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Introduction

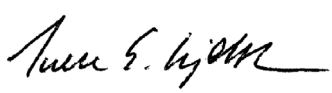
The European Society of Hypertension has on a regular basis issued ***Scientific Newsletters: Update on Hypertension Management*** with information on the latest news and research. Forty-nine newsletters were published between 2000 and 2010. They have provided important insights into the diagnostics and the management of hypertension and other associated diseases, and generated substantial interest within the medical community.

Over the past 10 years, the ESH newsletters were distributed as single-page documents during our annual meetings. Furthermore, they were available in PDF format on the ESH Portal. In the interest of not only preserving, but of indexing and making them more accessible for the hypertension community, we have decided to revise all previous issues and collate them with new material from 2011 into one single volume.

We believe that this publication will be complementary to other ESH educational material, such as the European Guidelines on the Management of Hypertension, numerous position statements, and the "ESH Manual of Hypertension". Hopefully, each of you will find this new volume of material to be useful in your clinical practice.

Sincerely,

Sverre E. Kjeldsen



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TREATMENT OF HYPERTENSION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Introduction

Hypertension in diabetes is one of the most widespread, important, and treatable cardiovascular risk factors in clinical practice. Data from randomised trials have shown the benefits of improved blood pressure control in patients with type 2 diabetes [1], but the blood pressure goal is still not well established due to lack of evidence. Recent international and national guidelines and recommendations have emphasised the screening, evaluation, and vigorous treatment of elevated blood pressure (BP) if combined with diabetes [2–4], especially systolic BP. Epidemiological data indicate some improving trends in blood pressure control, reflecting increased awareness and more appropriate treatment over time [5].

Randomised clinical trials including hypertensive patients with diabetes

Several intervention trials have formed the evidence-base for treatment of hypertension in diabetes. In the Systolic Hypertension in the Elderly Program (SHEP), low-dose, diuretic-based treatment (chlorthalidone) was found to be effective compared with placebo in preventing CV complications in elderly patients with type 2 diabetes mellitus and isolated systolic hypertension [6]. Similarly, the Systolic Hypertension in Europe (Syst-Eur) trial compared calcium-antagonist based treatment (nitrendipine) with placebo in elderly patients with isolated systolic hypertension and in a subgroup with type 2 diabetes (n = 492). In Syst-Eur, treatment for five years prevented 178 major CV events in every 1000 diabetic patients treated [7], i.e. approximately 6 patients had to be treated for five years to prevent one major CV event.

The Hypertension Optimal Treatment Study (HOT) [8] investigated the intensity of antihypertensive treatment using a calcium-antagonist (felodipine) as baseline therapy in hypertensive patients averaging 62 years of age and 170/105 mm Hg in baseline BP, including 1501 patients with type 2 diabetes. In HOT [8] the incidence of major CV events was lowered (p = 0.005) from 24.4 to 18.6 and 11.9 events/100 patient-years, respectively, in the randomised tertiles of diabetes patients who had achieved 85, 83, and 81 mm Hg, respectively, in diastolic BP. Approximately 20 patients needed to be treated for 5 years to prevent one major CV event when BP was further lowered from 84 to 81 mm Hg in these patients. Tight BP control to prevent macro- and microvascular complications was also successful after more than 8 years of follow-up of 1148 hypertensive patients in the United Kingdom Prospective Diabetes Study (UKPDS), especially for prevention of stroke and retinopathy [9]. However, no significant effect difference was found between captopril and atenolol [10], but patients on atenolol needed significantly more oral anti-glycaemic drugs due to weight increase.

The Captopril Prevention Project (CAPPP) [11] compared the effects of an ACE inhibitor with diuretic/β-blocker treatment in middle-aged hypertensive patients of whom 572 had type 2 diabetes at baseline; there were fewer CV events on captopril, and (as in HOPE) fewer hypertensive patients developed type 2 diabetes on ACE inhibitor compared to "standard therapy". In the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study all patients were above the age of 70 years, and as many as 719 of them had type 2 diabetes at baseline; however, CV mortality was the same on standard therapy, ACE inhibition, or calcium-antagonist treatment [12].

