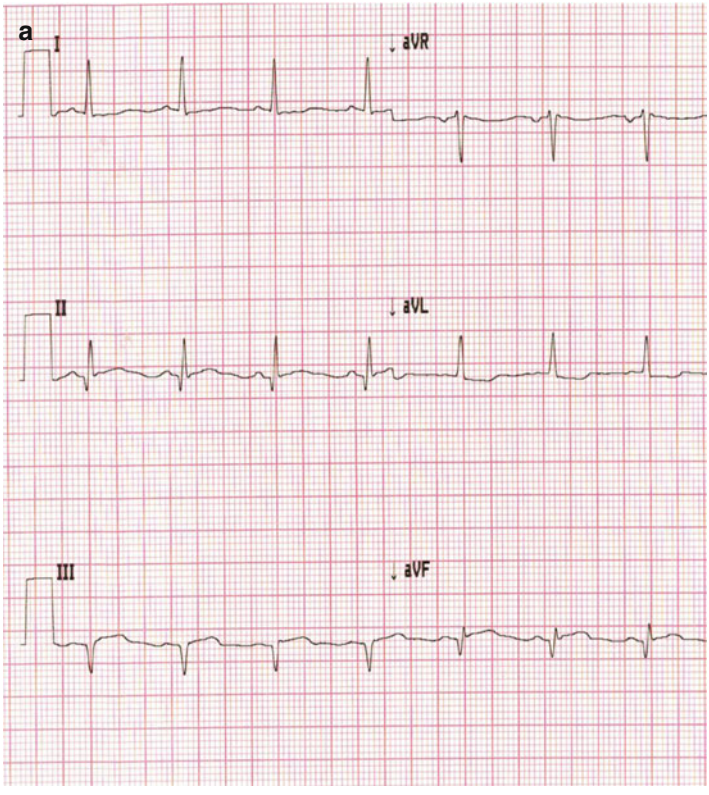

FIGURE 2.3 (**a**, **b**) Sinus rhythm with heart rate 84 bpm, normal atrioventricular and intraventricular conduction. Q wave in DII, DIII and aVF leads. ST-segment abnormalities. No signs of LVH

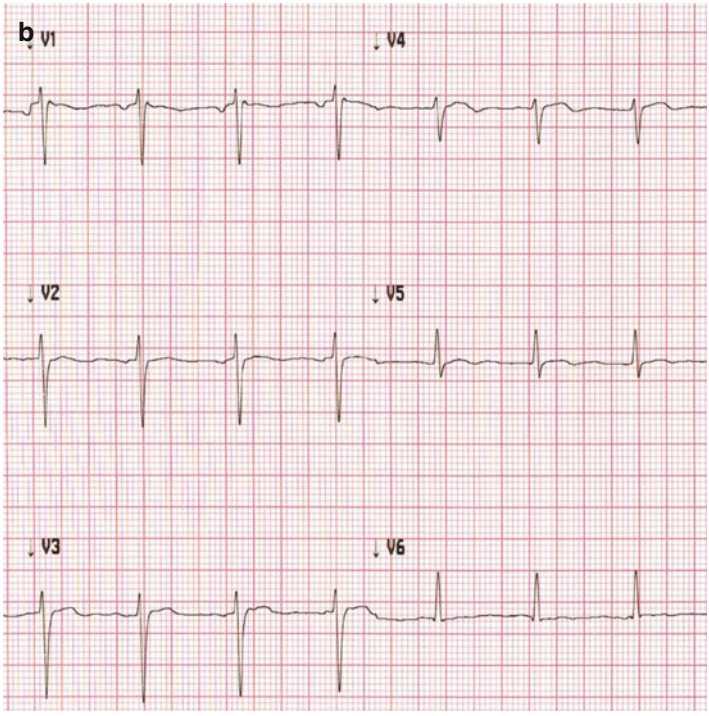

FIGURE 2.3 (continued)

Current Treatment

Bisoprolol 2.5 mg h 8:00, amlodipine 10 mg h 8:00, clopidogrel 75 mg h 8:00, furosemide 25 mg h 12:00, ramipril 5 mg h 20:00 and atorvastatin 40 mg h 22:00

Diagnosis

Arterial hypertension with unsatisfactory blood pressure control and associated clinical condition (previous inferior myocardial infarction). Additional modifiable cardiovascular

risk factors (previous chronic cigarette smoking, hypercholesterolaemia well controlled by statin therapy).

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has very high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Add another drug class (e.g. alpha-1 blocker).
2. Stop furosemide or switch it to another diuretic.
3. Titrate or switch the ACE-inhibitor therapy.
4. Titrate the beta-blocker therapy.
5. Titrate the Ca-antagonist therapy.

Treatment Evaluation

- Stop furosemide.
- Titrate bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00.
- Switch ramipril to lisinopril 20 mg 1 cp h 8:00.
- Down-step amlodipine to 5 mg 1 cp h 8:00.
- Maintain clopidogrel 75 mg 1 cp h 8:00 and atorvastatin 40 mg 1 cp h 22:00.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Maintain dietary salt and caloric restriction.
- Maintain regular physical activity (30' walk/daily).
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties).
- Abdominal echography with renal artery Doppler.
- Carotid ultrasound.

2.2 Follow-Up (Visit 1) at 4 Weeks

At follow-up visit, the patient refers an improvement of general clinical conditions. In particular, no more fatigue or weakness occurred. He also reports good adherence to prescribed medications without adverse reactions or drug-related side effects.

Physical Examination

- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Attenuated lower limb oedema
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 144/92 mmHg
- Sitting BP: 138/86 mmHg
- Standing BP: 134/84 mmHg

Current Treatment

Bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00; lisinopril 20 mg 1 cp h 8:00, amlodipine 5 mg 1 cp h 8:00, clopidogrel 75 mg 1 cp h 8:00 and atorvastatin 40 mg 1 cp h 22:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Normal dimension of aortic root. Left atrium of normal dimension (35 mm). Left ventricle (LV) with abnormal chamber dimension (LV end-diastolic diameter 52 mm), impaired LV relaxation at both conventional (E/A ratio <1) and tissue Doppler evaluations and global ventricular normal kinesis and preserved ejection fraction (57 %). Medio-basal inferior akinesia. Indexed LV mass within the normal range, 107 g/m^2; relative wall thickness, 0.40. Type 1 diastolic dysfunction. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (++) and tricuspid (+) regurgitations at Doppler ultrasound examination. PAPs 36 mmHg.

Abdominal Echography with Renal Artery Doppler

Moderate liver steatosis. Biliary tree not dilated. Normal spleen dimensions. Adrenal glands without signs of abnormal lesions. Abdominal aorta with normal dimension and atherosclerotic plaques. Kidneys with normal dimensions and cortical thickness. Renal arteries without signs of haemodynamically significant stenosis. Intrarenal index resistance bilaterally increased.

Carotid Ultrasound

Calcific atherosclerotic plaques at both carotid levels, without signs of haemodynamically significant stenosis.

Diagnosis

Essential hypertension with still unsatisfactory blood pressure control and associated clinical condition (inferior myocardial infarction, with preserved systolic function). Vascular (carotid and aortic atherosclerosis) organ damage. Additional modifiable cardiovascular risk factors (previous cigarette smoking, hypercholesterolaemia well controlled by therapy).

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The echographic signs of carotid and aorta atherosclerosis, although important to stratify the patient, do not modify the individual global cardiovascular risk profile. According to 2013 ESH/ESC global cardiovascular risk stratification [1], the patient has very high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Add another drug class (e.g. sartan).
2. Add another drug class (e.g. alpha-1 blocker).
3. Start a diuretic therapy.
4. Titrate the beta-blocker therapy.

Treatment Evaluation

- Switch lisinopril to fix combination lisinopril/hydrochlorothiazide 20/12.5 mg 1 cp h 8:00.
- Maintain bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00, amlodipine 5 mg 1 cp h 8:00, clopidogrel 75 mg 1 cp h 8:00 and atorvastatin 40 mg 1 cp h 22:00.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Maintain dietary salt and caloric restriction and daily walk.

2.3 Follow-Up (Visit 2) at 3 Months

At follow-up visit, the patient is in quite stable clinical conditions. He follows the dietetic and lifestyle prescriptions, with a reduction of body weight. He also reports good adherence to prescribed medications without adverse reactions or drug-related side effects.

Physical Examination

- Resting pulse: regular rhythm with normal heart rate (62 beats/min)
- Stable slight lower limb oedema
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 134/82 mmHg
- Sitting BP: 132/84 mmHg
- Standing BP: 128/82 mmHg

Current Treatment

Lisinopril/hydrochlorothiazide 20/12.5 mg 1 cp h 8:00, bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00, amlodipine 5 mg 1 cp h 8:00, clopidogrel 75 mg 1 cp h 8:00 and atorvastatin 40 mg 1 cp h 22:00

Diagnosis

Essential hypertension well controlled and associated clinical condition (inferior myocardial infarction, with preserved systolic function). Vascular (carotid and aortic atherosclerosis) organ damage. Additional modifiable cardiovascular risk factors (previous cigarette smoking, hypercholesterolaemia well controlled by therapy).

Treatment Evaluation

No change for current pharmacological therapy

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Maintain dietary salt and caloric restriction and daily walk.
- Blood tests: creatinine, potassium, glycaemia and lipid profile.
- Repeat 24-h blood pressure measurement.
- Repeat 12-lead electrocardiogram.
- Repeat cardiac stress test (treadmill).

2.4 Follow-Up (Visit 2) at 12 Months

At follow-up visit, the patient refers a stability of his general clinical conditions. He continues the lifestyle and pharmacological prescriptions with no adverse reactions

or drug-related side effects. He has a stable body weight. The home blood pressure levels remained well controlled.

Physical Examination

- Weight: 76 kg
- Body mass index (BMI): 26.6 kg/m^2
- Other parameters unchanged

Blood Pressure Profile

- Home BP (average): 132/80 mmHg
- Sitting BP: 130/80 mmHg
- Standing BP: 126/82 mmHg
- 24-h BP, 119/72 mmHg, and HR, 71 bpm
- Daytime BP, 128/79 mmHg, and HR, 78 bpm
- Night-time BP, 110/66 mmHg, and HR, 64 bpm

A 24-h ambulatory blood pressure profile is illustrated in Fig. 2.4.

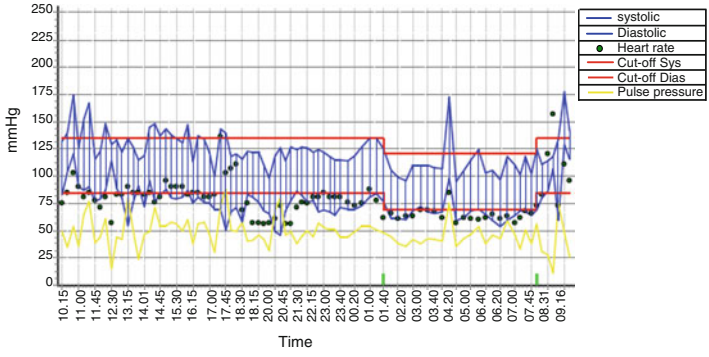

FIGURE 2.4 A 24-h ambulatory blood pressure profile

Haematological Profile

- Creatinine, 1.01 mg/dL, and eGFR (MDRD), 72 mL/min/1.73 m^2
- Potassium, 3.75 mEq/L
- Fasting plasma glucose: 84 mg/dL
- TOT-C, 150 mg/dL; LDL-C, 99 mg/dL; HDL-C, 42 mg/dL; and TG, 126 mg/dL
- Fasting plasma glucose: 87 mg/dL
- Fasting lipids: total cholesterol (TOT-C), 156 mg/dL; low-density lipoprotein cholesterol (LDL-C), 87 mg/dL; high-density lipoprotein cholesterol (HDL-C), 40 mg/dL; and triglycerides (TG), 145 mg/dL

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

12-Lead Electrocardiogram

Sinus rhythm with heart rate 62 bpm, normal atrioventricular and intraventricular conduction. Q wave in DII, DIII and aVF leads. ST-segment abnormalities. No signs of LVH. Superimposable to the previous one.

Cardiac Stress Test

Test stopped at 100 w × 2 min for muscular fatigue. No symptoms. Regular increment and decrement of heart rate and blood pressure values (heart rate, basal 62 bpm; maximal 96 bpm; blood pressure, basal 130\80 mmHg; maximal systolic, 180 mmHg). No significant arrhythmias or ST-T abnormalities emerged.

Current Treatment

Lisinopril/hydrochlorothiazide 20/12.5 mg 1 cp h 8:00, bisoprolol 2.5 mg 1 cp h 8:00 and 1 cp h 20:00, amlodipine 5 mg 1

cp h 8:00, clopidogrel 75 mg 1 cp h 8:00 and atorvastatin 40 mg 1 cp h 22:00

Treatment Evaluation

No change for current pharmacological therapy

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Maintain dietary salt restriction and daily walk.

2.5 Discussion

This clinical case shows a typical example of a patient exposed to a very high cardiovascular risk—hypertensive disease with associated clinical condition (previous STEMI with preserved systolic function)—in whom the behaviour of daily blood pressure is inhomogeneous. Indeed, at the first visit it is evident by the 24-h blood pressure monitoring that at the trough time (in the morning, before antihypertensive pills intake) the blood pressure values are not well controlled, as also confirmed by home blood pressure measurement. In contrast, few hours later (at the peak time of the drugs) the patient often becomes symptomatic for weakness and marked fatigue. Such symptoms disappear after assuming lying position. Concomitantly with symptoms, the 24-h blood pressure monitoring revealed very low systolic and diastolic values, thus providing a clinical explanation to the patient's complaint. This nonhomogeneous behaviour by blood pressure profile depends on several errors in the antihypertensive drug prescription. First, the ACE-inhibitor was administered at an incorrect dosage (ramipril 5 mg 1 cp h 20:00). The prescription of a drug for the treatment of hypertension should take into consideration the potency of the drug, i.e. the

degree of blood pressure reduction required, and the duration of action of the drug, i.e. the need to cover the dosing interval (possibly 24 h) in a homogeneous way. This is especially the case for ACE-inhibitors, compounds characterized by a flat dose–response curve. The significance of this flat dose–response curve is that a low dose of an ACE-inhibitor (as ramipril 5 mg is) has the same potency as a high dose but a shorter duration of action. If a low dosage is administered to a hypertensive patient, it causes blood pressure fluctuations, which have been associated with negative cardiovascular outcomes, especially in a very high cardiovascular risk profile. In contrast, other drug classes, including calcium channel antagonists, diuretics and beta-adrenoceptor antagonists, can be used at different dosages in order to modulate their haemodynamic effects [2]. Thus, it is conceivable that the evening low dosage of ramipril does not cover the patient more than few hours, thus exposing him at high blood pressure values in the morning.

The second point concerns the use of furosemide as a diuretic therapy, which in this patient is incorrect. Furosemide is a loop diuretic, characterized by a marked but short action, not ideal in a hypertensive patient with a preserved renal function. In addition, the administration time scheduled (h 12:00) likely accounts for the postprandial hypotensive symptoms reported. In contrast, low dose of thiazide-like diuretic, in association with an ACE-inhibitor, represents a correct combination therapy, ensuring effective and homogeneous 24-h blood pressure reduction.

The blood pressure treatment target in a high-risk patient deserves further comments. Previous ESH/ESC Guidelines [3] recommended <130/80 mmHg in high-risk hypertensives (with diabetes, cerebrovascular, cardiovascular or renal disease). However, analysis of available randomized controlled trials in patients who had previous coronary events does not provide consistent evidence that systolic blood pressure target should be <130 mmHg in hypertensive patients with overt coronary heart disease. On the contrary, a number of the correlative analyses raising suspicion about the existence of a

J-curve relationship between achieved blood pressure and cardiovascular outcomes included a high proportion of coronary heart disease patients, and it is not unreasonable that, if a J-curve occurs, it may occur particularly in patients with obstructive coronary disease. As stated by the 2013 ESH/ESC Guidelines, the recommendation to lower systolic blood pressure to <140 mmHg is indirectly strengthened by a post hoc analysis of the INVEST study (examining all patients with coronary heart disease) showing that outcome incidence is inversely related to consistent systolic blood pressure control (i.e. <140 mmHg) throughout follow-up visits [4]. As to which drugs are better in hypertensive patients, there is evidence for greater benefits from beta-blockers after a recent myocardial infarction [5], a condition in which ACE-inhibitors have also been successfully tested [6, 7]. In this patient, the dual-antiplatelet therapy for 1 year following the percutaneous angioplasty with stenting was an appropriate procedure [8], as well as the high dose of statin, in order to obtain LDL-cholesterol values <100 mg/dL.

Take-Home Messages

- Be aware of the clinical pharmacology of antihypertensive drugs in order to choose not only the class or the molecule best suited to the clinical characteristics of the patient but also the correct dosages to ensure effective and homogeneous 24-h blood pressure reduction.
- In hypertensive patients with coronary heart disease as associated clinical condition, a systolic blood pressure goal <140 mmHg should be considered.
- In hypertensive patients with a recent myocardial infarction, beta-blockers are recommended. In the case of other coronary heart diseases, all antihypertensive agents can be used, but beta-blockers and calcium antagonists are to be preferred, for symptomatic reasons (e.g. angina).

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Chapter 3
Clinical Case 3: Patient with Diabetes Mellitus

3.1 Clinical Case Presentation

A 72-year-old, Caucasian female, retired (former schoolteacher), presented to the outpatient clinic for clinical assessment of uncontrolled hypertension. The patient refers history of essential hypertension by the menopause status (about 20 years ago). She was treated with unspecified drugs that she does not remember. By about 10 years, she is treated with an alpha-1 blocker (doxazosin, 2 mg/day) and a Ca-antagonist (amlodipine, 5 mg), with satisfactory home and office blood pressure control. By about 6 months, she reported elevated home blood pressure values, confirmed by his general practitioner. She added a thiazide diuretic, without any blood pressure changes. In the meantime, she never changed her usual daily pills intake or the drugs' brand.

Family History

She has paternal history of type 2 diabetes mellitus and maternal history of hypertension. She also has a sister with type 2 diabetes mellitus.

A. Virdis, *Hypertension and Comorbidities*,
Practical Case Studies in Hypertension Management,
DOI 10.1007/978-3-319-39164-9_3,

Clinical History

She was previously a smoker (10–20 cigarettes daily) for 35 years, until 1 year ago. As additional modifiable cardiovascular risk factor, she has a type 2 diabetes mellitus, treated with insulin therapy (rapid-acting insulin 3 times a day plus long-acting insulin once a day) and hypercholesterolaemia, treated with atorvastatin 10 mg daily. There are no associated clinical conditions or non-cardiovascular diseases.

Physical Examination

- Weight: 78 kg
- Height: 166 cm
- Body mass index (BMI): 28.3 kg/m^2
- Waist circumference: 98 cm
- Respiration: normal
- Heart sounds: distal cardiac sounds; pansystolic regurgitant murmur
- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive or diabetic retinopathy

Haematological Profile

- Haemoglobin: 13.1 g/dL
- Haematocrit: 39.0 %
- Fasting plasma glucose: 134 mg/dL
- Glycated haemoglobin (HbA_{1c}): 7.1 %
- Fasting lipids: total cholesterol (TOT-C), 187 mg/dL; low-density lipoprotein cholesterol (LDL-C), 119 mg/dL; high-density lipoprotein cholesterol (HDL-C), 39 mg/dL; and triglycerides (TG), 144 mg/dL

- Electrolytes: sodium, 142 mEq/L, and potassium, 3.31 mEq/L
- Serum uric acid: 6.1 mg/dL
- Renal function: creatinine, 1.21 mg/dL; creatinine clearance (Cockcroft–Gault), 43 mL/min; and estimated glomerular filtration rate (eGFR) (MDRD), 44 mL/min/1.73 m^2
- Urine analysis: proteinuria 40 mg/dL and glucose, absent
- Normal liver function tests
- Normal thyroid function tests

Blood Pressure Profile

- Home BP (average): 165/94 mmHg
- Sitting BP: 170/96 mmHg (right arm > left arm)
- Standing BP: 164/94 mmHg at 1 min

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (64 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH (Sokolow–Lyon 2.0 mV, Cornell voltage 2.2 mV) (illustrated in Fig. 3.1) Peripheral (**a**) and precordial (**b**) leads.