In addition, nearly normotensive subjects with diabetes may sometimes benefit from the use of drugs with blood pressure lowering properties. The results of the Heart Outcomes Prevention Evaluation (HOPE) Study and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO) HOPE substudy [13] showed that treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril, compared with placebo, significantly lowered the risk of cardiovascular (CV) events (by 25%) and overt nephropathy in people with type 2 diabetes with a previous CV event or at least one other CV risk factor, including 56% with a history of hypertension. Uncontrolled diabetic hypertensives (BP > 160/90 mm Hg) were, however, not randomised. HOPE was not a hypertension trial, but gives a strong argument in favour of blockade of the renin–angiotensin system in CV risk patients with diabetes.

In the Losartan Intervention For Endpoint reduction (LIFE) trial [14] a subgroup of 1195 patients with diabetes, hypertension, and signs of left-ventricular hypertrophy (LVH) on electrocardiograms were randomised to either losartan-based or atenolol-based treatment. Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively; RR 0.61 (0.45–0.84), p = 0.002. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [15] a subgroup of 12,063 patients (36%) with diabetes were randomised to treatment with chlorothalidone, amlodipine, or lisinopril. There were no differences in the primary composite CV outcome between these three drugs, used in a very heterogenous study population. A similar result of equity between treatment arms for the primary composite CV end-point was found in the Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) based on a sub-analysis of 1302 patients with hypertension and diabetes randomised to either nifedipine slow-release or conventional therapy [16].

The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) has shown substantial benefits in patients randomised to a treatment based on amlodipine, with perindopril as add-on therapy if needed, versus atenol-based treatment, with thiazide as add-on therapy if needed, for the reduction of stroke and total mortality [17]. The ASCOT study was stopped prematurely because of the difference in all-cause mortality, indicating the benefits of an amlodipine-based treatment in comparison to older drug alternatives after 5.5 years' median follow-up. Though not significant, compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (429 vs. 474; unadjusted HR 0.90, 95% CI 0.79–1.02, p = 0.1052), fatal and non-fatal stroke (327 vs. 422; 0.77, 0.66–0.89, p = 0.0003), total cardiovascular events and procedures (1362 vs. 1602; 0.84, 0.78–0.90, p < 0.0001), and all-cause mortality (738 vs. 820; 0.89, 0.81–0.99, p = 0.025). Patients with diabetes had the same benefits of this treatment as non-diabetics, with no heterogeneity between subgroups [17].

In the ADVANCE trial it was shown that the addition of a combination of perindopril and indapamide to patients on antihypertensive treatment was associated with substantial clinical benefits, compared with placebo treatment [18]. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs. 938 [16.8%] placebo; hazard ratio 0.91, 95% CI 0.83–1.00, p = 0.04). The separate reductions in macrovascular and microvascular events were similar but were not independently significant. The relative risk of death from cardiovascular disease was reduced by 18% (211 [3.8%] active vs. 257 [4.6%] placebo; 0.82, 0.68–0.98, p = 0.03), and death from any cause was reduced by 14% (408 [7.3%] active vs. 471 [8.5%] placebo; 0.86, 0.75–0.98, p = 0.03). The actively treated group had a mean systolic blood pressure under treatment of 135 mm Hg.

In the ACCOMPLISH trial (60% patients with diabetes) it was shown that the fixed combination of benazapril and amlodipine resulted in a relative risk reduction of cardiovascular events compared to the fixed combination of benazapril and hydrochlorothiazide [19].

Finally, in the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) study a total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy targeting a systolic pressure of less than 120 mm Hg, or standard therapy targeting a systolic pressure of less than 140 mm Hg [20]. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive--therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; $p = 0.20$). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI 0.85 to 1.35; $p = 0.55$). The annual rates of stroke, a pre-specified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; $p = 0.01$). Serious adverse events attributed to antihypertensive treatment occurred more often in the intensive-therapy group (3.3%) than in the standard-therapy group (1.3%) ($p < 0.001$). Thus, in patients with type 2 diabetes at high risk of cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of major cardiovascular events.