Chest Radiography

Normal cardiac sections. No pleural or lung parenchymal lesions (Fig. 3.2).

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; hydrochlorothiazide 12.5 mg 1 cp h 8:00; doxazosin 2 mg 1 cp h 22:00; atorvastatin 10 mg 1 cp h 22:00. Insulin lispro 4 UI h 8:00, 8 UI h 13 and 8 UI h 20:00; insulin glargine 12 UI h 22:00.

Diagnosis

Uncontrolled arterial hypertension with renal damage (stage 3 chronic kidney disease-CKD). Type 2 diabetes mellitus. Additional modifiable cardiovascular risk factors (chronic cigarette smoking, hypercholesterolaemia).

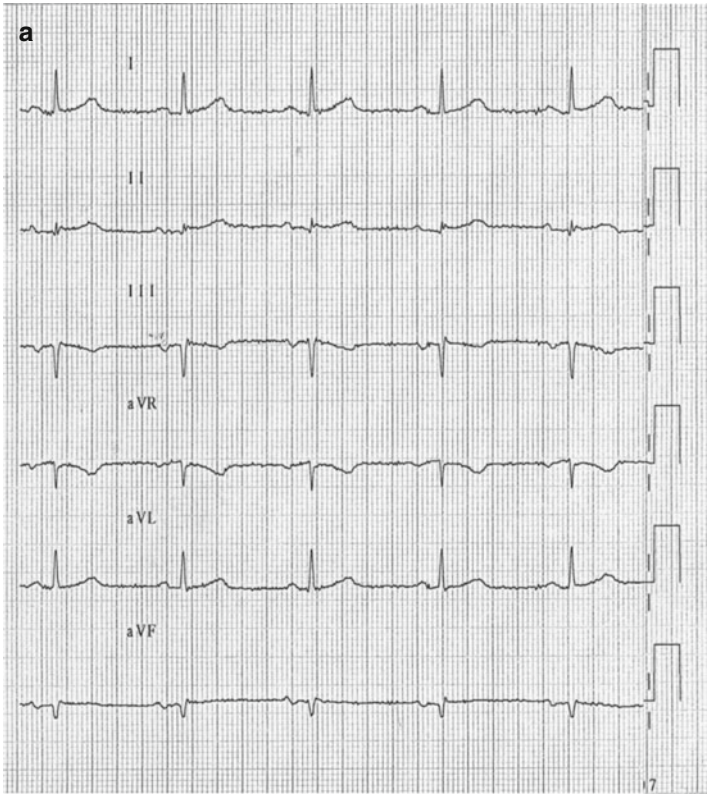

FIGURE 3.1 (**a**, **b**) Sinus rhythm with normal heart rate (64 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH

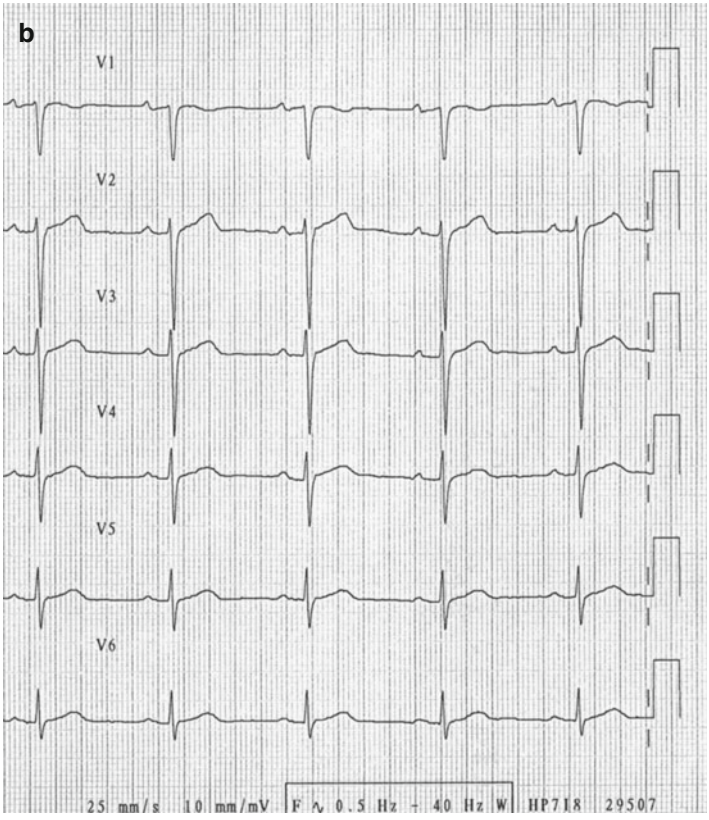

FIGURE 3.1 (continued)

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

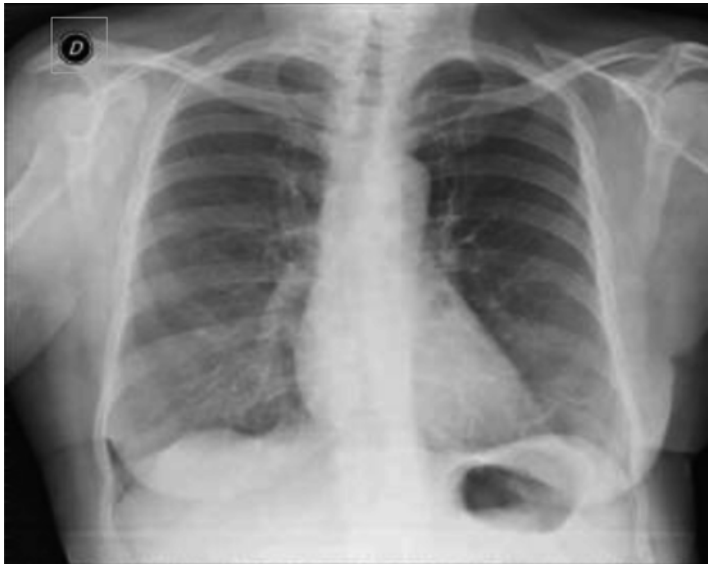

FIGURE 3.2 Standard postero-anterior chest radiograph showing normal cardiac sections. No acute pleural or lung parenchymal lesions

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Upstep the alpha-1 blocker or the Ca-antagonist.
2. Insert an ACE-inhibitor.
3. Upstep the diuretic.
4. Stop the diuretic.
5. Upstep the statin therapy.

Treatment Evaluation

- Upstep doxazosin to 4 mg 1 cp h 22:00.
- Maintain amlodipine 5 mg 1 cp h 8:00.
- Stop the diuretic.
- Upstep atorvastatin to 20 mg 1 cp h 22:00.
- Maintain the same insulin therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt and low-caloric restrictions
- Blood tests: serum creatinine, clearance creatinine, eGFR, potassium, urine analysis, 24-h proteinuria and urinary potassium
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties)
- Carotid vascular ultrasound
- Abdominal echography with renal artery Doppler

3.2 Follow-Up (Visit 1) at 6 Weeks

At follow-up visit, the patient reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels are quite unmodified and still elevated.

Physical Examination

- Weight: 78 kg
- Body mass index (BMI): 28.3 g/m^2
- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 164/95 mmHg
- Sitting BP: 166/96 mmHg
- Standing BP: 162/94 mmHg at 1 min

Haematological Profile

- Renal function: creatinine, 1.23 mg/dL; creatinine clearance (Cockcroft–Gault), 42 mL/min; eGFR (MDRD), 44 mL/min/1.73 m^2
- Potassium, 3.29 mEq/L
- 24-h proteinuria, 560 mg
- 24-h urinary potassium, 45 mEq

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; doxazosin 4 mg 1 cp h 22:00; atorvastatin 20 mg 1 cp h 22:00. Insulin lispro 4 UI h 8:00, 8 UI h 13 and 8 UI h 20:00; insulin glargine 12 UI h 22:00.

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Concentric left ventricle (LV) hypertrophy (LV mass indexed 136 g/m^2; relative wall thickness: 0.43) with normal chamber dimension (LV end-diastolic diameter 50 mm), impaired LV relaxation (E/A ratio < 1) at both conventional and tissue Doppler evaluations and normal ejection fraction (LV ejection fraction 56 %, LV fractional shortening 36 %). Normal dimension of aortic root and left atrium. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (+) regurgitations at Doppler ultrasound examination.

Carotid Ultrasound

Calcific atherosclerotic plaques at both carotid levels (max 1.8 mm, calcific, on the right common carotid), without signs of haemodynamically significant stenosis.

Abdominal Echography with Renal Artery Doppler

Liver with normal dimensions and steatosis. Regular biliary tree. Normal spleen dimensions. Pancreas and adrenal glands without signs of abnormal lesions. Abdominal aorta with normal calibre and several calcific atherosclerotic plaques. Right kidney with longitudinal diameter 98 mm and maintained cortical thickness.

Left kidney with longitudinal diameter 82 mm and reduced cortical thickness. Left renal artery with haemodynamically significant stenosis (RAR around 4). Right renal artery without signs of haemodynamically significant stenosis. Intrarenal index resistance bilaterally increased (right, 0.79; left, 0.80).

Diagnosis

Uncontrolled arterial hypertension with cardiac (concentric LV hypertrophy), renal (stage 3 CKD, hypertensive nephropathy, overt proteinuria) and vascular (atherosclerotic carotid and abdominal aorta) organ damages. Left renal artery stenosis. Type 2 diabetes mellitus. Additional modifiable cardiovascular risk factors (chronic cigarette smoking, hypercholesterolaemia).

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The echographic evidence of LV hypertrophy and vascular atherosclerosis and the presence of proteinuria >300 mg/24 h do not modify the individual global cardiovascular risk profile, which remains high, according to 2013 ESH/ESC global cardiovascular risk stratification [1].

Which is the best therapeutic option in this patient?

Possible answers are:

1. Titrate the Ca-antagonist.
2. Add another drug class (e.g. ACE-inhibitor).
3. Titrate the alpha-1 blocker.
4. Maintain the same therapy waiting to run further examinations.

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; doxazosin 4 mg 1 cp h 22:00; and atorvastatin 20 mg 1 cp h 22:00. Insulin lispro 4 UI h 8:00, 8 UI h 13 and 8 UI h 20:00; insulin glargine 12 UI h 22:00.

Treatment Evaluation

- Maintain the same therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt and low-caloric restrictions
- Abdominal magnetic resonance angiography

3.3 Follow-Up (Visit 2) at 2 Months

At follow-up visit, the patient is in quite stable clinical conditions. He refers no clinical symptoms. The home blood pressure is stable and not controlled.

Physical Examination

- Clinical parameters substantially unchanged.

Blood Pressure Profile

- Home BP (average): 166/96 mmHg
- Sitting BP: 162/94 mmHg
- Standing BP: 158/94 mmHg at 1 min

Abdominal Magnetic Resonance Angiography

Evidence of stenosis at the proximal level of the left renal artery. Left kidney of reduced dimensions compared with the contralateral (illustrated in Fig. 3.3).

Diagnosis

Uncontrolled essential arterial hypertension with cardiac (concentric LV hypertrophy), renal (stage 3 CKD, hypertensive and diabetic nephropathy) and vascular (atherosclerotic carotid and abdominal aorta) organ damages. Left renal artery stenosis. Type 2 diabetes mellitus. Additional modifiable cardiovascular risk factors (chronic cigarette smoking, hypercholesterolaemia).

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; doxazosin 4 mg 1 cp h 22:00; atorvastatin 20 mg 1 cp h 22:00. Insulin lispro 4 UI h 8:00, 8 UI h 13 and 8 UI h 20:00; insulin glargine 12 UI h 22:00.

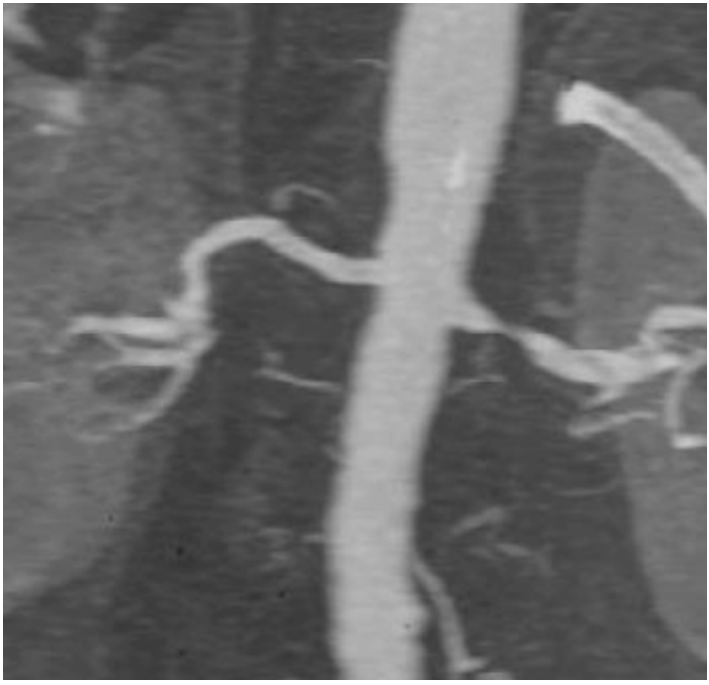

FIGURE 3.3 Abdominal magnetic resonance angiography showing the presence of stenosis at the proximal level of the left renal artery, with ipsilateral kidney of reduced dimensions

Which is the best therapeutic option in this patient?

Possible answers are:

1. Titrate the Ca-antagonist.
2. Add another drug class (e.g. ACE-inhibitor).
3. Titrate the alpha-1 blocker.
4. Maintain the same therapy while waiting to run further examinations

Treatment Evaluation

- Maintain amlodipine and doxazosin.
- Add perindopril 5 mg 1 cp h 8:00.
- Maintain the atorvastatin and insulin therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt and low-caloric restrictions
- Blood tests: serum creatinine, clearance creatinine, eGFR, potassium, 24-h proteinuria and lipid profile

3.4 Follow-Up (Visit 3) at 3 Months

At follow-up visit, the patient refers a stability of her general clinical conditions. She refers good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels are ameliorated but still uncontrolled.

Physical Examination

- Weight: 78 kg
- Body mass index (BMI): 28.3 g/m^2
- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 144/88 mmHg
- Sitting BP: 146/92 mmHg
- Standing BP: 144/90 mmHg

Haematological Profile

- Renal function: creatinine, 1.25 mg/dL; creatinine clearance (Cockcroft–Gault), 41 mL/min; and eGFR (MDRD), 42 mL/min/1.73 m^2
- Potassium, 3.81 mEq/L
- 24-h proteinuria: 356 mg
- TOT-C: 157 mg/dL; LDL-C: 90 mg/dL; HDL-C: 40 mg/dL; and TG 132 mg/dL

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; perindopril 5 mg 1 cp h 8:00; doxazosin 4 mg 1 cp h 22:00; atorvastatin 20 mg 1 cp h 22:00. Insulin lispro 4 UI h 8:00, 8 UI h 13 and 8 UI h 20:00; insulin glargine 12 UI h 22:00.

Treatment Evaluation

- Stop amlodipine 5 mg and perindopril 5 mg.
- Start a fix combination with perindopril 10 mg and amlodipine 5 mg 1 cp h 8:00.
- Maintain the remnant therapy (doxazosin 4 mg 1 cp h 22:00; atorvastatin 20 mg 1 cp h 22:00; insulin scheme).

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary low-salt and caloric restriction
- Daily 30-min walk
- Blood tests: serum creatinine, clearance creatinine, eGFR, potassium and 24-h proteinuria
- Abdominal echography with renal artery Doppler

3.5 Follow-Up (Visit 4) at 6 Months

At follow-up visit, the patient is in quite good clinical conditions. The home blood pressure levels are well controlled.

Physical Examination

- Weight: 77 kg
- Body mass index (BMI): 28.2 g/m^2
- Resting pulse: regular rhythm with normal heart rate (68 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 134/84 mmHg
- Sitting BP: 132/84 mmHg
- Standing BP: 130/82 mmHg

Haematological Profile

- Renal function: creatinine, 1.18 mg/dL; creatinine clearance (Cockcroft–Gault), 44 mL/min; and eGFR (MDRD), 45 mL/min/1.73 m^2
- Potassium, 4.01 mEq/L
- 24-h proteinuria: 165 mg

Current Treatment

Perindopril/amlodipine (fix combination) 10/5 mg 1 cp h 8:00; doxazosin 4 mg 1 cp h 22:00; atorvastatin 20 mg 1 cp h 22:00. Insulin lispro 4 UI h 8:00, 8 UI h 13 and 8 UI h 20:00; insulin glargine 12 UI h 22:00.

Treatment Evaluation

Add acetylsalicylic acid 100 mg 1 cp h 14:00. No change for current pharmacological therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary low-salt and caloric restriction
- Daily 30' walk
- Every 6 months: serum creatinine, clearance creatinine, eGFR, potassium and 24-h proteinuria
- Every year: abdominal echography with renal artery Doppler

3.6 Discussion

The two major aspects of the present clinical case, which deserve comments, are the presence of diabetes mellitus and the evidence of renal artery stenosis.

Arterial hypertension is a common feature of type 2 diabetes mellitus [2]. While it is worldwide recognized the prognostic importance to reduce systolic blood pressure (SBP) when values are >140 mmHg in these patients, available evidence fails to show any further benefits at target of SBP <130 mmHg. The comparison of CV-event reductions in various trials indicates that, for similar SBP differences, the benefit of more intensive lowering of SBP becomes gradually smaller when the SBP differences are in the lower part of the 139–130 mmHg range [3]. Supportive evidence against lowering SBP <130 mmHg comes from the ACCORD trial [4]. As a concern, the diastolic blood pressure (DBP), target between 80 and 85 mmHg, is supported by the results of the HOT and UKPDS studies [5, 6]. In the present clinical case, the patient showed diabetic nephropathy (overt proteinuria), with no

evidence of diabetic retinopathy or neuropathy. It was documented that proteinuria is delayed or reduced by treatment, but trials in diabetic populations have been unable to demonstrate that proteinuria reduction is also accompanied by a reduction in hard CV outcomes [7–9].

The choice of antihypertensive drugs should be based on efficacy and tolerability. All classes of antihypertensive agents are useful, according to a meta-analysis [10]. BP control is quite difficult in diabetes; thus most of the patients need combination therapy. Because of a greater effect of RAS blockers on urinary protein excretion [11], it appears reasonable to have either an ACE-inhibitor or an ARB in the combination. Thiazide and thiazide-like diuretics are useful and are often used together with RAS blockers. Calcium antagonists have been shown to be useful, especially when combined with an RAS blocker.

The second major aspect of this clinical case concerns the evidence of renal artery stenosis. The possibility that a renal artery stenosis might occur has to be suspected anytime that, in a patient with essential hypertension on chronic therapy, the blood pressure values suddenly rise. This is particularly evident in an elderly patient, especially if smoker and diabetic, two major atherosclerotic risk factors. Rarely the renovascular artery stenosis secondary to atherosclerosis progresses to renal insufficiency [12]. In this patient, the first level examination was represented by the renal artery Doppler, which needs a further confirmation by a second level exam, i.e. the magnetic resonance angiography or the spiral computed tomography. In this case, the abdominal magnetic resonance was preferred, according to the reduced renal function of the patient.

It is worth of noting that in this clinical case, the occurrence of renal artery stenosis is in coexistence with the presence of essential hypertension, according to the clinical history. The nephropathy has a hypertensive (see elevated intrarenal resistance arteries) and a diabetic (see overt proteinuria) origin. The 2013 ESH/ESC Guidelines [1] underline that it is still debated whether patients with hypertension or renal

insufficiency benefit from interventions: mostly percutaneous renal artery stenting. While there is convincing information favouring this procedure in younger (mostly female) patients with uncontrolled hypertension in fibromuscular hyperplasia (high percentage of success) [13], the matter is highly controversial in atherosclerotic renovascular hypertension. Two retrospective studies have reported improvements (though not in mortality) in patients with bilateral renal artery stenosis complicated by recurrent episodes of acute heart failure [14]. In all other conditions with renal artery stenosis, uncertainties continue regarding the benefit of angioplasty and stenting, despite several controlled trials. Two randomized clinical trials and 21 cohort studies published before 2007 showed no uniform pattern of benefit. The more recent ASTRAL trial, including 806 patients randomized between angioplasty and stenting, plus medical therapy vs. medical therapy alone, did not provide any evidence of clinically meaningful benefit on BP, renal function or CV events [15]. Although no final conclusions can be drawn from ASTRAL because of some limitations in its design (patients with a strong indication for intervention were excluded from randomization) and the lack of statistical power, intervention is at present not recommended in atherosclerotic renal artery stenosis if renal function has remained stable over the past 6–12 months and if hypertension can be controlled by an acceptable medical regimen. Suitable medical regimens should include RAS blockers, except in bilateral renal artery stenosis or in unilateral artery stenosis with evidence of functional importance by ultrasound examinations or scintigraphy.

Take-Home Messages

- An SBP target of >140 mmHg is strongly recommended in hypertensive patients with diabetes mellitus. No evidence shows any further benefits at target of SBP <130 mmHg. The DBP target is recommended to be between 80 and 85 mmHg.

- RAS inhibitors have specific renoprotective effects and represent the drugs of choice for the treatment of hypertension in patients with diabetes mellitus.
- In the presence of atherosclerotic renal artery stenosis, intervention of revascularization is not recommended if renal function has remained stable and if hypertension can be controlled by an acceptable medical regimen. Medical regimen should include RAS blockers.

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Chapter 4
Clinical Case 4: Patient with End-Stage Renal Disease

4.1 Clinical Case Presentation

A 68-year-old, Caucasian male, retired (former bricklayer), presented to the outpatient clinic for clinical assessment of uncontrolled hypertension. The patient refers history of essential hypertension by the age of 45 years. For several years, he exclusively followed a non-pharmacological therapy, based on low-sodium intake and aerobic physical activity. By about 10 years, he started a treatment with a beta-blocker (atenolol 50 mg) and an alpha-1 blocker doxazosin 2–4 mg/day, with ineffective blood pressure control. Five years later, because of severe bradycardia, he was switched from atenolol to a Ca-antagonist amlodipine 10 mg/day, subsequently down-stepped to 5 mg/day because of lower limb oedema, with apparent satisfactory blood pressure control. Concomitantly, 10 years ago he was diagnosed a chronic kidney disease (CKD), which has progressively worsened over time to an actual stage 4 CKD, treated with furosemide 25 mg/day, 1,25-dihydroxycholecalciferol (calcitriol) 0.25 μg/day and calcium carbonate 500 mg/day. By about 6 months, his general practitioner increased the dosage of doxazosin to 6 mg/day, in addition to current pharmacological therapy.

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DOI 10.1007/978-3-319-39164-9_4,

Family History

He has paternal history of hypertension and diabetes and maternal history of coronary artery disease.

Clinical History

He never smoked. He has no history of alcohol consumption and sedentary lifestyle. He also has hypercholesterolaemia, treated with atorvastatin 20 mg daily. He is also affected by hypothyroidism, treated with levothyroxine 50 μg daily.

Physical Examination

- Weight: 82 kg
- Height: 165 cm
- Body mass index (BMI): 30.1 g/m^2
- Waist circumference: 112 cm
- Respiration: normal
- Heart sounds: S1–S2 regular; pansystolic regurgitant murmur
- Resting pulse: regular rhythm with normal heart rate (68 beats/min)
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive retinopathy

Haematological Profile

- Haemoglobin: 11.8 g/dL
- Haematocrit: 35.9 %
- Fasting plasma glucose: 97 mg/dL
- Fasting lipids: total cholesterol (TOT-C), 144 mg/dL; low-density lipoprotein cholesterol (LDL-C), 76 mg/dL; high-density lipoprotein cholesterol (HDL-C), 37 mg/dL; and triglycerides (TG), 158 mg/dL

- Electrolytes: sodium, 142 mEq/L; potassium, 3.64 mEq/L; and calcium, 8.8 mg/dL
- Serum uric acid: 6.2 mg/dL
- Renal function: creatinine, 2.76 mg/dL; creatinine clearance (Cockcroft–Gault), 29 mL/min; and estimated glomerular filtration rate (eGFR) (MDRD), 23 mL/min/1.73 m^2
- Urine analysis (dipstick): proteinuria 80 mg/dL
- Normal liver function tests
- Normal thyroid function tests

Blood Pressure Profile

- Home BP (average): 164/104 mmHg
- Sitting BP: 166/102 mmHg (left arm > right arm)
- Standing BP: 124/96 mmHg at 1 min
- Standing BP: 146/100 mmHg at 2 min
- Standing BP: 158/102 mmHg at 3 min
- 24-h BP: 128/82 mmHg; HR: 64 bpm
- Daytime BP: 159/103 mmHg; HR: 68 bpm
- Night-time BP: 84/53 mmHg; HR: 59 bpm

A 24-h ambulatory blood pressure profile is illustrated in Fig. 4.1.

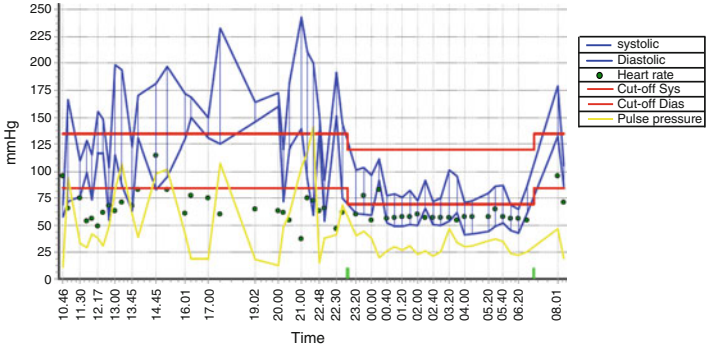

FIGURE 4.1 A 24-h ambulatory blood pressure profile

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (68 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH (Sokolow–Lyon 1.8 mV, Cornell voltage 1.4 mV) (illustrated in Fig. 4.2) Peripheral (**a**) and precordial (**b**) leads.

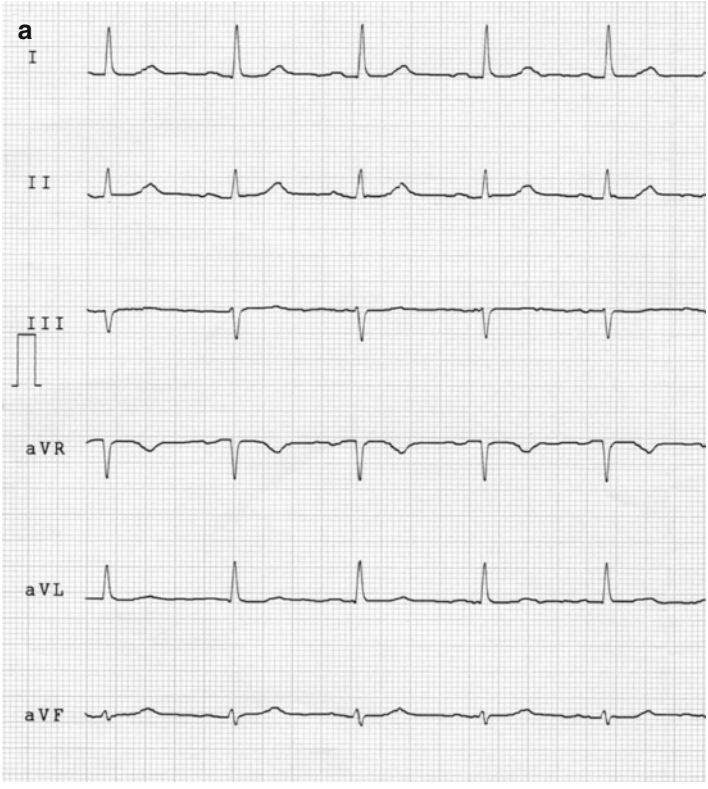

FIGURE 4.2 (**a**, **b**) Sinus rhythm with normal heart rate (68 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH

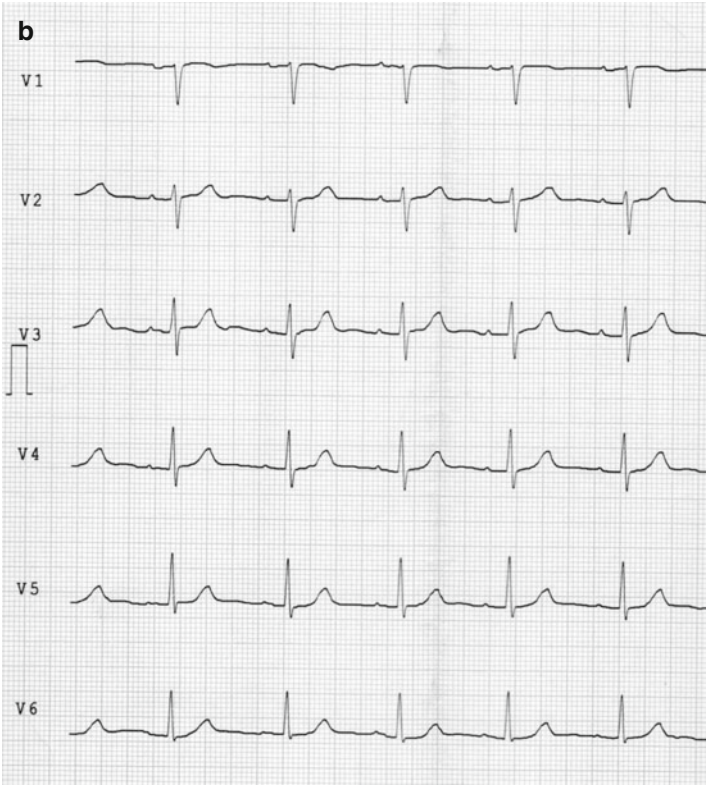

FIGURE 4.2 (continued)

Current Treatment

Levothyroxine 50 µg 1 cp h 7:00; calcitriol 0.25 µg 1 cp h 8:00; Ca carbonate 500 mg 1 cp h 8:00; amlodipine 5 mg 1 cp h 8:00; furosemide 25 mg 1 cp h 8:00; doxazosin 4 mg 1+ ½ cp h 22:00; and atorvastatin 20 mg 1 cp h 22:00

Diagnosis

Uncontrolled arterial hypertension with associated clinical condition (stage 4 CKD). Orthostatic hypotension. Additional modifiable cardiovascular risk factor (hypercholesterolaemia; obesity). Hypothyroidism pharmacologically treated.

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has very high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Upstep the alpha-1 blocker.
2. Down-step the alpha-1 blocker.
3. Insert an ACE-inhibitor.
4. Titrate the diuretic therapy.
5. Switch the statin therapy.

Treatment Evaluation

- Maintain amlodipine 5 mg 1 cp h 8:00.
- Down-step doxazosin to 4 mg 1 cp h 22:00.
- Insert perindopril 5 mg 1 cp h 8:00.

- Upstep furosemide to 50 mg/daily.
- No changes for current non-cardiovascular pharmacological therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt and low-caloric restrictions
- Blood tests: serum creatinine, clearance creatinine, eGFR, potassium, calcium, urine analysis and 24 h proteinuria
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties)
- Abdominal echography with renal artery Doppler

4.2 Follow-Up (Visit 1) at 6 Weeks

At follow-up visit, the patient reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels are ameliorated, but still elevated. The orthostatic hypotension is reduced, but still present.

Physical Examination

- Weight: 81 kg
- Body mass index (BMI): 29.7 g/m^2
- Resting pulse: regular rhythm with normal heart rate (66 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 144/92 mmHg
- Sitting BP: 148/94 mmHg

- Standing BP: 130/92 mmHg at 1 min
- Standing BP: 140/96 at 3 min

Haematological Profile

- Creatinine, 2.94 mg/dL; creatinine clearance (Cockcroft–Gault), 27.5 mL/min; and eGFR, MDRD, 22 mL/min/1.73 m^2
- Potassium, 3.8 mEq/L, and calcium, 9.0 mg/dL
- Urine analysis (dipstick): proteinuria 24 mg/dL
- 24-h proteinuria: 320 mg/24 h

Current Treatment

Levothyroxine 50 μg 1 cp h 7:00; calcitriol 0.25 μg 1 cp h 8:00; Ca carbonate 500 mg 1 cp h 8:00; amlodipine 5 mg 1 cp h 8:00; furosemide 25 mg 2 cp h 8:00; perindopril 5 mg 1 cp h 8:00; doxazosin 4 mg 1 cp h 22:00; and atorvastatin 20 mg 1 cp h 22:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Eccentric left ventricle (LV) hypertrophy (LV mass indexed 122 g/m^2; relative wall thickness, 0.41) with normal chamber dimension (LV end-diastolic diameter 51 mm), impaired LV relaxation (E/A ratio < 1) at both conventional and tissue Doppler evaluations and normal ejection fraction (LV ejection fraction 54 %, LV fractional shortening 36 %). Normal dimension of aortic root and left atrium. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (+) regurgitations at Doppler ultrasound examination.

Abdominal Echography with Renal Artery Doppler

Liver steatosis. Regular biliary tree. Normal spleen dimensions. Adrenal glands without signs of abnormal lesions. Abdominal aorta with normal calibre and calcific atherosclerotic plaques. Kidneys with normal dimensions (longitudinal diameter: right 102 mm, left 106 mm) and reduced cortical thickness. Renal arteries without signs of haemodynamically significantly stenosis. Intrarenal index resistance bilaterally increased (right: 0.82; left 0.83).

Diagnosis

Uncontrolled arterial hypertension with associated clinical condition (stage 4 CKD, proteinuria > 300 mg/24 h) and cardiac (eccentric LV hypertrophy) and vascular (atherosclerotic abdominal aorta) organ damages. Orthostatic hypotension. Hypercholesterolaemia. Obesity. Hypothyroidism pharmacologically treated.

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The echographic evidence of LV hypertrophy and vascular atherosclerosis, as well as the presence of proteinuria > 300 mg/24 h, does not modify the individual global cardiovascular risk profile in a patient with associated clinical disease (established renal disease), which remains very

high, according to 2013 ESH/ESC global cardiovascular risk stratification [1].

Which is the best therapeutic option in this patient?

Possible answers are:

1. Titrate the Ca-antagonist.
2. Add another drug class (e.g. beta-blocker).
3. Titrate the ACE-inhibitor.
4. Down-step the alpha-1 blocker.

Treatment Evaluation

- Stop amlodipine 5 mg and perindopril 5 mg.
- Start fix combination with perindopril 10 mg and amlodipine 10 mg 1 cp h 8:00.
- Down-step doxazosin to 2 mg 1 cp h 22:00.
- Maintain furosemide 25 mg 2 cp h 8:00.
- Maintain the remnant non-cardiovascular therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt and low-caloric restrictions
- Daily 30-min walk
- Blood tests: serum creatinine, clearance creatinine, eGFR, potassium, calcium, urine analysis and 24 h proteinuria

4.3 Follow-Up (Visit 2) at 3 Months

At follow-up visit, the patient is in quite stable clinical conditions. He refers no clinical symptoms. He also reports good adherence to prescribed medications. The home blood

pressure is stable and well controlled. The orthostatic hypotension disappeared.

Physical Examination

- Weight: 80 kg
- Body mass index (BMI): 29.4 g/m^2
- Resting pulse: regular rhythm with normal heart rate (67 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 132/82 mmHg
- Sitting BP: 130/84 mmHg
- Standing BP: 124/82 mmHg at 1 min

Haematological Profile

- Creatinine, 2.68 mg/dL; creatinine clearance (Cockcroft–Gault), 29.8 mL/min; and eGFR, MDRD, 24 mL/min/1.73 m^2
- Potassium, 3.65 mEq/L, and calcium, 9.0 mg/dL
- Urine analysis (dipstick): proteinuria 16 mg/dL
- 24-h proteinuria: 215 mg/24 h

Current Treatment

Levothyroxine 50 μg 1 cp h 7:00; calcitriol 0.25 μg 1 cp h 8:00; Ca carbonate 500 mg 1 cp h 8:00; perindopril/amlodipine 10/10 mg 1 cp h 8:00; furosemide 25 mg 2 cp h 8:00; doxazosin 2 mg 1 cp h 22:00; and atorvastatin 20 mg 1 cp h 22:00

Which is the best therapeutic option in this patient?

Possible answers are:

1. Maintain the same therapy.
2. Down-step the diuretic therapy.
3. Titrate the statin therapy.
4. Down-step the alpha-1 blocker.

Treatment Evaluation

Maintain the same therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Dietary salt and low-caloric restrictions.
- Daily 30' walk.
- Blood tests: blood cell count, serum creatinine, clearance creatinine, eGFR, potassium, calcium, urine analysis, 24 h proteinuria, plasma glucose, lipid profile, and thyroid function profile.
- Repeat 24-h blood pressure measurement.
- Repeat 12-lead electrocardiogram.
- Repeat echocardiogram.

4.4 Follow-Up (Visit 3) at 1 Year

At follow-up visit, the patient refers a stability of his general clinical conditions. He refers good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels remained substantially well controlled.

Physical Examination

- Weight: 82 kg
- Body mass index (BMI): 30.1 kg/m^2
- Slight lower limb oedema
- Clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 126/80 mmHg
- Sitting BP: 130/78 mmHg
- Standing BP: 128/76 mmHg
- 24-h BP, 114/67 mmHg; HR, 80 bpm
- Daytime BP, 127/78 mmHg; HR, 86 bpm
- Night-time BP, 101/57 mmHg; HR, 75 bpm

A 24-h ambulatory blood pressure profile is illustrated in Fig. 4.3.

Haematological Profile

- Haemoglobin: 11.6 g/dL
- Haematocrit: 34.2 %

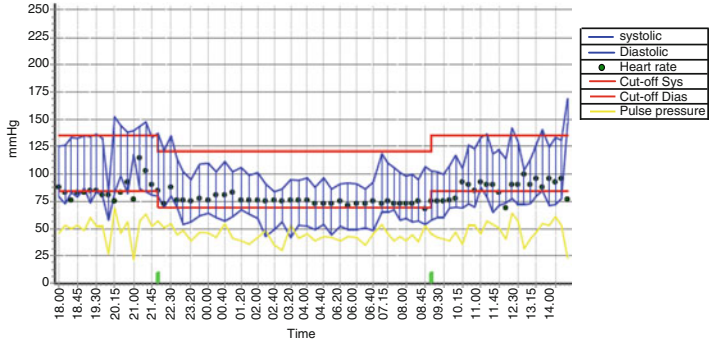

FIGURE 4.3 A 24-h ambulatory blood pressure profile

- Creatinine, 2.78 mg/dL; creatinine clearance (Cockcroft–Gault), 29 mL/min; and eGFR, MDRD, 23 mL/min/1.73 m^2
- Urine analysis (dipstick): proteinuria 20 mg/dL
- 24-h proteinuria: 234 mg/24 h
- Electrolytes: sodium 140 mEq/L; potassium, 3.7 mEq/L; and calcium 9.0 mg/dL
- Serum uric acid: 6.5 mg/dL
- Fasting plasma glucose: 94 mg/dL
- TOT-C: 155 mg/dL; LDL-C: 87 mg/dL; HDL-C: 39 mg/dL; and TG 145 mg/dL
- Thyroid function profile: normal

Current Treatment

Levothyroxine 50 μg 1 cp h 7:00; calcitriol 0.25 μg 1 cp h 8:00; Ca carbonate 500 mg 1 cp h 8:00; perindopril/amlodipine 10/10 mg 1 cp h 8:00; furosemide 25 mg 2 cp h 8:00; doxazosin 2 mg 1 cp h 22:00; and atorvastatin 20 mg 1 cp h 22:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (64 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH (Sokolow–Lyon 1.6 mV, Cornell voltage 1.7 mV). Similar to the previous one.