Recent observational studies support the view that an achieved systolic blood pressure level below 130 mmHg is of benefit for stroke prevention but not for reduction of cardiovascular events [21, 22].

Summary

The general consensus for the treatment of hypertension in type 2 diabetes is now to aim for a well-controlled SBP of 130–139 mm Hg and, if possible, closer to the lower values in this range, but the exact BP goal has not been fully established [4]. Such a strategy is usually based on polypharmacy with synergistic drug combinations. This should be part of an overall risk factor control, also addressing smoking, dyslipidaemia, microalbuminuria, and hyperglycaemia to optimise the control [23]. Treatment with an RAS blocking agent has been shown to be effective in preventing macro- and microvascular events in high-risk diabetics with controlled hypertension.

Conclusions

1. Patients with type 2 diabetes should be treated for hypertension when BP is above 140 and/or 90 mm Hg, aiming at a systolic BP well below this threshold but not below 120 mm Hg. 2. These patients usually need two or more drugs/combination therapy to reach the BP target, especially for systolic BP. 3. Though ACE inhibitors have been proven to be cardiovascular-protective and some angiotensin-II receptor blockers nephroprotective, there is no consensus on the "drug of choice" for all hypertensive type 2 diabetic patients. 4. Most studies support the notion that blood pressure reduction *per se* is more important than individual properties of specific drugs in most cases. 5. Blockade of the renin-angiotensin system seems to be an appropriate choice as one of the partner drugs in offering combination therapy to hypertensive patients with diabetes or glucose intolerance. 6. It is recommended that trends be followed in the quality of health care for patients with hypertension and diabetes, for example by local, regional, or national registers.

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HYPERTENSION IN PREGNANCY: RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT

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Hypertensive disorders in pregnancy remain a major cause of maternal, foetal, and neonatal morbidity and mortality not only in less developed, but also in industrialized countries. Pregnant women with hypertension are at higher risk of severe complications such as abruptio placentae, cerebrovascular accident, organ failure, and disseminated intravascular coagulation. The foetus is at risk of intrauterine growth retardation, prematurity, and intrauterine death.

Physiologically, blood pressure (BP) falls in the second trimester (a mean decrease of 6–10 mm Hg in mean arterial pressure). In the third trimester, it returns to pre-pregnancy levels. This fluctuation occurs in both normotensive and chronically hypertensive women.

Definition of hypertension in pregnancy

The definition of hypertension in pregnancy previously included an elevation in BP during the second trimester from a baseline reading in the first trimester, or to pre-pregnancy levels, but a definition **based on absolute blood pressure values (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg)** is now preferred.

Blood pressure measurement

It is essential to confirm high BP readings on two occasions, using mercury sphygmomanometry in the sitting position as the gold standard. Korotkoff Phase V is now recommended for measurement of DBP in pregnancy. Only validated measuring devices and validated ambulatory BP monitoring (ABPM) devices should be used in pregnancy (see: www.dableducational.org).

Classification of hypertension in pregnancy

Hypertension in pregnancy is not a single entity but comprises:

- **pre-existing hypertension**, which complicates 1–5% of pregnancies and is defined as BP ≥ 140/90 mm Hg that either predates pregnancy or develops before 20 weeks of gestation. Hypertension usually persists more than 42 days post partum. It may be associated with proteinuria;
- **gestational hypertension**, which is pregnancy-induced hypertension with or without proteinuria. Gestational hypertension associated with significant proteinuria (> 300 mg/l or > 500 mg/24 h or dipstick 2+ or more) is known as **pre-eclampsia**. Hypertension develops after 20 weeks of gestation. In most cases, it resolves within 42 days post partum. Gestational hypertension is characterized by poor organ perfusion;
- **pre-existing hypertension plus superimposed gestational hypertension with proteinuria**. Pre-existing hypertension is associated with further worsening of BP and protein excretion ≥ 3 g/day in 24-hour urine collection after 20 weeks' gestation; it corresponds to "chronic hypertension with superimposed pre-eclampsia" in previous terminology;
- **antenatally unclassifiable hypertension** — hypertension with or without systemic manifestation, if BP was first recorded after 20 weeks of gestation. Re-assessment is necessary at or after 42 days post partum. If hypertension is resolved by then, the condition should be re-classified as gestational hypertension with or without proteinuria. If the hypertension is not resolved by then, the condition should be re-classified as pre-existing hypertension.