Echocardiogram with Doppler Ultrasound

Eccentric left ventricle (LV) hypertrophy (LV mass indexed 114 g/m^2; relative wall thickness, 0.40) with normal chamber dimension (LV end-diastolic diameter 49 mm), impaired LV relaxation (E/A ratio <1) at both conventional and tissue

Doppler evaluations and normal ejection fraction (LV ejection fraction 56 %, LV fractional shortening 37 %). Normal dimension of aortic root and left atrium. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (+) regurgitations at Doppler ultrasound examination.

Conclusions: slight eccentric LV hypertrophy, ameliorated compared with the previous one.

Treatment Evaluation

No change for current pharmacological therapy

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt restriction
- Daily 30' walk

4.5 Discussion

It is worldwide recognized and summarized in the 2013 ESH/ESC Guidelines [1] that office blood pressure bears an independent continuous relationship with, among others, the incidence of end-stage renal disease [2], an effect observed at all ages and in all ethnic groups. In particular, hypertension is the second primary diagnosis for those patients who start dialysis, preceded only by diabetes mellitus. This statement is particularly appropriated and adaptable to this clinical case, which shows a picture of a chronic progressive impairment of renal function in a nondiabetic patient with a long history of uncontrolled essential hypertension. It is evident that the delayed onset of pharmacological treatment (about 10 years), together with a period of ineffective blood pressure control, is a major

cause of CKD. The patient is at very high CV risk, as documented by the stage 4 CKD (eGFR < 30 mL/min) and overt proteinuria (>300 mg/24 h). It is important to highlight that while a low eGFR points to diminished renal function, the finding of an increased rate of protein excretion points, in general, to a derangement in glomerular filtration barrier. The presence of overt proteinuria generally indicates the existence of established renal parenchymal disease. In both diabetic and nondiabetic hypertensive patients, microalbuminuria and even more proteinuria have been shown to predict CV events, and continuous relationships between CV and non-CV mortality and incremental proteinuria have been reported in several studies [3, 4]. Both in the general population and in diabetic patients, the concomitance of an increased urinary protein excretion and a reduced eGFR indicates a greater risk of CV and renal events than either abnormality alone, making these risk factors independent and cumulative [5]. Thus, proteinuria and low eGFR provide complementary information in defining kidney dysfunction. Therefore, concomitant evaluation of both markers should be considered to adequately assess kidney dysfunction and cardiovascular risk [6].

Another important comment to this clinical case concerns the choice of the pharmacological therapy adopted by the patient's general practitioner. Thus, it is not acceptable that, at the beginning of pharmacological treatment and in concomitance with the diagnosis of CKD, the first-line therapy included beta- and alpha-1 blockers. In this scenario, a RAS blocker would have to be inserted because RAS blockers are more effective in reducing albuminuria and renal events, including end-stage renal disease and doubling of creatinine, than other antihypertensive agents [7–9]. For these reasons, consensus has emerged that ACE-inhibitors and angiotensin-II receptor blockers have specific renoprotective effects. Guidelines specify that these are the drugs of choice for the treatment of hypertension in patients with renal disease [1]. Of note, a slight increase (up to 20 %) in serum creatinine may sometimes occur when antihypertensive therapy—particularly by RAS blockers—is instituted or intensified, such

as what occurred in this clinical case (see visit 1 vs. first). This is usually a temporary phenomenon and should not be taken as a sign of progressive renal deterioration.

A final consideration concerns the blood pressure target to be achieved in these patients. Available data are not conclusive, especially for specific effects of RAS blockers. Indeed, in those trials conducted in CKD patients, patients randomized to a lower target blood pressure (125–130 mmHg) showed no differences in terms of renal disease progression or events as compared to those randomized to a higher target (<140 mmHg) [10–12], with exceptions for those with overt proteinuria [13, 14]. For these reasons, the 2013 ESH/ESC Guidelines [1] recommend that lowering systolic blood pressure to <140 mmHg should be considered in patients with CKD. When overt proteinuria is present, systolic blood pressure values <130 mmHg may be considered, provided that changes in eGFR are monitored. Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. Aldosterone antagonists cannot be recommended in CKD, especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalaemia.

Take-Home Messages

- The concomitance of an increased urinary protein excretion and a reduced eGFR indicates a greater risk of CV and renal events than either abnormality alone, making these risk factors independent and cumulative.
- RAS inhibitors have specific renoprotective effects and represent the drugs of choice for the treatment of hypertension in patients with chronic renal disease.
- In patients with chronic kidney disease, lowering systolic blood pressure to <140 mmHg should be considered. When overt proteinuria is present, systolic blood pressure values <130 mmHg may be considered, provided that changes in eGFR are monitored.

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Chapter 5
Clinical Case 5: Patient with Essential Hypertension and Congestive Heart Failure

5.1 Clinical Case Presentation

An 80-year-old, Caucasian male, retired (former engine driver), presented to the outpatient clinic for clinical assessment. Long history (>20 years) of non-treated essential hypertension. About 10 years ago, he started a beta-blocker (atenolol 50 mg) plus Ca-antagonist (nifedipine 60 mg). Five years later, he added a diuretic (chlorthalidone 25 mg/day) with home blood pressure around 145–140/95–90 mmHg. He was diagnosed with stage two chronic kidney disease. One year ago he referred chest pain, and he underwent a coronary angiography which showed "coronary arteries free of significant atherosclerotic lesions and marked dilation of left ventricle, with generalized hypokinesia". He received diagnosis of *dilated cardiomyopathy with systolic dysfunction*. He also underwent an implantation of a pacemaker ICD-DDDR. From then, he has been prescribed furosemide 25 mg 1 cp daily, amlodipine 10 mg daily, ramipril 10 mg daily, bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00, acetylsalicylic acid (ASA) 100 mg daily and doxazosin 4 mg 1 cp h 22:00. Six months ago he was diagnosed with permanent atrial fibrillation. At present, he refers blood pressure around 110/70 mmHg, and he complains fatigue, limited exercise tolerance and sometimes shortness of breath. No chest pain is referred.

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Family History

He has paternal and maternal history of hypertension. He also has one sister with hypertension, obesity and hypercholesterolaemia and one daughter with hypertension.

Clinical History

He is a cigarette smoker (around 20 cigarettes daily, for >30 years, recently down-stepped to 4–5 daily). He also has hypercholesterolaemia treated with simvastatin 20 mg daily. He has no history of alcohol abuse. He has also a benign prostatic hyperplasia.

Physical Examination

- Weight: 91 kg
- Height: 178 cm
- Body mass index (BMI): 28.7 kg/m^2
- Waist circumference: 101 cm
- Respiration: attenuated breath sounds and late-inspiratory fine bilateral crackles
- Heart sounds: distal cardiac sounds and S3 and pansystolic regurgitant murmur
- Resting pulse: abnormal rhythm with heart rate of 80 beats/min
- Neck vein distension, with hepatojugular reflux; hepatomegaly
- Lower limb oedema
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive retinopathy

Haematological Profile

- Haemoglobin: 13.1 g/dL
- Haematocrit: 44.5 %

- Fasting plasma glucose: 91 mg/dL
- Fasting lipids: total cholesterol (TOT-C), 163 mg/dL; low-density lipoprotein cholesterol (LDL-C), 100 mg/dL; high-density lipoprotein cholesterol (HDL-C), 36 mg/dL; and triglycerides (TG), 131 mg/dL
- Electrolytes: sodium, 139 mEq/L, and potassium, 4.86 mEq/L
- Serum uric acid: 5.3 mg/dL
- Renal function: creatinine, 2.01 mg/dL; creatinine clearance (Cockcroft–Gault), 37 mL/min; and estimated glomerular filtration rate (eGFR) (MDRD), 32 mL/min/1.73 m^2
- BNP, 485 pg/mL
- Urinary albumin/creatinine ratio (morning urine sample): 46 mg/g
- Normal liver function tests
- Normal thyroid function tests

Blood Pressure Profile

- Home BP (average): 110/70 mmHg
- Sitting BP: 116/78 mmHg (right arm = left arm)
- Standing BP: 96/72 mmHg at 1 min

Chest Radiography

Enlargement of left cardiac sections. Pacemaker in left hemithorax with double catheter in right atrium and right ventricle. Raised right hemi-diaphragm, with ipsilateral slight pleural effusion (Fig. 5.1).

12-Lead Electrocardiogram

Atrial fibrillation with ventricular response of 70 bpm. ST-segment abnormalities. No signs of LVH (Sokolow–Lyon 1.5 mV, Cornell voltage 2.0 mV) (illustrated in Fig. 5.2). Peripheral (**a**) and precordial (**b**) leads.

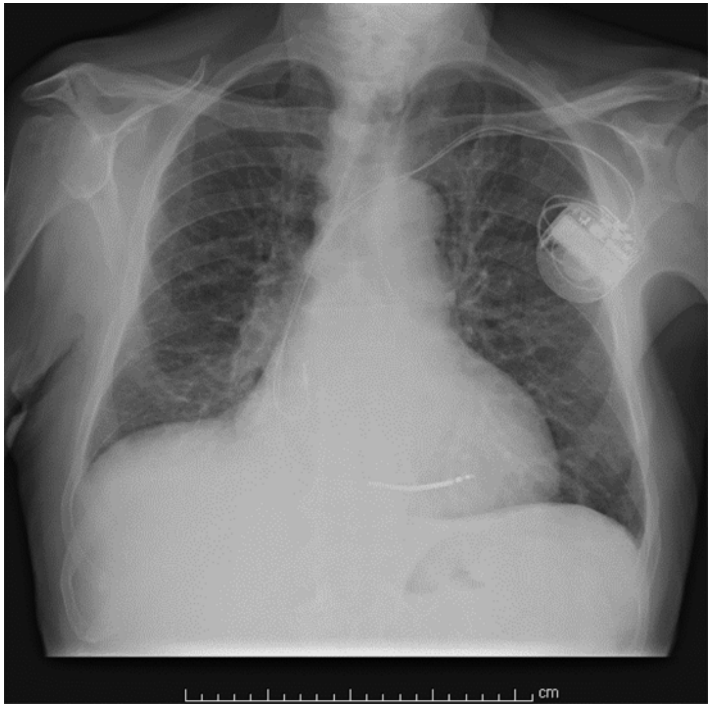

FIGURE 5.1 Standard postero-anterior chest radiograph showing enlargement of left cardiac sections. The presence of a pacemaker in left hemi-thorax with double catheter in right atrium and right ventricle. Raised right hemi-diaphragm, with ipsilateral slight pleural effusion

Current Treatment

Furosemide 25 mg 1 cp h 8:00, amlodipine 10 mg 1 cp h 8:00, ramipril 10 mg 1 cp h 8:00, bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00, ASA 100 mg 1 cp h 14:00, doxazosin 4 mg 1 cp h 22:00 and simvastatin 20 mg 1 cp h 22:00

Diagnosis

Overtreated arterial hypertension with associate clinical condition (congestive heart failure secondary to dilated cardiomyopathy

with systolic dysfunction) and stage 3 chronic kidney disease. Permanent atrial fibrillation. Cardiac pacemaker. Orthostatic hypotension. Additional modifiable cardiovascular risk factors (chronic cigarette smoking, hypercholesterolaemia).

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has very high cardiovascular risk.

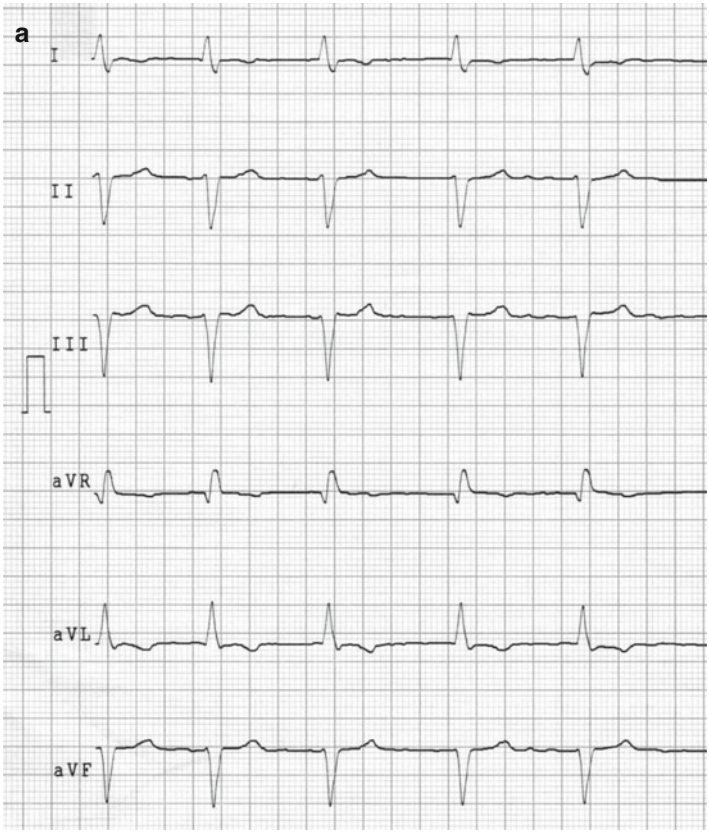

FIGURE 5.2 (**a**, **b**) Atrial fibrillation with ventricular response of 70 bpm. ST-segment abnormalities. No signs of LVH

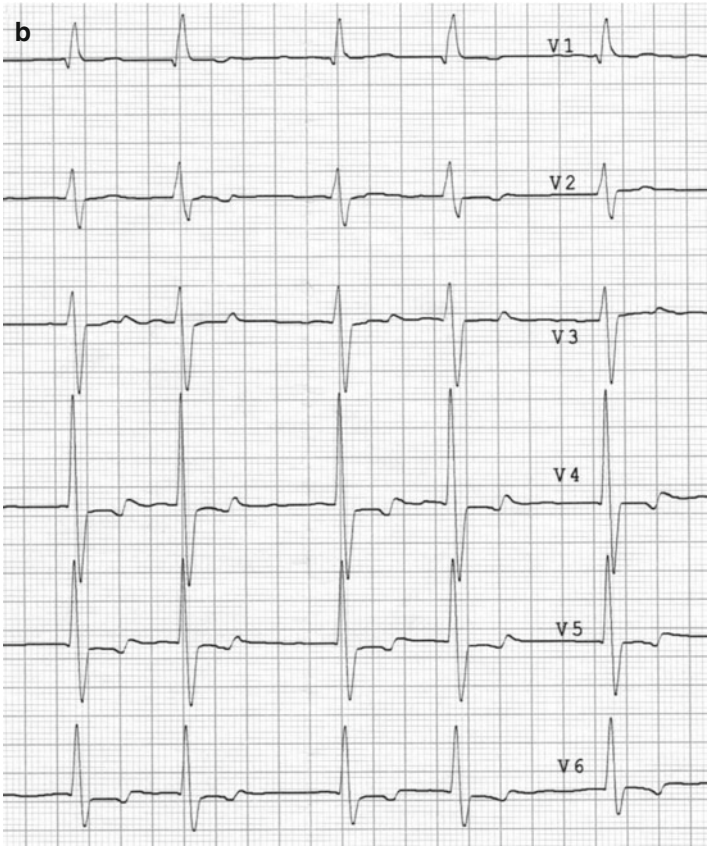

FIGURE 5.2 (continued)

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Treatment Evaluation

- Maintain bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00.
- Maintain the dose of ACE-inhibitor.
- Upstep furosemide to 25 mg 2 cp h 8:00.
- Down-step amlodipine to 5 mg 1 cp h 8:00.
- Down-step doxazosin to 2 mg 1 cp h 22:00.
- Stop simvastatin and start atorvastatin 20 mg 1 cp h 20:00.
- Stop ASA and start warfarin 5 mg to obtain an optimal range (INR between 2 and 3).

Which is the best therapeutic option in this patient?

Possible answers are:

1. Down-step the dose of dihydropyridinic calcium antagonist or the ACE-inhibitor.
2. Modify the dose of diuretic.
3. Down-step or stop the alpha-1 blocker.
4. Titrate the beta-blocker therapy.
5. Switch the statin therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Quit smoking.
- Dietary salt restriction.
- Blood tests: serum creatinine, clearance creatinine, eGFR, potassium, B-type natriuretic peptide (BNP), INR and lipid profile.
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties).
- Abdominal echography with renal artery Doppler.

5.2 Follow-Up (Visit 1) at 4 Weeks

At follow-up visit, the patient refers an improvement of the limited exercise tolerance and the shortness of breath. He quitted smoking, but he did not follow the dietary prescriptions. He also reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels increased, within the normal range.

Physical Examination

- Weight: 89 kg (–2 kg)
- Respiration: attenuated fine bilateral basal crackles
- Resting pulse: abnormal rhythm with heart rate of 74 bpm
- Reduced the neck vein distension and the lower limb oedema
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 120/78 mmHg
- Sitting BP: 124/76 mmHg
- Standing BP: 116/74 mmHg

Haematological Profile

- Plasma potassium, 4.82 mEq/L
- Creatinine, 2.06 mg/dL; Cockcroft–Gault, 37 mL/min; and eGFR (MDRD), 31 mL/min/1.73 m^2
- BNP, 265 pg/mL
- INR, 2.4
- TOT-C, 154 mg/dL; LDL-C, 90 mg/dL; HDL-C, 39 mg/dL; and TG, 124 mg/dL

Current Treatment

Bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00; furosemide 25 mg 2 cp h 8:00; amlodipine 5 mg 1 cp h 8:00, ramipril 10 mg 1 cp h 8:00, warfarin 5 mg 1 cp h 8:00, atorvastatin 20 mg 1 cp h 20:00 and doxazosin 2 mg 1 cp h 22:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Aortic root calcific, of normal dimensions. Left atrium dilated (45 mm). Left ventricle (LV) with abnormal chamber dimension (LV end-diastolic diameter 70 mm), impaired LV relaxation at both conventional (E/A ratio 1.5—pseudo-normalization) and tissue Doppler evaluations and global ventricular hypokinesia with reduced ejection fraction (LV ejection fraction 31 %). Indexed LV mass increased, 184 g/m^2; relative wall thickness, 0.29. Type 2 diastolic dysfunction. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Aortic (+), mitral (++) and tricuspid (+) regurgitations at Doppler ultrasound examination. PAPs 36 mmHg.

Abdominal Echography with Renal Artery Doppler

Hepatomegaly with liver steatosis. No signs of portal hypertension. Biliary tree not dilated. Normal spleen dimensions. Adrenal glands without signs of abnormal lesions. Abdominal aorta with normal dimension and diffuse atherosclerotic plaques.

Kidneys with normal dimensions and reduced cortical thickness. Renal arteries without signs of haemodynamically significant stenosis. Intrarenal index resistance bilaterally increased (right: 0.81; left 0.80).

Diagnosis

Arterial hypertension with congestive heart failure (dilated cardiomyopathy with severe systolic dysfunction and type 2 diastolic dysfunction; AHA classification stage C, NYHA II). Renal (stage 3 chronic kidney disease, hypertensive nephropathy) and vascular (atherosclerotic abdominal aorta) damages. Permanent atrial fibrillation. Cardiac pacemaker. Additional modifiable cardiovascular risk factors (chronic cigarette smoking, hypercholesterolaemia).

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The echocardiographic evidence of dilated cardiomyopathy with systolic and dysfunction does not modify the individual global cardiovascular risk profile, which remains very high, according to 2013 ESH/ESC global cardiovascular risk stratification [1].

Which is the best therapeutic option in this patient?

Possible answers are:

1. Down-step or stop doxazosin.
2. Add another drug class (e.g. aldosterone antagonist).
3. Modify the diuretic therapy.
4. Titrate the beta-blocker therapy.

Treatment Evaluation

- Maintain bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00.
- Stop doxazosin.
- Maintain the remnant therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Quit smoking.
- Dietary salt and caloric restriction.
- Blood tests: creatinine, potassium and BNP.

5.3 Follow-Up (Visit 2) at 3 Months

At follow-up visit, the patient is in quite stable clinical conditions. He refers to carry out ordinary physical activity without symptoms. He also reports good adherence to prescribed medications. The home blood pressure is stable and well controlled.

Physical Examination

- Weight: 88 kg
- Clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 120/72 mmHg
- Sitting BP: 124/76 mmHg
- Standing BP: 120/74 mmHg

Haematological Profile

- Creatinine, 1.91 mg/dL; Cockcroft–Gault, 39 mL/min; and eGFR (MDRD), 38 mL/min/1.73 m^2
- Plasma potassium, 4.9 mEq/L
- BNP, 241 pg/mL

Current Treatment

Bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00; furosemide 25 mg 2 cp h 8:00; amlodipine 5 mg 1 cp h 8:00, ramipril 10 mg 1 cp h 8:00, warfarin 5 mg 1 cp h 8:00 and atorvastatin 20 mg 1 cp h 20:00

Which is the best therapeutic option in this patient?

Possible answers are:

1. Maintain the same therapy.
2. Modify the diuretic therapy.
3. Down-step the ACE-inhibitor.
4. Titrate the beta-blocker therapy.

Treatment Evaluation

Maintain bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00; furosemide 25 mg 2 cp h 8:00, amlodipine 5 mg 1 cp h 8:00, ramipril 10 mg 1 cp h 8:00, warfarin 5 mg 1 cp h 8:00 and atorvastatin 20 mg 1 cp h 20:00

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Dietary salt and caloric restriction.

- Daily slow walk.
- Blood tests: complete blood count, creatinine, plasma electrolytes and BNP.
- Repeat 12-lead electrocardiogram.
- Repeat echocardiogram aimed at evaluating left ventricular function.

5.4 Follow-Up (Visit 2) at 6 Months

At follow-up visit, the patient refers a stability of his general clinical conditions. He refers good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels remained substantially well controlled.

Physical Examination

- Weight: 88 kg
- Body mass index (BMI): 27.8 kg/m^2
- Waist circumference: 100 cm
- Other parameters unchanged

Blood Pressure Profile

- Home BP (average): 120/70 mmHg
- Sitting BP: 124/76 mmHg
- Standing BP: 118/72 mmHg

Haematological Profile

- Creatinine, 2.2 mg/dL; Cockcroft–Gault, 33 mL/min; and eGFR (MDRD), 29 mL/min/1.73 m^2
- Plasma potassium, 4.97 mEq/L
- BNP, 211 pg/mL

Current Treatment

Bisoprolol 1.25 mg 1 cp h 8:00 and 1 cp h 20:00; furosemide 25 mg 2 cp h 8:00; amlodipine 5 mg 1 cp h 8:00, ramipril 10 mg 1 cp h 8:00, warfarin 5 mg 1 cp h 8:00 and atorvastatin 20 mg 1 cp h 20:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

12-Lead Electrocardiogram

Atrial fibrillation with ventricular response of 73 bpm. ST-segment abnormalities. No signs of LVH (Sokolow–Lyon 1.5 mV, Cornell voltage 2.0 mV) (illustrated in Fig. 5.3). Peripheral (**a**) and precordial (**b**) leads.

Echocardiogram with Doppler Ultrasound

Aortic root calcific, of normal dimensions. Left atrium dilated (45 mm). Left ventricle (LV) with abnormal chamber dimension (LV end-diastolic diameter 67 mm), impaired LV relaxation at both conventional (E/A ratio 1.3—pseudo-normalization) and tissue Doppler evaluations and global ventricular hypokinesia with reduced ejection fraction (LV ejection fraction 35 %). Indexed LV mass increased, 176 g/m^2; relative wall thickness, 0.30. Type 2 diastolic dysfunction. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Aortic (+), mitral (++) and tricuspid (+) regurgitations at Doppler ultrasound examination. PAPs 36 mmHg.

Treatment Evaluation

No change for current pharmacological therapy

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary low-salt and caloric intake (continued)
- Daily slow walk

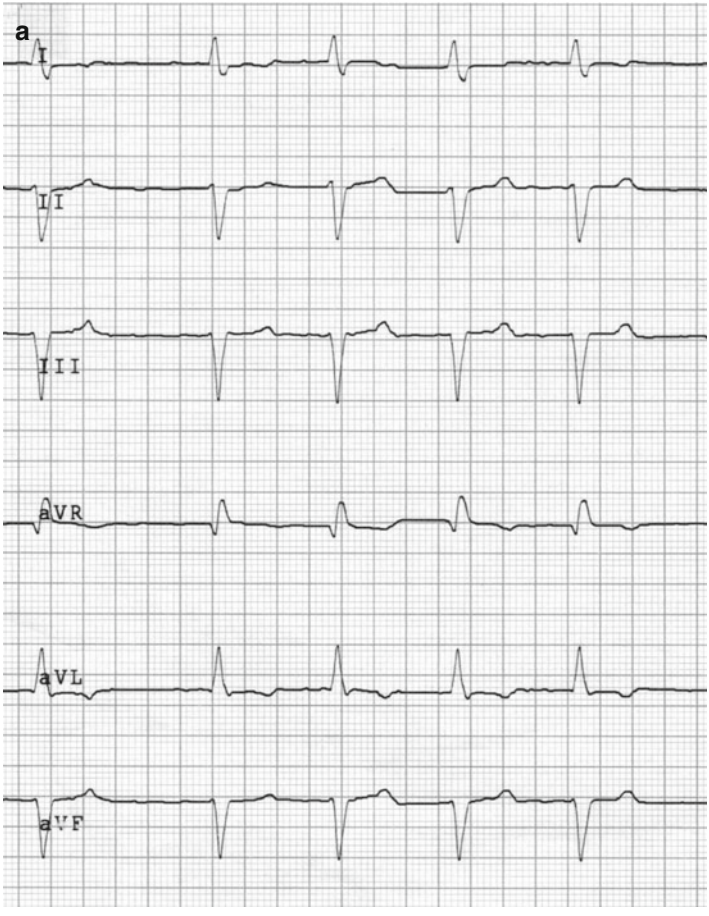

FIGURE 5.3 (**a**, **b**) Atrial fibrillation with ventricular response of 73 bpm. ST-segment abnormalities. No signs of LVH

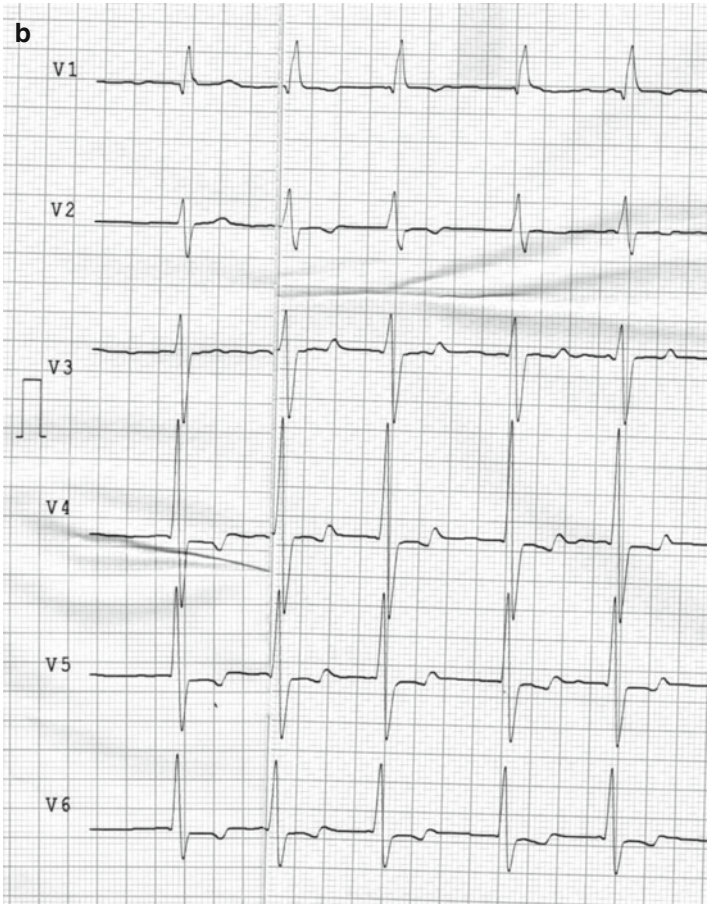

FIGURE 5.3 (continued)

5.5 Discussion

This clinical case shows an emblematic example of a patient with a long history of arterial hypertension, which has been never controlled in the past. This patient, with a strong family history of hypertension, has been exposed to high blood pressure values for more than 10 years. The patient, or his general

practitioner, likely underestimated the problem. As a logical consequence, he went to meet the natural history of hypertension, and he developed its major clinical complications, i.e. the vascular atherosclerosis, heart failure, permanent atrial fibrillation and chronic kidney disease. Of course, the chronic cigarette smoking habit further accelerated and amplified such complications. The lack of specific symptoms and the coronary angiography excluded an ischaemic coronary artery disease as a main cause of heart failure. With respect to the kidney disease, although the patient did not regularly checked his renal function, the clinical history as well as the evidence of enhanced bilateral intrarenal index resistances undoubtedly indicates a condition of hypertensive nephropathy.

At the first visit, the patient complained fatigue, limited exercise tolerance and sometimes shortness of breath. These symptoms were in part linked to very low blood pressure values, accordingly to the limited left ventricular ejection fraction. These low blood pressure values are the consequence of the antihypertensive therapy, which included full doses of ACE-inhibitor and Ca-antagonist, beta- and alpha-1 blockers. In addition, the presence of pleural effusion at the chest radiography was the consequence of a quite fluid retention. This suspect was sustained by high values of plasma BNP. In the preliminary evaluation of the patient, our primary aim of the therapeutic strategy was focused on the down-step of the antihypertensive therapy because there are no evidences demonstrating a further beneficial effect when reducing systolic blood pressure below 130 mmHg. Accordingly, as recommended by 2013 ESH/ESC Guidelines, in hypertensive patients with congestive heart disease, systolic blood pressure goal of <140 mmHg should be considered [1]. Therefore, we decided to reduce the dose of amlodipine and of doxazosin, maintaining the ACE-inhibitor because the ACE-inhibitors, but not Ca-antagonist or doxazosin, represent the first-line therapy in a patient with heart failure and with chronic kidney disease [2]. Concomitantly, we increased the dose of furosemide, in order to reduce the fluid retention and, consequently, the symptoms complained

by the patient. The heart rate, within the correct range, allowed us to maintain the dose of beta-blocker.

Worth of noting, the ACE-inhibitor was definitively confirmed upon the subsequent result of the abdominal echography with renal artery Doppler, which excluded the presence of a bilateral renal artery stenosis. The correct therapeutic strategy adopted at the first visit was confirmed during the follow-up. Thus, the patient referred an amelioration of his clinical condition. Since the first visit, the physical examination showed a slight reduction of body weight (2–3 kg), as a likely consequence of a reduced fluid retention. Plasma levels of BNP, progressively reduced at follow-up, were also encouraging.

With respect to heart failure with impaired diastolic and systolic functions, the physical signs and the symptoms reported by the patient, as well as the echocardiographic parameters, indicate the presence of a heart failure condition at stage C (heart failure ACCF/AHA classification) [2]. Accordingly, the correct therapy includes the ACE-inhibitor, beta-blocker and furosemide. Among the beta-blockers, bisoprolol was a correct choice by the general practitioner, when considering its prognostic beneficial effect in congestive heart failure, as documented by the CIBIS II trial [3]. Of note, in this patient it was expected to introduce an aldosterone receptor antagonist, such as spironolactone, as suggested by the ACCF/AHA guidelines [2]. However, the reduced renal function and the normal-high kalaemia suggest caution. With respect to the evaluation of ischaemic stroke risk in patient with atrial fibrillation, this patient is considered at high risk (CHA_2DS_2-VASc = 5). According to the 2012 ESC Guidelines, an oral anticoagulation for antithrombotic therapy is mandatory (class I, level A) [4]. Properly, in this patient the general practitioner prescribed him warfarin, instead of a novel oral anticoagulant (NOAC), because of the reduced eGFR. Indeed, the current ESC Guidelines [4] as well as the European Heart Rhythm Association [5] state that there are no outcome data for NOACs in patients with advanced chronic kidney disease (CrCl < 30 mL/min), and they recommend against their use in such patients.

Take-Home Messages

- In hypertensive patients with congestive heart failure, the target systolic blood pressure is < 140 mmHg.
- In patients with congestive heart failure, the first-line cardiovascular agents include ACE-inhibitors, or sartans if not tolerated, third generation beta-blockers and diuretics. In selected patients, consider the utilization of aldosterone antagonist.
- In patients with permanent atrial fibrillation in whom anticoagulant therapy is recommended, an evaluation of renal function is mandatory. In patients with advanced chronic kidney disease (CrCl < 30 mL/min), novel oral anticoagulants should be avoided.

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Chapter 6
Clinical Case 6: Patient with Essential Hypertension and Atrial Fibrillation

6.1 Clinical Case Presentation

A 72-year-old, Caucasian male, retired (former school teacher), presented to the outpatient clinic for clinical assessment of uncontrolled essential hypertension.

He has history of essential hypertension by about 20 years, initially treated with Ca-antagonist (nifedipine 30 mg) with satisfactory blood pressure control. For a long period, he missed any periodical medical control. About 5 years ago, he was diagnosed an atrial fibrillation, refractory to pharmacological conversion. From then, he modified the therapy to a combination with ACE-inhibitor (lisinopril 20 mg), beta-blocker (atenolol 50 mg) and warfarin (2.5–5 mg, according to INR range). He reports marked fluctuations and substantially uncontrolled home blood pressure values (single measurement by mercury sphygmomanometer). He complains often difficulty to maintain the INR within a normal range. He also complains dry cough, mainly nocturnal.

Family History

He has paternal history of hypertension and dyslipidaemia. He also has one brother with hypertension and permanent atrial fibrillation.

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Clinical History

He never smoked cigarettes. He regularly practises physical activity (5 km walk, daily). He has mild hypercholesterolaemia treated with simvastatin/ezetimibe 10/10 mg daily (previous intolerance to higher dosages of statin). He also has mild depressive syndrome, treated with sertraline 25 mg/daily, with good mood at present.

Physical Examination

- Weight: 70 kg
- Height: 165 cm
- Body mass index (BMI): 25.7 kg/m^2
- Waist circumference: 96 cm
- Respiration: normal
- Heart sounds: S1–S2 regular; pansystolic murmur, suggestive of mitral regurgitation; no adjunctive third or fourth sounds
- Resting pulse: abnormal rhythm with heart rate of 76 beats/min
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive retinopathy

Haematological Profile

- Haemoglobin: 14.1 g/dL
- Haematocrit: 47.5 %
- Fasting plasma glucose: 86 mg/dL
- Fasting lipids: total cholesterol (TOT-C), 173 mg/dL; low-density lipoprotein cholesterol (LDL-C), 102 mg/dL; high-density lipoprotein cholesterol (HDL-C), 47 mg/dL; and triglycerides (TG), 120 mg/dL
- Electrolytes: sodium, 142 mEq/L, and potassium, 4.49 mEq/L

- Serum uric acid: 5.2 mg/dL
- Renal function: creatinine, 1.2 mg/dL; and estimated glomerular filtration rate (eGFR) (MDRD), 59 mL/min/1.73 m^2
- INR: 1.7 (range of 2–3)
- Urine analysis (dipstick): normal
- Liver function tests: normal
- Thyroid function tests: normal

Blood Pressure Profile

- Home BP (average): 170/104 mmHg
- Sitting BP (mean of three measurements): 150/98 mmHg (right arm); 150/96 mmHg (left arm)
- Standing BP: 148/96 mmHg at 1 min
- 24-h BP, 140/84 mmHg; HR, 86 bpm
- Daytime BP, 151/90 mmHg; HR, 94 bpm
- Night-time BP, 112/67 mmHg; HR, 65 bpm

A 24-h ambulatory blood pressure profile is illustrated in Fig. 6.1.

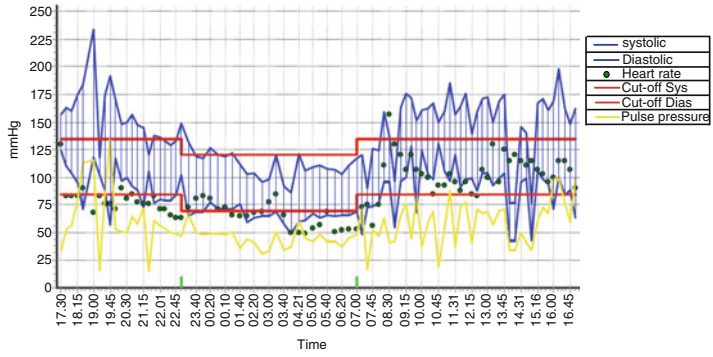

FIGURE 6.1 A 24-h ambulatory blood pressure profile

12-Lead Electrocardiogram

Atrial fibrillation with ventricular response of 76 bpm. No signs of LVH (Sokolow–Lyon 2.1 mV, Cornell voltage 1.9 mV) (illustrated in Fig. 6.2). Peripheral (**a**) and precordial (**b**) leads.

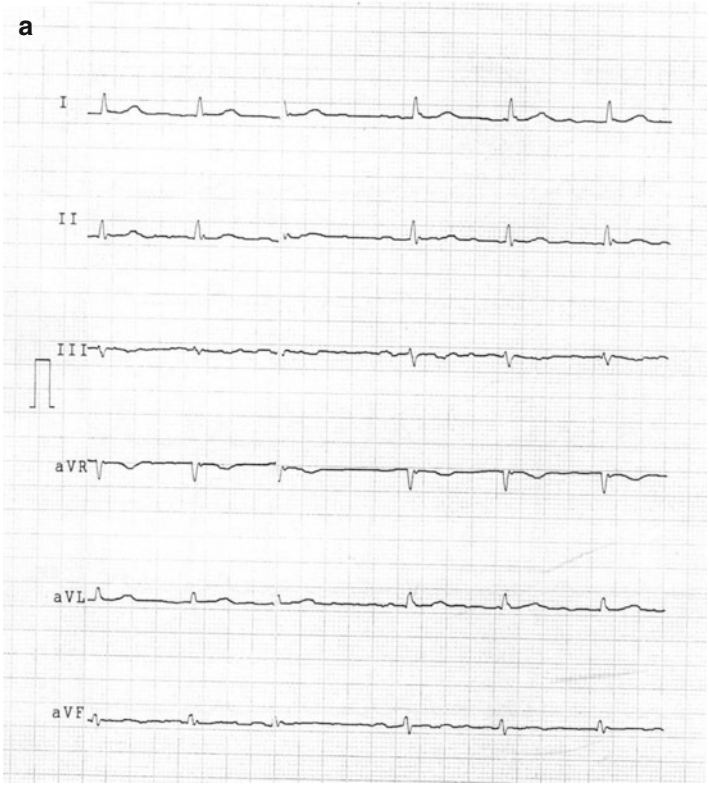

FIGURE 6.2 (**a**, **b**) Atrial fibrillation with ventricular response of 76 bpm. No signs of LVH

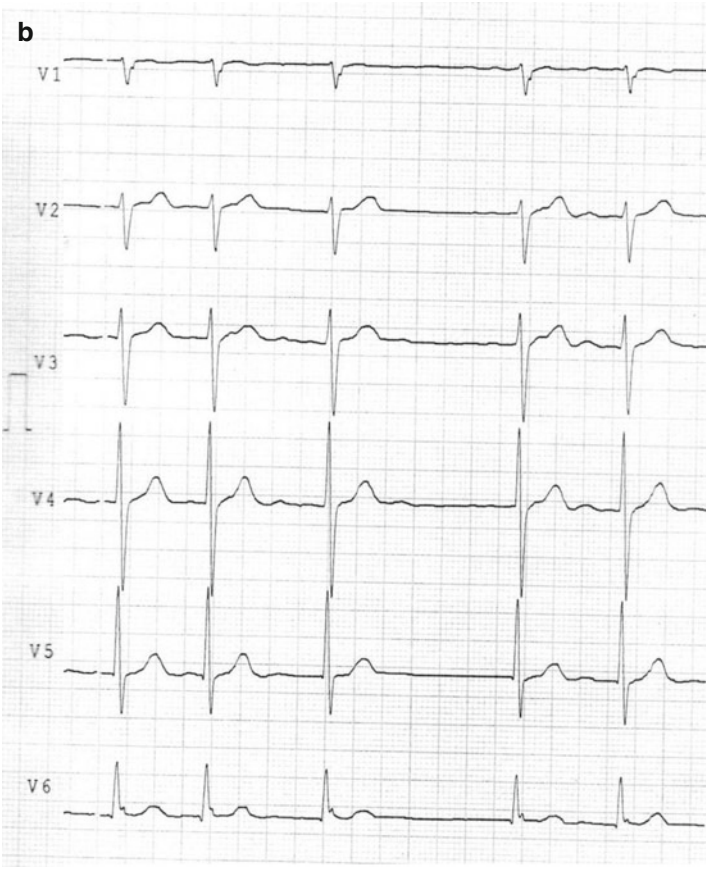

FIGURE 6.2 (continued)

Current Treatment

Lisinopril 20 mg h 8:00; atenolol 50 mg h 20:00; warfarin (2.5–5 mg) h 16:00; simvastatin/ezetimibe 10/10 mg h 22:00; and sertraline 25 mg h 8:00

Diagnosis

Arterial hypertension with unsatisfactory blood pressure control on combination therapy. Chronic kidney damage (stage 3 chronic kidney disease). Permanent atrial fibrillation with anticoagulant therapy in worse therapeutic range. Hypercholesterolaemia.