Oedema occurs in up to 60% of normal pregnancies and is no longer used in the diagnosis of pre-eclampsia.

Recommended laboratory investigations

Hypertensive disorders in pregnancy, particularly gestational hypertension with or without proteinuria, may induce changes in the haematologic, renal, and hepatic profiles, which may adversely affect prognosis and both neonatal and maternal outcomes. Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy are presented in Table 1.

The majority of women with pre-existing hypertension in pregnancy have mild to moderate hypertension (140–179/90–109 mm Hg), and are at low risk of cardiovascular complications within the short timeframe of pregnancy. Women with essential hypertension and normal renal function have good maternal and neonatal prognosis; they are candidates for non-pharmacological therapy because there is no evidence that drug treatment results in improved neonatal outcome. With antihypertensive treatment, there seems to be only less risk of developing severe hypertension.

Non-pharmacological management and prevention of hypertension in pregnancy

Non-pharmacological management should be considered for pregnant women with SPB of 140–150 mm Hg or DBP of 90–99 mm Hg or both, measured in a clinical setting. A short-term hospital stay may be required for diagnosis and for ruling out severe gestational hypertension (pre-eclampsia), in which the only effective treatment is delivery. Management, depending on BP, gestational age, and presence of associated maternal and foetal risk factors includes close supervision, limitation of activities, and some bed rest in the left lateral position. **A regular diet without salt restriction is advised** as salt restriction may induce low intravascular volume. Preventive interventions aimed

Table 1. Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy

Haemoglobulin and haematocrit	Haemoconcentration supports diagnosis of gestational hypertension with or without proteinuria. It indicates severity. Levels may be low in very severe cases because of haemolysis
Platelet count	Low levels < 100,000 × 10^9/L may suggest consumption in the microvasculature. Levels correspond to severity and are predictive of recovery rate in post-partum period, especially for women with HELLP syndrome*
Serum AST, ALT	Elevated levels suggest hepatic involvement. Increasing levels suggest worsening severity
Serum LDH	Elevated levels are associated with haemolysis and hepatic involvement. May reflect severity and may predict potential for recovery post partum, especially for women with HELLP syndrome*
Proteinuria (24-h urine collection)	Standard to quantify proteinuria. If > 2 g/day, very close monitoring is warranted. If > 3 g/day, delivery should be considered
Urinalysis	Dipstick test for proteinuria has significant false-positive and false-negative rates. If dipstick results are positive (≥ 1), 24-h urine collection is needed to confirm proteinuria. Negative dipstick results do not rule out proteinuria, especially if DBP ≥ 90 mm Hg
Serum uric acid	Elevated levels aid in differential diagnosis of pre-eclampsia and may reflect severity
Serum creatinine	Levels drop in pregnancy. Elevated levels suggest increasing severity of hypertension; assessment of 24-h creatinine clearance may be necessary

*HELLP — Haemolysis, Elevated Liver enzyme levels, and Low Platelet count

Table 2. Antihypertensive drugs in pregnancy

Central alpha agonists	Methyldopa is the drug of choice
β-blockers	Atenolol and metoprolol appear to be safe and effective in late pregnancy
Alpha-/β-blockers	Labetalol has comparable efficacy with methyldopa; in the case of severe hypertension it could be given intravenously
Calcium-channel blockers	Oral nifedipine or IV isradipine could be given in hypertensive emergencies. Potential synergism with magnesium sulphate may induce hypotension
ACE inhibitors, angiotensin II antagonists, direct renin inhibitors	Foetal abnormalities including death can be caused, and these drugs are contraindicated in pregnancy
Diuretics	Diuretics are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in pre-eclampsia
Direct vasodilators	Hydralazine is no longer the parenteral drug of choice because of its perinatal adverse effects