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Add another drug class (e.g. dihydropyridinic calcium antagonist).
2. Add another drug class (e.g. diuretic therapy).
3. Switch ACE-inhibitor to a sartan.
4. Titrate atenolol or switch it to another beta-blocker.
5. Titrate the statin therapy.

Treatment Evaluation

- Stop lisinopril and start losartan 100 mg 1 cp h 8:00.
- Start amlodipine 5 mg 1 cp h 8:00.

- Maintain atenolol 50 mg h 20:00; warfarin (2.5–5 mg) h 16:00; simvastatin/ezetimibe 10/10 mg h 22:00; and sertraline 25 mg h 8:00.

Prescriptions

- Periodical home blood pressure evaluation, according to recommendations from guidelines (utilization of an automated blood pressure monitor, take multiple measurements)
- Dietary salt restriction
- Blood tests: creatinine, INR
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties)
- Abdominal echography with renal artery Doppler
- Carotid ultrasound

6.2 Follow-Up (Visit 1) at 2 Weeks

At follow-up visit, the patient is in general good clinical conditions. He reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The dry cough disappeared. The home blood pressure levels, measured according to the recommendations, were improved but still uncontrolled.

Physical Examination

- Resting pulse: abnormal rhythm with heart rate of 78 beats/min
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 148/94 mmHg
- Sitting BP (mean of three measurements): 146/94 mmHg (right arm)
- Standing BP: 142/92 mmHg at 1 min

Current Treatment

Losartan 100 mg 1 cp h 8:00; amlodipine 5 mg 1 cp h 8:00; atenolol 50 mg 1 cp h 20:00; warfarin (2.5–5 mg) h 16:00; simvastatin/ezetimibe 10/10 mg h 22:00; and sertraline 25 mg h 8:00

Haematological Profile

- Creatinine, 1.23 mg/dL; eGFR (MDRD), 58 mL/min/1.73 m^2
- INR: 3.1 (range of 2–3)

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Normal dimension of aortic root. Left atrium dilated (53 mm). Left ventricle (LV) with normal chamber dimension (LV end-diastolic diameter 49 mm). Normal systolic ejection fraction (LV ejection fraction 58 %). Normal regional kinesis. Increased LV mass, 138 g/m^2; relative wall thickness, 0.41. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (++) and tricuspid (+) regurgitations at Doppler ultrasound examination. PAPs 30 mmHg.

Abdominal Echography with Renal Artery Doppler

Slight liver steatosis. No signs of portal hypertension. Biliary tree not dilated. Normal spleen dimensions. Adrenal glands without signs of abnormal lesions. Abdominal aorta with normal dimension and rare atherosclerotic plaques.

Kidneys with normal dimensions and cortical thickness. Renal arteries without signs of haemodynamically significant stenosis. Intrarenal index resistance bilaterally increased (right: 0.79; left: 0.80).

Carotid Ultrasound

Calcific atherosclerotic plaques at both carotid levels, not haemodynamically relevant.

Diagnosis

Essential hypertension with unsatisfactory blood pressure control, with cardiac (eccentric hypertrophy), vascular (carotid and aortic atherosclerosis) and renal (stage 3 chronic kidney disease) organ damages. Permanent atrial fibrillation with unstable target INR. Additional modifiable cardiovascular risk factor (hypercholesterolaemia).

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The presence of cardiac and vascular organ damages does not modify the individual global cardiovascular risk profile. According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Switch warfarin to a novel oral anticoagulant (NOAC).
2. Titrate the dose of warfarin.
3. Add another drug class (e.g. diuretic).
4. Add another drug class (e.g. aldosterone antagonist).

Treatment Evaluation

- Stop losartan.
- Start losartan 100 mg plus hydrochlorothiazide 25 mg (fix combination) 1 cp h 8:00.
- Stop warfarin. Repeat INR and, when < 2, start apixaban 5 mg twice daily.
- Maintain amlodipine 5 mg 1 cp h 8:00; atenolol 50 mg 1 cp h 20:00; simvastatin/ezetimibe 10/10 mg h 22:00; and sertraline 25 mg h 8:00.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt restriction
- Blood tests: creatinine, uric acid, potassium and complete blood cell count (CBC)

6.3 Follow-Up (Visit 2) at 3 Months

At follow-up visit, the patient is in quite stable clinical conditions. He also reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure is well controlled.

Physical Examination

- Resting pulse: abnormal rhythm with heart rate of 74 beats/min
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 130/82 mmHg
- Sitting BP: 132/82 mmHg
- Standing BP: 126/80 mmHg

Haematological Profile

- Haemoglobin: 13.9 g/dL
- Haematocrit: 46.5 %
- Renal function: creatinine, 1.21 mg/dL, and estimated glomerular filtration rate (eGFR) (MDRD), 59 mL/min/1.73 m^2
- Serum uric acid: 6.2 mg/dL

Current Treatment

Losartan–hydrochlorothiazide 100/25 mg 1 cp h 8:00; amlodipine 5 mg 1 cp h 8:00; atenolol 50 mg 1 cp h 20:00; apixaban 5 mg 1 cp h 8:00 and 1 cp h 20:00; simvastatin/ezetimibe 10/10 mg h 22:00; and sertraline 25 mg h 8:00

Treatment Evaluation

- Maintain the current therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Dietary salt restriction.

- Blood tests: creatinine, potassium, fasting plasma glucose, lipid profile and CBC.
- Repeat 12-lead electrocardiogram.
- Repeat echocardiogram.

6.4 Follow-Up (Visit 2) at 1 Year

At follow-up visit, the patient refers a stability of his general clinical conditions. He regularly performed physical activity (5 km walk, daily). He also reported good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels remained substantially well controlled.

Physical Examination

- Weight: 69 kg
- Body mass index (BMI): 25.5 kg/m^2
- Waist circumference: 96 cm
- Other parameters unchanged

Blood Pressure Profile

- Home BP (average): 134/84 mmHg
- Sitting BP: 130/82 mmHg
- Standing BP: 128/84 mmHg

Haematological Profile

- Haemoglobin: 14.3 g/dL
- Haematocrit: 48.5 %
- Fasting plasma glucose: 82 mg/dL
- TOT-C, 168 mg/dL; LDL-C, 94 mg/dL; HDL-C, 48 mg/dL; and TG, 131 mg/dL
- Potassium, 4.3 mEq/L

- Renal function: creatinine, 1.23 mg/dL, and eGFR (MDRD), 58 mL/min/1.73 m^2

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

12-Lead Electrocardiogram

Atrial fibrillation with ventricular response of 78 bpm. No signs of LVH (Sokolow–Lyon 2.1 mV, Cornell voltage 1.9 mV). Similar to the previous one (illustrated in Fig. 6.3). Peripheral (**a**) and precordial (**b**) leads.

Echocardiogram with Doppler Ultrasound

Normal dimension of aortic root. Left atrium dilated (52 mm). Left ventricle (LV) with normal chamber dimension (LV end-diastolic diameter 50 mm). Normal systolic ejection fraction (LV ejection fraction 59 %). Normal regional kinesis. Increased LV mass, 136 g/m^2; relative wall thickness, 0.40. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (++) and tricuspid (+) regurgitations at Doppler ultrasound examination. PAPs 31 mmHg. Similar to the previous one.

Current Treatment

Losartan–hydrochlorothiazide 100/25 mg 1 cp h 8:00; amlodipine 5 mg 1 cp h 8:00; atenolol 50 mg 1 cp h 20:00; apixaban 5 mg 1 cp h 8:00 and 1 cp h 20:00; simvastatin/ezetimibe 10/10 mg h 22:00; and sertraline 25 mg h 8:00

Treatment Evaluation

No change for current pharmacological therapy

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Dietary low-salt intake (continued).
- Maintain physical activity.

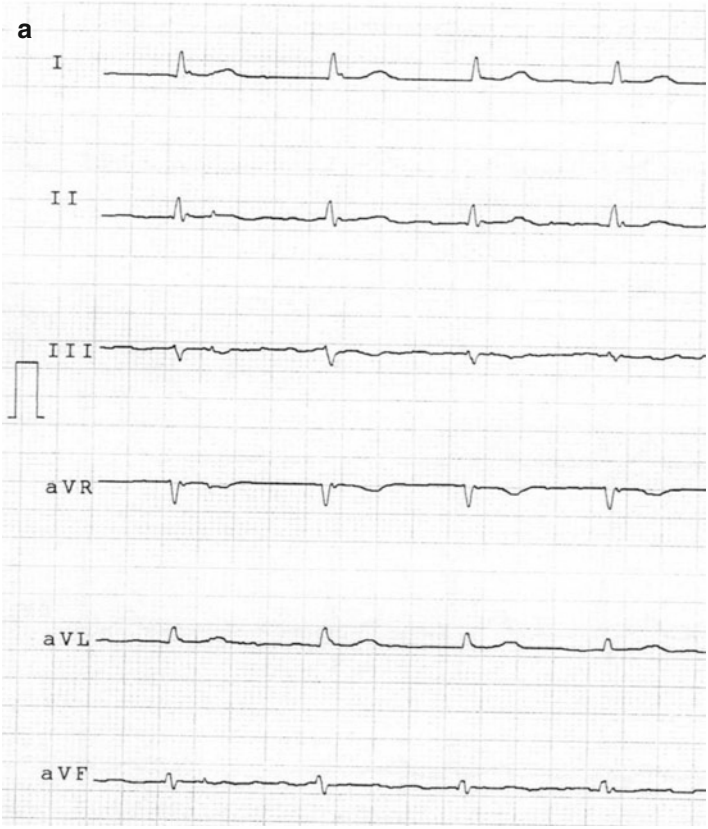

FIGURE 6.3 (**a**, **b**) Atrial fibrillation with ventricular response of 78 bpm. No signs of LVH

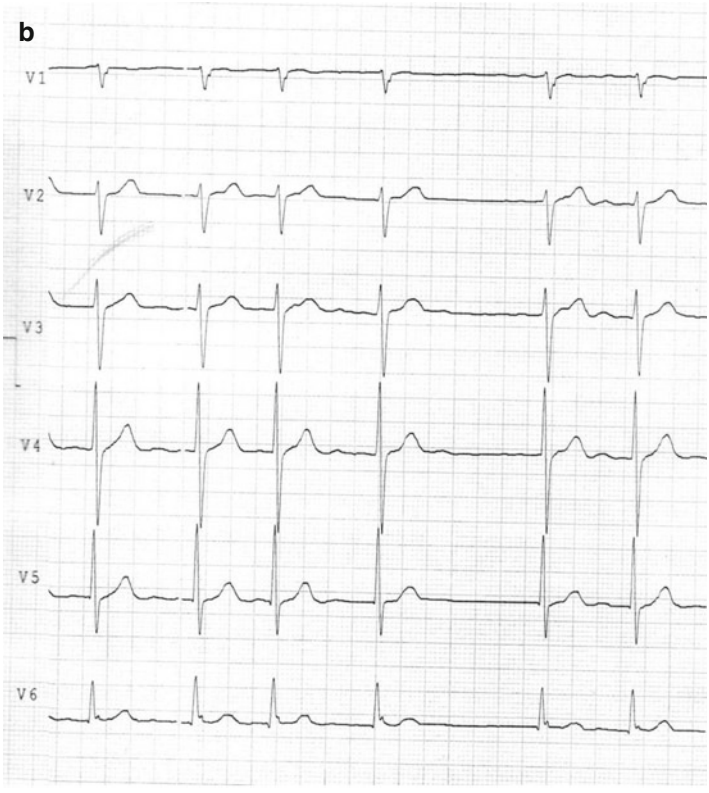

FIGURE 6.3 (continued)

6.5 Discussion

This clinical case represents an emblematic example of a coexistence of hypertension with atrial fibrillation, being hypertension a common etiological factor for this cardiac arrhythmia [2]. The first comment to this case concerns the correct measurement of blood pressure in patients with atrial fibrillation and which device should be used. In the presence of atrial fibrillation, blood pressure measurement is often difficult and uncertain because of high beat-to-beat variability

in ventricular filling time, stroke volume and contractility, leading to blood pressure fluctuation. At the first visit, it was evident that the patient (who was usual to take a single measurement) wrongly measured blood pressure. This error may explain the marked fluctuations of home blood pressure values. Indeed, the ESH Guidelines acknowledge the problem of blood pressure measurement in atrial fibrillation and recommend several measurements to be made (at least three), in order to limit the error [1]. Therefore, it is important that clinicians encourage patients with atrial fibrillation to take repeated measurements of blood pressure to improve accuracy. As there are concerns about the device to be used, despite the growing use of electronic oscillometric sphygmomanometers, there continues to be a concern about the accuracy of electronic devices in the presence of atrial fibrillation. The ESH Guidelines do not specify which sphygmomanometer should be used. An ESH statement on requirements for professional office blood pressure monitors [3] noted that oscillometric devices may not record blood pressure accurately in patients with arrhythmias and that further studies are needed to clarify this issue. Thus, the presence of atrial fibrillation may represent a reason to utilize the auscultatory measurement in the office. As there is concern about the out of office measurement, a recent meta-analysis examined the literature on measurements taken with oscillometric recorders in comparison with those from manual mercury sphygmomanometers [4]. The authors concluded that these monitors "appear to be accurate for systolic but not diastolic blood pressure". The currently available automated blood pressure monitors that have been validated in individuals with sinus rhythm appear to be accurate in measuring systolic but not diastolic in individuals with sustained atrial fibrillation. In conclusions, clinicians should encourage the patients with atrial fibrillation to adopt automated monitors with a validated algorithm for this arrhythmia. Patients should take several readings and average them.

In this clinical case, the patient underwent an ambulatory blood pressure monitoring (ABPM). Published evidence regarding the role of ABPM in patients with arrhythmias, specifically in patients with atrial fibrillation, is scarce. In spite of these limitations, there is no reason at present to exclude such patients from ABPM procedures [5].

Another crucial aspect of this clinical case concerns the utilization of anticoagulant therapy. Hypertensive patients with atrial fibrillation should be assessed for the risk of thromboembolism by the score mentioned in the ESC Guidelines [6], and, unless contraindications exist, they need oral anticoagulation therapy to prevent stroke and other embolic events. In this clinical case, at the first visit, the patient was assuming vitamin K antagonist, with difficulties to maintain INR within the normal range. When considering that the stroke prevention with a vitamin K antagonist is effective where the individual mean time in therapeutic range is good, mainly > 70% [7], it is conceivable that current anticoagulant therapy failed to protect our patient. Newer oral anticoagulant drugs, either direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban), have been shown to be non-inferior and sometimes superior to warfarin [1]. For these reasons, in this clinical case, warfarin was switched to NOAC (i.e. apixaban). The eGFR > 30 mL/min allowed prescribing it at full dosage (5 mg twice daily).

Finally, a brief comment on antihypertensive therapy in a patient with permanent atrial fibrillation. The target blood pressure is < 140/90 mmHg in these patients. Beta-blockers and non-dihydropyridine calcium antagonists are recommended as antihypertensive agents in patients with atrial fibrillation and high ventricular rate. If beta-blockers are chosen, the optimal combination therapy includes non-dihydropyridine calcium antagonist (i.e. amlodipine in this clinical case) and ACE-inhibitor or sartan when ACE inhibitor is not tolerated (i.e. losartan), plus diuretic when necessary.

Take-Home Messages

- In the presence of atrial fibrillation, blood pressure measurement is often difficult and uncertain because of high beat-to-beat variability in ventricular filling time, stroke volume and contractility, leading to blood pressure fluctuation.
- Patients with atrial fibrillation should utilize automated monitors with a validated algorithm for this arrhythmia to take home blood pressure. Several readings should be obtained and averaged, to improve accuracy.
- Hypertensive patients with atrial fibrillation should be assessed for the risk of thromboembolism, and, unless contraindications exist, they need oral anticoagulation therapy.

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Chapter 7
Clinical Case 7: Patient with Severe Obesity

7.1 Clinical Case Presentation

A 52-year-old, Caucasian male, workman, presented to the outpatient clinic for clinical assessment of uncontrolled hypertension. By about 10 years, he refers elevated blood pressure values, treated with a fix combination therapy based on beta-blocker (atenolol 100 mg) and diuretic (chlorthalidone 25 mg). 5 years ago, because of excessive bradycardia, atenolol and chlorthalidone were down-stepped to 50/12.5 mg/day. A Ca-antagonist (amlodipine, 10 mg) was added, with satisfactory home and office blood pressure control. By about 1 year, as a consequence of lower limbs oedema, his general practitioner reduced the dose of amlodipine to 5 mg/day and started therapy with doxazosin 2 mg/day. Since that period, the lower limb oedema, although still present, was ameliorated, but home and clinic blood pressure values were uncontrolled (around 150/95 mmHg).

Family History

He has paternal history of cerebral stroke, hypertension and obesity and maternal history of type 2 diabetes mellitus.

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Clinical History

He was previously a heavy smoker (20–30 cigarettes daily) for 15 years, until 20 years ago. As additional modifiable cardiovascular risk factor, he refers a sedentary lifestyle and history of progressive weight gain by about 20 years. At present, he shows a severe obesity. He underwent several diagnostic procedures that excluded secondary forms of obesity. He has hypercholesterolaemia, not pharmacologically treated. He also received diagnosis of severe obstructive sleep apnoea syndrome (OSAS), treated with nocturnal continuous positive airway pressure (CPAP) therapy. As non-cardiovascular disease, the patient has a lumbar disc hernia, occasionally treated with non-steroidal anti-inflammatory drugs (2–3 times per week).

Physical Examination

- Weight: 139 kg
- Height: 175 cm
- Body mass index (BMI): 45.4 kg/m^2
- Waist circumference: 138 cm
- Respiration: normal
- Heart sounds: distal cardiac sounds and pansystolic regurgitant murmur
- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Slight lower limb oedema
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive retinopathy

Haematological Profile

- Haemoglobin: 14.9 g/dL
- Haematocrit: 41.9 %

- Fasting plasma glucose: 79 mg/dL
- Glycated haemoglobin (HbA_{1c}): 5.8 %
- Fasting lipids: total cholesterol (TOT-C), 271 mg/dL; low-density lipoprotein cholesterol (LDL-C), 179 mg/dL; high-density lipoprotein cholesterol (HDL-C), 61 mg/dL; and triglycerides (TG), 155 mg/dL
- Electrolytes: sodium, 141 mEq/L, and potassium, 3.92 mEq/L
- Serum uric acid: 6.4 mg/dL
- Renal function: creatinine, 1.14 mg/dL; creatinine clearance (Cockcroft–Gault), 149 mL/min; and estimated glomerular filtration rate (eGFR) (MDRD), 70 mL/min/1.73 m^2
- Urine analysis: normal
- Normal liver function tests
- Normal thyroid function tests

Blood Pressure Profile

- Home BP (average): 150/95 mmHg
- Sitting BP: 160/98 mmHg (right arm = left arm; cuff adapted to the arm circumference)
- Standing BP: 154/94 mmHg at 1 min

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (74 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH (Sokolow–Lyon 2.0 mV, Cornell voltage 2.0 mV) (illustrated in Fig. 7.1). Peripheral (**a**) and precordial (**b**) leads.