at reducing the incidence of gestational hypertension, especially pre-eclampsia, including calcium supplementation (2 g/d), fish oil and nutrient supplementation, and **low-dose acetylsalicylic acid therapy**, have failed to produce consistently the benefits initially expected, especially in the foetus. Calcium supplementation of at least 1 g/d during pregnancy almost halved the risk of pre-eclampsia without causing any harm. The effect was greatest for high-risk women. However, the evidence for added calcium in the prevention of hypertensive disorders is conflicting. Low-dose aspirin is, however, used prophylactically in women who have a history of early onset (< 28 weeks) pre-eclampsia. Increased energy intake is not beneficial in the prevention of gestational hypertension. Although **weight reduction** may be helpful in reducing BP in non-pregnant women, it **is not recommended during pregnancy** in obese women. Weight reduction can be associated with reduced neonatal weight and lower subsequent growth in infants of dieting obese mothers.

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. While there is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial, treatment of less severe hypertension is controversial. Although it might be beneficial for the mother with hypertension to reduce her BP, lower BP may impair uteroplacental perfusion and thereby jeopardize foetal development. Much of the uncertainty about the benefits of lowering BP in pregnant women with mild pre-existing hypertension stems from published trials that are too small to detect a modest reduction in obstetrical complications.

Pharmacological management of hypertension in pregnancy

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the foetus. SBP ≥ 170 or DBP ≥ 110 mm Hg in a pregnant woman should be considered an emergency, and hospitalization is absolutely essential. Pharmacological treatment with intravenous labetalol or oral methyldopa or nifedipine should be initiated. Intravenous hydralazine should no longer be thought of as the drug of choice as its use is associated with more perinatal adverse effects than other drugs. Otherwise, the thresholds at which to start antihypertensive treatment are: SBP of 140 mm Hg or DBP of 90 mm Hg in women with gestational hypertension (with or without proteinuria), pre-existing hypertension before 28 weeks of gestation or with the superimposition of gestational hypertension or with hypertension and subclinical organ damage or symptoms at any time during pregnancy. The thresholds in other circumstances are SBP of 150 mm Hg and DBP of 95 mm Hg. For non-severe hypertension methyldopa, labetalol, calcium antagonists, and beta-blockers are the drugs of choice. Beta-blockers appear to be less effective than calcium antagonists. Calcium-channel blockers are considered to be safe if they are not given concomitantly with magnesium sulphate (risk of hypotension due to potential synergism). ACE inhibitors, angiotensin II antagonists, and direct renin inhibitors are strictly contraindicated in pregnancy. The plasma volume is reduced in pre-eclampsia; diuretic therapy is therefore inappropriate unless there is oliguria. Magnesium sulphate intravenously is recommended for the prevention of eclampsia and the treatment of seizures.

Women with pre-existing hypertension are advised to continue their current medication except for ACE inhibitors, angiotensin II antagonists, and direct renin inhibitors. In women with pre-existing hypertension with DBP ≥ 100 mm Hg (lower when end-organ damage or underlying renal disease is present) and in women with acute hypertension (DBP ≥ 105 mm Hg), methyldopa, labetalol, or calcium-channel blockers are recommended (see Table 2).

Delivery induction

Induction of delivery is appropriate in gestational hypertension with proteinuria and adverse conditions such as visual disturbances, coagulation abnormalities, or foetal distress.

Hypertension and lactation

Breast-feeding does not increase BP in the nursing mother. Bromocryptin, which is used to suppress lactation, may induce hypertension. All antihypertensive agents taken by the nursing mother are excreted into breast milk. Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine, the concentrations of which in breast milk are similar to those in maternal plasma.

Long-term cardiovascular consequences in pregnancy-induced hypertension

Women with gestational hypertension or pre-eclampsia are at increased risk of hypertension and stroke in later adult life as well as of ischaemic heart disease. Hypertensive disorders in pregnancy have been newly recognized as an important risk factor for CVD in women. Therefore, lifestyle modifications, regular BP control, and control of metabolic factors are recommended after delivery to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk in the future.

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HOW WELL IS HYPERTENSION CONTROLLED IN EUROPE?

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Introduction

Despite increased awareness of the importance of lowering blood pressure to values below 140/90 mm Hg, the outcomes of achieving this target remain disappointing [1–4]. The "rule of halves", coined in the United States during the 1960s, seems still to be valid to describe the observation that only half of those with hypertension were aware of it; and of those who were aware, only half were receiving treatment; and of that half receiving treatment, only half had their hypertension controlled [5]. A recent review on differences in prevalence, awareness, treatment, and control of hypertension between developing and developed counties supported the "rue of halves" [6] and showed that there were no significant differences between developed and developing countries regarding the prevalence, awareness, treatment, and control of hypertension, except for a higher prevalence among men in developed countries. Even in randomized controlled trials, where patient motivation and physician expertise are ensured, it has been difficult to achieve optimal blood pressure despite a significant difference in the observed response rates [7].

Results of surveys

The National Health and Nutrition Examination Survey 1999–2004 database indicates that the blood pressure control rate in hypertensive subjects in the United States was 29.2 ± 2.3% in 1999–2000 and 36.8 ± ± 2.3% in 2003–2004 [8]. In Canada, only 15.8% had blood pressure treated, and controlled. Higher rates of treatment and control were observed among older adults, those with type 2 diabetes, and those with a previous myocardial infarction [9].

The situation is no better in the rest of the world and varies considerably between countries and regions (Figure 1) [3, 4]. Hypertension control rates also vary within countries by age, gender, race/ethnicity, socioeconomic status, education, and quality of health care and are particularly low in some economically developing countries [3, 4].

Several epidemiological surveys in European countries involving random samples either socio-demographically representative of the total adult population or selected during clinical visits also show that although the improvement over the years has been encouraging, patients with well-controlled blood pressure, attaining target blood pressure goals of < 140/90 mm Hg, represent a small fraction of the hypertensive population (Figure 2) [3, 10–16]. In the adult English population, the rates of awareness and treatment have increased since 1994, and control rates among hypertensive men and women have approximately doubled to 21.5% and 22.8%, respectively [10]. Recent data from the Czech Republic on cardiovascular mortality and blood pressure levels, prevalence, awareness, treatment, and control of hypertension from 1985 to 2007/2008 indicate an improvement in blood pressure control from 3.9 to 24.6% over the same period [11]. Arterial hypertension represents a serious medical, social, and economic problem in Poland, and the NATPOL PLUS study carried out in the year 2002 has shown that the overall control rate is 12%, and the control rate in treated hypertensives is 21% [16]. Data from national surveys on hypertension treatment and control in Europe have demonstrated that age-adjusted control rates in treated hypertensive patients aged 35–64 years were 21% for Sweden, 28% for Italy, and 30% for Germany [12]. In a multi-centre, cross-sectional study of the population greater than 60 years of age in Spanish primary care centres among hypertensive subjects, 35.7% had their blood pressure under control [13]. The Hypertension Study in General Practice in Hellas (Hypertenshell), a cross-sectional study for assessing the prevalence, level of awareness, treatment, and control of hypertension in Greece, has demonstrated that 32.8% were treated and controlled (men 33.3%, women 32.3%) [14]. A population-based cross-sectional epidemiology survey carried out in 2003 in Turkey showed that subjects who were aware of their condition and treated had a control ratio of 20.7% [17]. Recent data about Turkey from the observational TRES 1 Study showed that blood pressure control was improved after physician education on ESH guidelines from 26.5% to 55.1% ($p < 0.001$) and control was poorer when the baseline blood pressure values were higher [18].