Chest Radiography

Normal cardiac sections. No pleural or lung parenchymal lesions. Previous left collarbone fracture (Fig. 7.2).

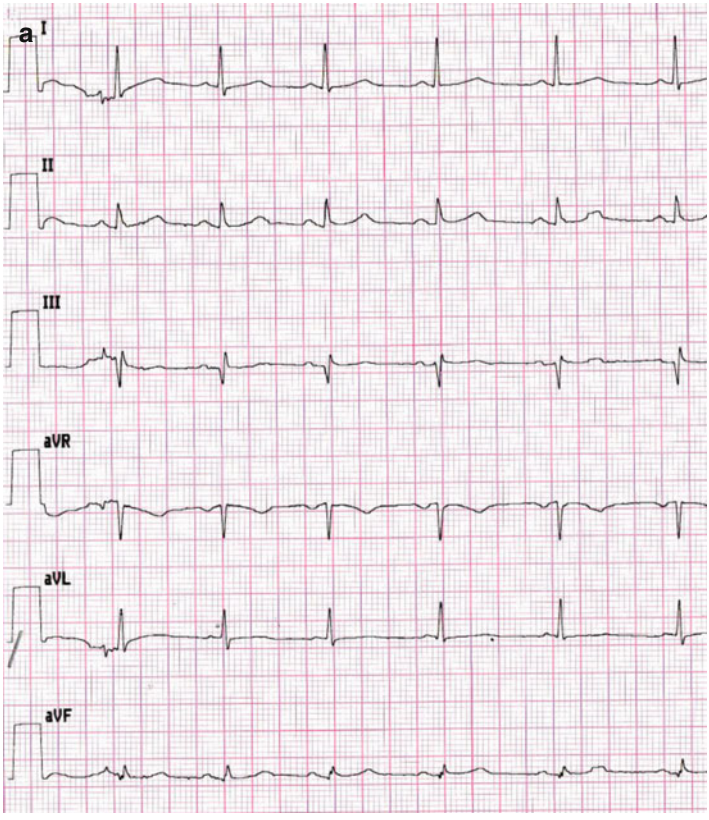

FIGURE 7.1 (**a**, **b**) Sinus rhythm with normal heart rate (74 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH

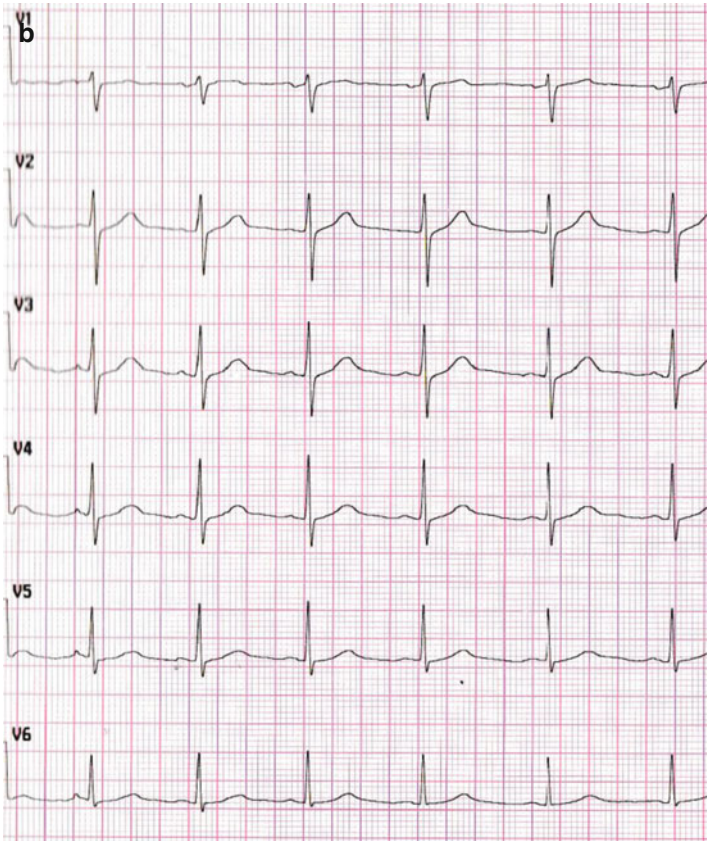

FIGURE 7.1 (continued)

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; atenolol/chlorthalidone 50/12.5 mg 1 cp h 8:00; and doxazosin 2 mg 1 cp h 22:00. Occasionally NSAID (nimesulide 100–200 mg, 2–3 times per week). Nocturnal CPAP.

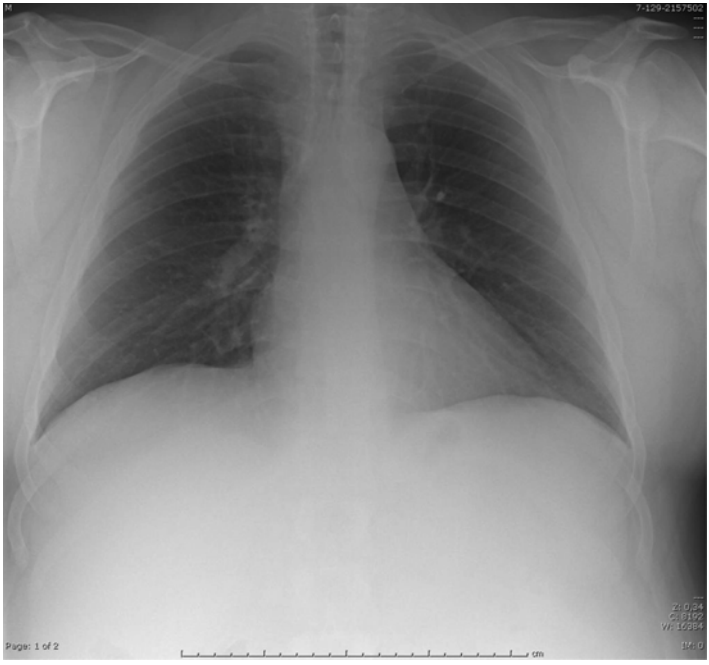

FIGURE 7.2 Standard postero-anterior chest radiograph showing normal cardiac sections. No acute pleural or lung parenchymal lesions. Previous left collarbone fracture

Diagnosis

Uncontrolled arterial hypertension, hypercholesterolaemia and severe obesity complicated by severe OSAS

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Upstep the alpha-1 blocker.
2. Insert an ACE-inhibitor.
3. Upstep the diuretic.
4. Insert a statin.
5. Maintain the same antihypertensive therapy.

Treatment Evaluation

- Maintain the same antihypertensive therapy until results from further cardiovascular diagnostic procedures.
- Atorvastatin 10 mg 1 cp h 22:00.
- Advise against the occasional use of NSAID. Prefer paracetamol as analgesic.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines, including the use of an appropriate cuff, adapted to the circumference arm
- Dietary salt and low-caloric restrictions
- Blood tests: lipid profile, creatine phosphokinase (CPK) and liver function tests
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties)
- Carotid vascular ultrasound
- Abdominal echography with renal artery Doppler

7.2 Follow-Up (Visit 1) at 6 Weeks

At follow-up visit, the patient reports good adherence to prescribed medication (atorvastatin) without adverse reactions or drug-related side effects. The home blood pressure levels are still elevated.

Physical Examination

- Weight: 138 kg
- Body mass index (BMI): 45.4 kg/m^2
- Waist circumference: 138 cm
- Clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 150/95 mmHg (right arm)
- Sitting BP: 160/96 mmHg (right arm)
- Standing BP: 154/94 mmHg at 1 min

Haematological Profile

- TOT-C, 225 mg/dL; LDL-C, 139 mg/dL; HDL-C, 60 mg/dL; and TG, 131 mg/dL
- CPK: 106 mg/dL
- Liver function tests: normal

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; atenolol/chlorthalidone 50/12.5 mg 1 cp h 8:00; and doxazosin 2 mg 1 cp h 22:00. Occasionally NSAID (nimesulide 100–200 mg, 2–3 times per week). Nocturnal CPAP.

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Eccentric left ventricle (LV) hypertrophy (LV mass indexed 134 g/m^2; relative wall thickness: 0.41) with normal chamber dimension (LV end-diastolic diameter 51 mm), impaired LV relaxation (E/A ratio < 1) at both conventional and tissue Doppler evaluations and normal ejection fraction (LV ejection fraction 59 %, LV fractional shortening 38 %). Normal dimension of aortic root and left atrium. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (+) regurgitations at Doppler ultrasound examination.

Carotid Ultrasound

Calcific atherosclerotic plaques at both carotid levels (max 2.1 mm, calcific, on left common carotid), without signs of haemodynamically significant stenosis.

Abdominal Echography with Renal Artery Doppler

Liver with increased dimensions and steatosis. Regular biliary tree. Normal spleen dimensions. Pancreas and adrenal glands without signs of abnormal lesions. Abdominal aorta with normal calibre and rare atherosclerotic plaques. Kidneys with normal longitudinal diameter (right 116 mm; left 134 mm) and maintained cortical thickness. No signs of renal artery stenosis (RAR around 2.5). Intrarenal index resistance bilaterally increased (right: 0.79; left: 0.81).

Diagnosis

Uncontrolled arterial hypertension with cardiac (eccentric LV hypertrophy), renal (hypertensive nephropathy) and

vascular (atherosclerotic carotid and abdominal aorta) organ damages. Hypercholesterolaemia and severe obesity complicated with OSAS.

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The echographic evidence of LV hypertrophy and vascular atherosclerosis does not modify the individual global cardiovascular risk profile, which remains high, according to 2013 ESH/ESC global cardiovascular risk stratification [1].

Which is the best therapeutic option in this patient?

Possible answers are:

1. Titrate the Ca-antagonist.
2. Add another drug class (e.g. ACE-inhibitor).
3. Stop beta-blocker.
4. Maintain the same therapy while waiting to run further examinations.

Current Treatment

Amlodipine 5 mg 1 cp h 8:00; atenolol/chlorthalidone 50/12.5 mg 1 cp h 8:00; and doxazosin 2 mg 1 cp h 22:00. Occasionally NSAID (nimesulide 100–200 mg, 2–3 times per week). Nocturnal CPAP.

Treatment Evaluation

- Stop beta-blocker and diuretic.
- Stop amlodipine.
- Start perindopril 10 mg, indapamide 2.5 mg and amlodipine 5 mg (fix combination) 1 cp h 8:00.
- Maintain doxazosin 2 mg 1 cp h 22:00.
- Upstep atorvastatin to 20 mg 1 cp h 22:00.
- Maintain nocturnal CPAP.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt and low-caloric restrictions
- Surgical consultancy for future bariatric surgical intervention

7.3 Follow-Up (Visit 2) at 3 Months

At follow-up visit, the patient is in quite stable clinical conditions. He refers no clinical symptoms. The home blood pressure is stable, ameliorated but still not well controlled.

Physical Examination

- Clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 144/92 mmHg (right arm)
- Sitting BP: 145/90 mmHg (right arm)
- Standing BP: 142/90 mmHg at 1 min

Surgical Consultancy

The patient has indication to undergo a bariatric surgery intervention.

Current Treatment

Perindopril/indapamide/amlodipine 10/2.5/5 mg (fix combination) 1 cp h 8:00; doxazosin 2 mg 1 cp h 22:00; and atorvastatin 20 mg 1 cp h 22:00. Nocturnal CPAP

Which is the best therapeutic option in this patient?

Possible answers are:

1. Titrate the Ca-antagonist.
2. Add another drug class (e.g. sartan).
3. Titrate the alpha-1 blocker.
4. Titrate the ACE-inhibitor

Treatment Evaluation

- Upstep doxazosin to 4 mg 1 cp h 22:00.
- Maintain the other therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt and low-caloric restrictions
- Blood tests: serum creatinine, eGFR, potassium, glycaemia, HbA_{1c} and lipid profile

7.4 Follow-Up (Visit 3) at 6 Months

At follow-up visit, the patient refers a stability of his general clinical conditions. He refers good adherence to prescribed medications without adverse reactions or drug-related side effects. He lost 5 kg of body weight. He is in a waiting list for the bariatric surgery. The home blood pressure levels are well controlled.

Physical Examination

- Weight: 133 kg
- Body mass index (BMI): 43.4 kg/m^2
- Waist circumference: 134 cm
- Clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 136/85 mmHg (right arm)
- Sitting BP: 134/84 mmHg (right arm)
- Standing BP: 132/82 mmHg at 1 min

Haematological Profile

- Creatinine, 1.11 mg/dL, and eGFR (MDRD), 71 mL/min/1.73 m^2
- Potassium: 3.82 mEq/L
- TOT-C, 186 mg/dL; LDL-C, 102 mg/dL; HDL-C, 62 mg/dL; and TG, 109 mg/dL
- Glycaemia: 86 mg/dL
- HbA_{1c}: 5.9 %

Current Treatment

Perindopril/indapamide/amlodipine 10/2.5/5 mg (fix combination) 1 cp h 8:00; doxazosin 4 mg 1 cp h 22:00; and atorvastatin 20 mg 1 cp h 22:00. Nocturnal CPAP.

Treatment Evaluation

- No change for current pharmacological treatment

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary low-salt and caloric restriction

Which is the most useful diagnostic test to repeat during the follow-up in this patient?

Possible answers are:

1. Electrocardiogram
2. Echocardiogram
3. Vascular Doppler ultrasound
4. Evaluation of renal parameters (e.g. creatininemia, eGFR, ClCr and UACR)
5. 24-h ambulatory BP monitoring

7.5 Discussion

In the present clinical case, the clinical history of hypertension is in a strict link with the condition of severe obesity. The presence of severe obesity likely represents a further cause, together with the positive family history, of increased blood pressure (BP) values in this patient. In addition, it represents a cause of resistance to antihypertensive medication.

It is widely recognized that hypertension is closely related to excess body weight [2], and weight reduction is followed by a decrease in BP. This is confirmed in a very large meta-analysis, showing that mean SBP and DBP reductions associated with an average weight loss of 5.1 kg were 4.4 and 3.6 mmHg, respectively [3]. For these reasons, weight reduction is strongly recommended in overweight and obese hypertensive patients for control of risk factors. As already commented, weight loss can also improve the efficacy of antihypertensive medications and the cardiovascular risk profile. Weight loss maintenance is quite difficult to obtain. Therefore, a multidisciplinary approach, including low-caloric diet and regular exercise, is mandatory. Weight loss can also be obtained by antiobesity drugs, such as orlistat, and, to a greater degree, by bariatric surgery, which appears to decrease cardiovascular risk in severely obese patients [4]. In this clinical case, the bariatric surgical intervention was proposed to the patient.

Obstructive sleep apnoea syndrome is very frequent in obese patients, and it appears to be responsible for a large proportion of cases of BP increase or the absence of BP reduction at night-time. Although a few prospective studies have linked severe obstructive sleep apnoea to fatal and nonfatal CV events and all-cause mortality, this association appears to be closer for stroke [5]. Because of the relationship between obesity and obstructive sleep apnoea, weight loss and exercise are commonly recommended, but unfortunately no large-scale controlled trials are available [6]. Continuous positive airway pressure therapy is a successful procedure for reducing obstructive sleep apnoea; however, on the basis of four available meta-analyses, the effect of prolonged, continuous, positive airway pressure therapy on ambulatory BP is very small (1–2 mmHg reduction) [7]. This may be due to poor adherence to this complex procedure or a limited follow-up period, but a recent study with a follow-up longer than 3 years has found no difference in BP or in drug usage between sleep apnoea patients who continued or those who quitted positive air pressure therapy [8].

Which is the first-line antihypertensive therapy in a hypertensive patient with obesity? Because of the difficulties in normalizing BP values in patients with severe obesity, several compounds are needed to reduce BP values. Therefore, the first-line drug does not exist. Of course, when considering the activated renin–angiotensin–aldosterone system occurring in obesity, physicians should always utilize an ACE-inhibitor or, if not tolerated, an Ang II receptor antagonist. Reduced BP < 140/90 is the target in these patients. As a final consideration, during the follow-up evaluation of this hypertensive patient with obesity and eccentric LV hypertrophy, repeated electrocardiographic assessment is not useful because it does not allow assessing LV hypertrophy in a condition of obesity. Thus, repeated echocardiographic assessment of LV geometry and function represents the only way to able to provide indirect evidence of the therapeutic effectiveness of the prescribed antihypertensive therapy, as also recommended by current guidelines [1].

Take-Home Messages

- The presence of severe obesity represents a major cause of increased blood pressure, and it favours the resistance to antihypertensive medication.
- RAS inhibitors should represent a first-line therapy in hypertensive patients with obesity.
- Obstructive sleep apnoea syndrome is very frequent in obese patients and it appears to be responsible for a large proportion of cases of blood pressure increase or the absence of blood pressure reduction at night-time.

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Chapter 8
Clinical Case 8: Patient with Essential Hypertension and Previous Stroke

8.1 Clinical Case Presentation

A 71-year-old, Caucasian female, retired (former employee), presented to the outpatient clinic for uncontrolled hypertension. The patient refers history of essential hypertension by the age of 70 years. She was treated with monotherapy based on beta-blocker (atenolol 50 mg) with effective blood pressure control. She was used to measure blood pressure exclusively during her general practitioner's periodical visits (2–3 visits per year, mainly in the morning). Six months ago, she received a diagnosis of ischaemic stroke (transient episode of dysarthria, altered vision and right hemiplegia). Since then, the neurologist added acetylsalicylic acid (ASA) 100 mg to the therapy. Patient started to measure blood pressure at home, reporting unsatisfactory blood pressure control.

Family History

She has unknown family history of hypertension. She has one son in a good health.

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DOI 10.1007/978-3-319-39164-9_8,

Clinical History

She never smoked. She has no history of alcohol assumption and a sedentary lifestyle. She is affected by dyslipidaemia, treated with simvastatin 10 mg daily (discontinued intake).

Physical Examination

- Weight: 61 kg
- Height: 165 cm
- Body mass index (BMI): 22.4 g/m^2
- Waist circumference: 86 cm
- Respiration: normal
- Heart sounds: S1–S2 regular, normal and no murmurs
- Resting pulse: regular rhythm with normal heart rate (62 beats/min)
- Carotid arteries: no murmurs
- Femoral and foot arteries: palpable
- Fundoscopy: no signs of hypertensive retinopathy
- Neurologic exam: right arm and leg with hyperactive deep tendon reflexes

Haematological Profile

- Haemoglobin: 13.8 g/dL
- Haematocrit: 39.7 %
- Fasting plasma glucose: 100 mg/dL
- Fasting lipids: total cholesterol (TOT-C), 278 mg/dL; low-density lipoprotein cholesterol (LDL-C), 186 mg/dL; high-density lipoprotein cholesterol (HDL-C), 68 mg/dL; and triglycerides (TG), 221 mg/dL
- Electrolytes: sodium, 143 mEq/L, and potassium, 4.26 mEq/L
- Serum uric acid: 5.3 mg/dL
- Renal function: creatinine, 0.80 mg/dL; creatinine clearance (Cockcroft–Gault), 69 mL/min; and estimated glo-

merular filtration rate (eGFR) (MDRD), 71 mL/min/1.73 m^2
- Urinary albumin/creatinine ratio (morning urine sample): 16 mg/g
- Normal liver function tests
- Normal thyroid function tests

Blood Pressure Profile

- Home BP (average): 165/102 mmHg
- Sitting BP: 170/104 mmHg (right arm > left arm)
- Standing BP: 164/98 mmHg at 1 min

CT Scan

Exam executed without contrast enhancement. Evidence of hypodense ischaemic lesion at the level of left anterior nucleus capsular and radiata area. Ventricles with normal dimensions. No signs of median line deviation (Fig. 8.1).