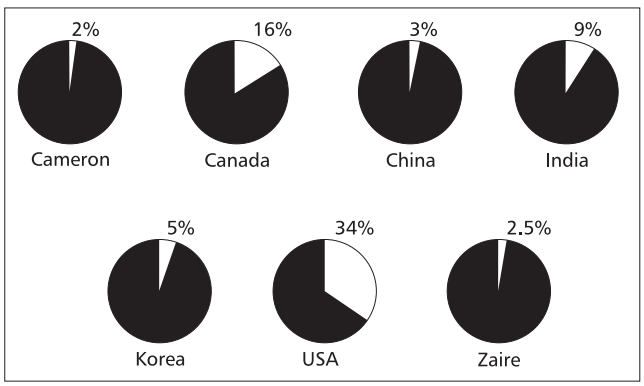

Figure 1. Percentage of patients with controlled blood pressure (< 140/90 mm Hg) in different countries around the world [3–4]

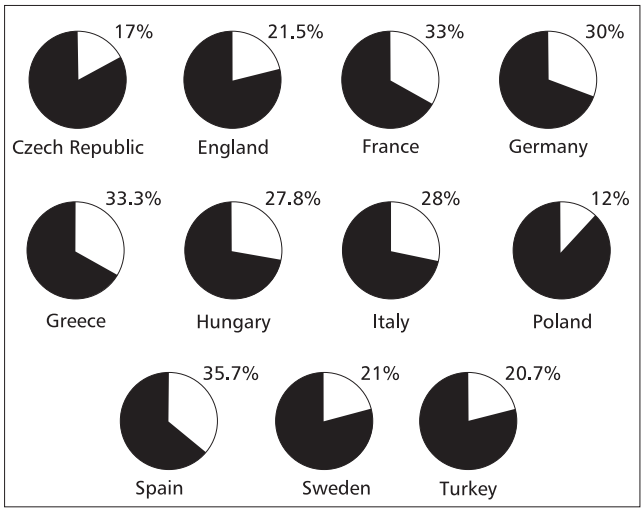

Figure 2. Percentage of patients who reach the blood pressure goal (< 140/90 mm Hg) in Europe [9–16]

The BP CARE Study derived data about hypertensive patients from Eastern European countries (Albania, Belarus, Bosnia, the Czech Republic, Latvia, Romania, Serbia, Slovakia, and Ukraine), showing that although 87% of patients were under combination therapy, blood pressure control was 27.1%. Blood pressure control was found to be variable among different countries, worse for systolic than for diastolic blood pressure, slightly better in patients followed by specialists than by general practitioners, unrelated to patient age, and unsatisfactory in high-risk hypertensives and in patients with coronary heart disease, stroke, or renal failure [19].

In the treated hypertensive population, the number of patients with inadequate blood pressure control has been found to be high not only when measured in the clinic, but also when assessed by ambulatory blood pressure monitoring or home measurement (Table 1) [20, 21]. Inadequate blood pressure control among patients receiving treatment for hypertension indicates a lack of satisfactory blood pressure control with antihypertensive drug therapy and is not a reflection of the white-coat effect [20, 21].

Table 1. Percentage of treated hypertensive patients with satisfactory blood pressure control [17, 18]

	DBP controlled	SBP controlled	SBP and DBP controlled
< 140/90 mm Hg (clinic)	17.5%	12.6%	8.9%
< 120/85 mm Hg (24 hour)	26.5%	16.4%	15.4%

Conclusions

The high blood pressure readings commonly found in treated hypertensive individuals reveal that inadequate blood pressure control is a global problem and cannot be solely ascribed to a lack of access to medical care or poor compliance with therapy. Achieving blood pressure control remains a daunting challenge given the positive and continuous relationship between levels of blood pressure, both systolic and diastolic, and the risk of cardiovascular disease [22]. Much remains to be learned to understand the obstacles for adequate blood pressure control in the population, and efforts need to be intensified to improve BP control rates.