Chest Radiography

Slight increment of left cardiac section. No pleural or lung parenchymal lesions (Fig. 8.2).

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (62 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH (Sokolow–Lyon 1.4 mV, Cornell voltage 1.5 mV) (illustrated in Fig. 8.3). Peripheral (**a**) and precordial (**b**) leads.

Current Treatment

Atenolol 50 mg 1 cp h 8:00, ASA 100 mg 1 cp h 14:00 and simvastatin 10 mg 1 cp h 22:00

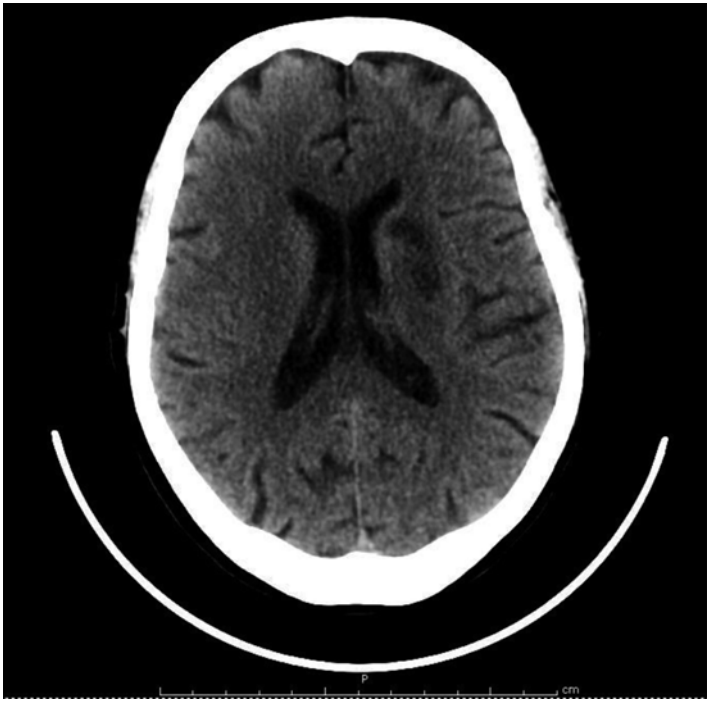

FIGURE 8.1 CT scan without contrast enhancement. Evidence of hypodense ischaemic lesion at the level of left anterior nucleus capsular and radiata area

Diagnosis

Uncontrolled arterial hypertension with associate clinical condition (previous ischaemic stroke). Additional modifiable cardiovascular risk factor (hypercholesterolaemia).

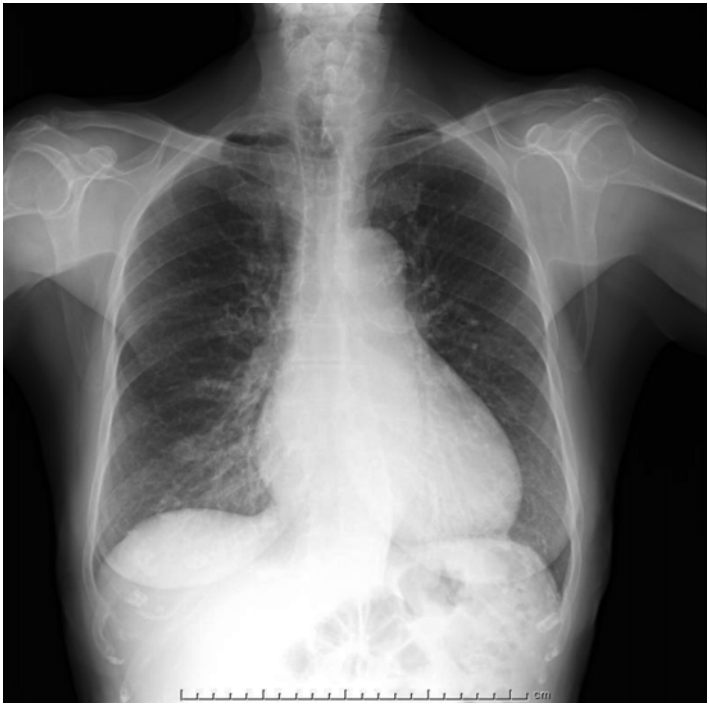

FIGURE 8.2 Standard postero-anterior chest radiograph showing slight increased left cardiac section. No acute pleural or lung parenchymal lesions

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

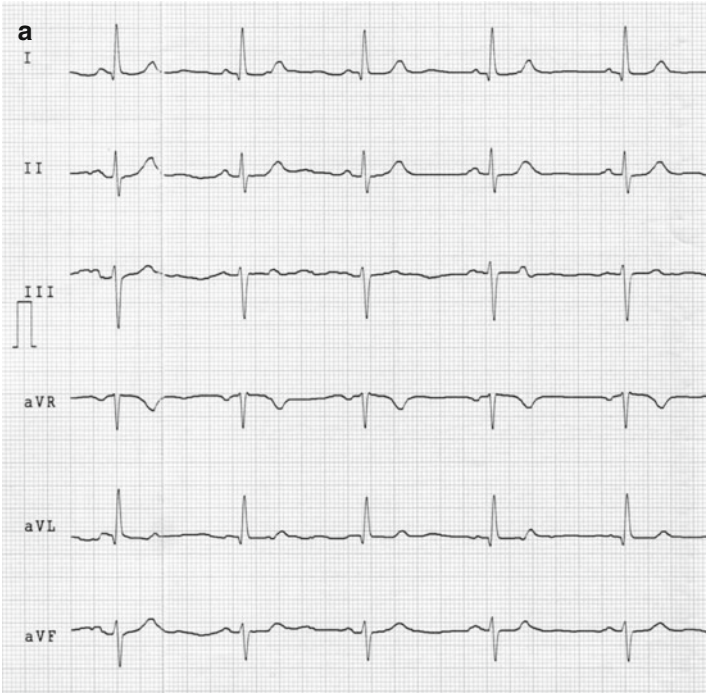

FIGURE 8.3 (**a**, **b**) Sinus rhythm with normal heart rate (62 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH

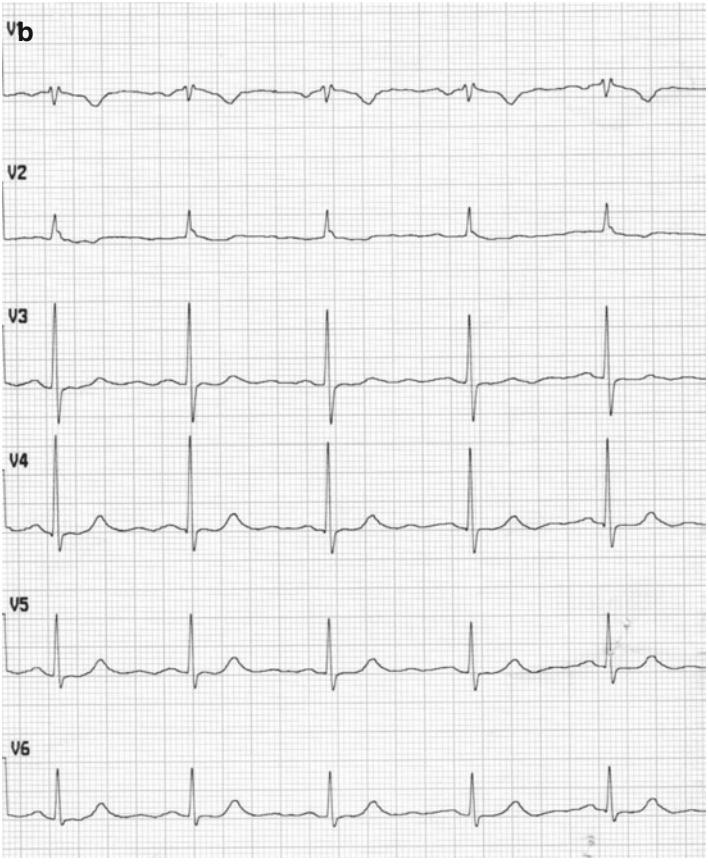

FIGURE 8.3 (continued)

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has very high cardiovascular risk.

Which is the best therapeutic option in this patient?

Possible answers are:

1. Insert a thiazide diuretic.
2. Insert a Ca-antagonist.
3. Insert an ACE-inhibitor.
4. Titrate the beta-blocker therapy.
5. Switch the statin therapy.

Treatment Evaluation

- Maintain atenolol 50 mg 1 cp h 8:00.
- Insert amlodipine 5 mg 1 cp h 8:00.
- Insert perindopril 5 mg 1 cp h 8:00.
- Stop simvastatin and start atorvastatin 20 mg 1 cp h 22:00.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt restriction
- Blood tests: serum creatinine, clearance creatinine, eGFR, potassium and lipid profile
- Echocardiogram aimed at evaluating left ventricular (LV) mass and function (systolic and diastolic properties)
- Carotid vascular ultrasound
- Abdominal echography with renal artery Doppler

8.2 Follow-Up (Visit 1) at 4 Weeks

At follow-up visit, the patient reports good adherence to prescribed medications without adverse reactions or drug-related side effects. The home blood pressure levels are ameliorated, but still elevated.

Physical Examination

- Weight: 61 kg
- Body mass index (BMI): 23.8 g/m^2
- Resting pulse: regular rhythm with normal heart rate (64 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 145/92 mmHg
- Sitting BP: 148/94 mmHg
- Standing BP: 144/90 mmHg

Haematological Profile

- Creatinine, 0.82 mg/dL; creatinine clearance (Cockcroft–Gault), 68 mL/min; and eGFR, MDRD, 70 mL/min/1.73 m^2
- TOT-C, 171 mg/dL; LDL-C, 97 mg/dL; HDL-C, 51 mg/dL; and TG, 114 mg/dL
- Potassium, 4.3 mEq/L

Current Treatment

Atenolol 50 mg 1 cp h 8:00; amlodipine 5 mg 1 cp h 8:00; perindopril 5 mg 1 cp h 8:00; ASA 100 mg 1 cp h 14:00; and atorvastatin 20 mg 1 cp h 22:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

Echocardiogram with Doppler Ultrasound

Eccentric left ventricle (LV) hypertrophy (LV mass indexed 117 g/m^2; relative wall thickness: 0.41) with high-normal chamber dimension (LV end-diastolic diameter 54 mm), impaired LV relaxation (E/A ratio < 1) at both conventional and tissue Doppler evaluations and normal ejection fraction (LV ejection fraction 56 %, LV fractional shortening 37 %). Normal dimension of aortic root and left atrium. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (+) and tricuspid (+) regurgitations at Doppler ultrasound examination.

Carotid Ultrasound

Several calcific atherosclerotic plaques at both carotid levels, without signs of haemodynamically significant stenosis.

Abdominal Echography with Renal Artery Doppler

Moderate liver steatosis. Biliary tree not dilated. Normal spleen dimensions. Adrenal glands without signs of abnormal lesions. Abdominal aorta with normal dimension and rare atherosclerotic plaques. Kidneys with normal dimensions (longitudinal diameter: right 106 mm, left 110 mm) and cortical thickness. Renal arteries without signs of haemodynamically significant stenosis. Intrarenal index resistance bilaterally increased (right, 0.78; left, 0.80).

Diagnosis

Uncontrolled arterial hypertension with associate clinical condition (previous ischaemic stroke), cardiac (eccentric LV hypertrophy), vascular (atherosclerotic carotid and abdominal aorta) and renal (hypertensive nephropathy) organ

damages. Additional modifiable cardiovascular risk factor (hypercholesterolaemia).

Which is the global cardiovascular risk profile in this patient?

Possible answers are:

1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

The echographic evidence of LV hypertrophy and vascular atherosclerosis does not modify the individual global cardiovascular risk profile in a patient with previous clinical event, which remains very high, according to 2013 ESH/ESC global cardiovascular risk stratification [1].

Which is the best therapeutic option in this patient?

Possible answers are:

1. Titrate the Ca-antagonist.
2. Add another drug class (e.g. doxazosin).
3. Titrate the ACE-inhibitor and add a diuretic.
4. Titrate the beta-blocker therapy.

Treatment Evaluation

- Maintain atenolol 50 mg 1 cp h 8:00.
- Stop amlodipine 5 mg and perindopril 5 mg.
- Start a fix combination with perindopril 10 mg, indapamide 2.5 mg and amlodipine 5 mg 1 cp h 8:00.
- Maintain the remnant therapy (ASA 100 mg 1 cp and atorvastatin 20 mg).

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt restriction
- Daily 30-min walk
- Blood tests: creatinine, uric acid, potassium and lipid profile

8.3 Follow-Up (Visit 2) at 3 Months

At follow-up visit, the patient is in quite stable clinical conditions. She refers no clinical symptoms. She also reports good adherence to prescribed medications. The home blood pressure is stable and well controlled.

Physical Examination

- Weight: 60 kg
- Clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 132/81 mmHg
- Sitting BP: 128/78 mmHg
- Standing BP: 126/76 mmHg

Haematological Profile

- TOT-C, 164 mg/dL; LDL-C, 81 mg/dL; HDL-C, 63 mg/dL; and TG, 102 mg/dL
- Electrolytes: potassium, 3.84 mEq/L
- Serum uric acid: 6.1 mg/dL
- Creatinine, 0.88 mg/dL, and eGFR (MDRD), 63 mL/min/1.73 m^2

Current Treatment

Perindopril/indapamide/amlodipine (fix combination) 10/2.5/5 mg 1 cp h 8:00; atenolol 50 mg 1 cp h 8:00 and ASA 100 mg 1 cp h 14:00; and atorvastatin 20 mg 1 cp h 22:00

Which is the best therapeutic option in this patient?

Possible answers are:

1. Maintain the same therapy.
2. Down-step the diuretic therapy.
3. Titrate the statin therapy.
4. Titrate the beta-blocker therapy.

Treatment Evaluation

Maintain the same therapy.

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines.
- Dietary salt restriction.
- Daily 30' walk.
- Blood tests: creatinine, uric acid, blood cell count, plasma sodium, potassium, glucose and lipid profile.
- Repeat 12-lead electrocardiogram.
- Repeat echocardiogram.

8.4 Follow-Up (Visit 3) at 1 Year

At follow-up visit, the patient refers a stability of her general clinical conditions. She refers good adherence to prescribed medications without adverse reactions or drug-related side

effects. The home blood pressure levels remained substantially well controlled.

Physical Examination

- Weight: 62 kg
- Body mass index (BMI): 22.7 kg/m^2
- Clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 128/78 mmHg
- Sitting BP: 132/78 mmHg
- Standing BP: 128/76 mmHg

Haematological Profile

- Creatinine, 0.82 mg/dL, and eGFR (MDRD), 68 mL/min/1.73 m^2
- Haemoglobin: 14.1 g/dL
- Haematocrit: 40.2 %
- Electrolytes: sodium, 142 mEq/L, and potassium, 3.81 mEq/L
- Serum uric acid: 6.3 mg/dL
- Fasting plasma glucose: 97 mg/dL
- TOT-C, 170 mg/dL; LDL-C, 85 mg/dL; HDL-C, 64 mg/dL; and TG, 106 mg/dL

Current Treatment

Perindopril/indapamide/amlodipine (fix combination) 10/2.5/5 mg 1 cp h 8:00; atenolol 50 mg 1 cp h 8:00 and ASA 100 mg 1 cp h 14:00; and atorvastatin 20 mg 1 cp h 22:00

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

12-Lead Electrocardiogram

Sinus rhythm with normal heart rate (64 bpm), normal atrioventricular and intraventricular conduction. No signs of LVH (Sokolow–Lyon 1.5 mV, Cornell voltage 1.6 mV). Similar to the previous one.

Echocardiogram with Doppler Ultrasound

Slight eccentric left ventricle (LV) hypertrophy (LV mass indexed 102 g/m^2; relative wall thickness: 0.39) with normal chamber dimension (LV end-diastolic diameter 48 mm), impaired LV relaxation (E/A ratio < 1) at both conventional and tissue Doppler evaluations and normal ejection fraction (LV ejection fraction 60 %, LV fractional shortening 39 %). Normal dimension of aortic root and left atrium. Right ventricle with normal dimension and function. Pericardium without relevant abnormalities. Mitral (+) and tricuspid (+) regurgitations at Doppler ultrasound examination. *Conclusions*: slight eccentric LV hypertrophy, significantly ameliorated compared with the previous one.

Treatment Evaluation

No change for current pharmacological therapy

Prescriptions

- Periodical home blood pressure evaluation according to recommendations from guidelines
- Dietary salt restriction
- Daily 30’ walk

8.5 Discussion

Stroke is the second most frequent cause of death worldwide, preceded only by heart disease. Overall, two thirds of strokes occur in patients over 65 years old. Arterial hypertension and high blood cholesterol are two major risk factors for stroke. The present clinical case is a typical example of a patient with a well-defined diagnosis of hypertension and hypercholesterolaemia, who failed to reach targeted blood pressure and blood cholesterol levels. In particular, arterial hypertension was treated with a beta-blocker by her physician, without obtaining a sufficient control. This unsatisfactory blood pressure control was a likely consequence of a wrong blood pressure measurement. Indeed, the blood pressure was taken exclusively at the doctor's clinic, usually in the morning, at the pharmacological peak time of the drug. It is conceivable that a home blood pressure measure, taken in the morning at the pharmacological trough time of the drug, or even better a 24-h ambulatory blood pressure monitoring would have unmasked the real blood pressure behaviour. The echographic revelation of an eccentric LV hypertrophy strongly supports the presence of an uncontrolled arterial hypertension. It is accepted that systolic blood pressure, more than the diastolic, has a direct relation with stroke incidence. How far should systolic blood pressure be reduced in a patient with previous stroke to prevent the recurrence of an event? The 2013 ESH/ESC Guidelines [1] extensively comment this aspect, highlighting the concept that no evidence is yet available and that recurrent stroke is prevented by reducing systolic blood pressure to <130 mmHg. Is there a preferred first-line antihypertensive therapy in a patient with a previous stroke? As prevention of stroke is the most consistent benefit of antihypertensive therapy and has been observed in almost all large randomized clinical trials using different drug regimens, all regimens are acceptable for stroke prevention provided that blood pressure is effectively reduced [2]. In details, meta-analyses and metaregression analyses suggest that calcium antagonists may have a slightly greater effectiveness on

stroke prevention [3], but the two successful trials in secondary stroke prevention used the diuretic indapamide alone or in combination with the ACE-inhibitor perindopril [4]. Greater cerebrovascular protective effects have also been reported for sartans in comparison with a variety of other drugs [5]. For all these reasons, in the present clinical case the first step has been to reduce systolic blood pressure values to around 130 mmHg. To this aim, a combination of the ACE-inhibitor perindopril, the diuretic indapamide and the Ca-antagonist amlodipine was used.

The second point concerns the hypercholesterolaemia. This risk factor was treated with low dose of simvastatin. Unfortunately, the patient did not assume this pill regularly. Moreover, she did not provide any blood cholesterol measurement under statin intake. At the time of the first visit, patient showed a high-risk lipid profile. Therefore, it is conceivable to assume that 10 mg simvastatin, irregularly assumed, failed to normalize blood cholesterol levels.

With respect to the targeted LDL-cholesterol levels, beneficial effects of statin therapy have been shown in patients with a previous stroke, with LDL-cholesterol targets definitely lower than 135 mg/dL [6]. Whether they benefit from a target <70 mg/dL is open to future research.

Take-Home Messages

- Long-time uncontrolled arterial hypertension and hypercholesterolaemia represent two of the major risk factors for ischaemic stroke.
- Reducing systolic blood pressure to around 130 mmHg is the main target to prevent ischaemic stroke or recurrent stroke. To this aim, all therapeutic regimens are acceptable.
- In patients with previous stroke, beneficial effects of statin therapy have been demonstrated, with LDL-cholesterol targets definitely lower than 135 mg/dL.

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