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HYPERTENSION IN CHRONIC RENAL FAILURE

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Hypertension is one of the most important complications resulting from chronic renal failure. Renal parenchymal disease is the most frequent form of secondary hypertension, comprising about 5% of all hypertension cases. The prevalence of hypertension in different parenchymal diseases is shown in Table 1. The prevalence of arterial hypertension is related to severity of renal insufficiency, reaching 80–90% in end-stage renal failure.

Figure 1 shows the mechanisms by which chronic renal failure contributes to hypertension. Sodium and water retention play an important role due to their difficult elimination by the kidney. The consequences are an increase of exchangeable sodium, vascular wall sodium [1], and an expansion of the extracellular volume with an increase in cardiac output. The renin-angiotensin system is stimulated, especially in patients with mild to moderate chronic renal failure. This results in haemodynamic changes such as vasoconstriction and sympathetic nervous system activation, as well as non-haemodynamic actions such as the activation of endothelial cells, mesangial cells, inflammation, and fibrosis. The outcome from this effect of angiotensin II is progressive renal damage and hypertension [2].

The sympathetic nervous system is activated with consequent increases in norepinephrine levels, peripheral resistance, and cardiac output. Baroreceptor desensitization is also found in patients with end-stage renal disease [3]. Endothelium function is also impaired. Nitric oxide, a vasodilator agent, is reduced in chronic renal failure mainly due to an increase of the inhibitor asymmetrical dimethylarginine (ADMA) [4]. Prostaglandins and kinins have been found to be normal, high, or low in renal failure according to different authors; however, the administration of non-steroid anti-inflammatory drugs produces an increase in blood pressure, a decrease in the glomerular filtration rate, and a reduction of urinary prostaglandins [5]. Endothelin and thromboxane, both of them vasoconstrictor agents, are elevated in chronic renal failure. The atrial natriuretic peptide is also elevated in renal failure, favouring an increase of urinary sodium excretion, relaxation of the smooth muscle cells, and inhibition of renin release [6].

Table 1. Prevalence of hypertension in renal parenchymal disease

Focal glomerulosclerosis 75–85%	Diabetic nephropathy 65–75%
Membranoproliferative glomerulonephritis 60–70%	Membranous nephropathy 35–45%
Mesangioproliferative glomerulonephritis 30–40%	Ig A nephropathy 20–30%
Minimal change disease 10–15%	Interstitial nephritis 15–25%
Polycystic kidney disease 55–65%	

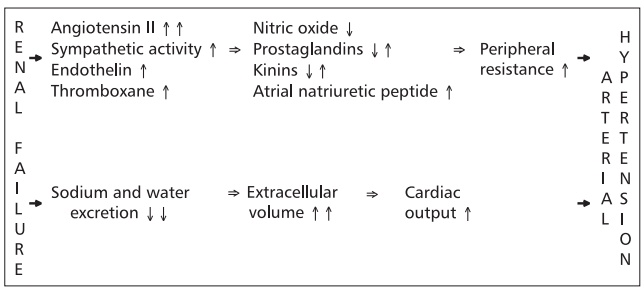

Figure 1. Mechanisms underlying arterial hypertension in chronic renal failure

Erythropoietin administration in patients with chronic renal failure is a common practice and can produce hypertension in about 20% of patients due to an increase in platelet cytosolic calcium [7].

The most important issues in the basal clinical evaluation of arterial hypertension in chronic renal failure are listed in Table 2 in which two sections are clearly differentiated: clinical history with physical examination, and complementary examinations. Besides measuring blood pressure in the office and at home, 24-hour ambulatory blood pressure monitoring should be carried out because it has been demonstrated that patients whose night-time blood pressure does not decrease (non-dippers) have a worse prognosis with regard to morbidity, mortality, and the progression of chronic renal failure [8].

Treatment

Arterial hypertension in chronic renal failure is a serious complication that may lead to end-stage renal disease in a short period of time. For this reason, both the European Society of Hypertension and Cardiology and the seventh report of the Joint National Committee Guidelines recommend a reduction in blood pressure below 130/80 mm Hg in all patients with renal failure and at least below 120/80 mm Hg particularly when proteinuria is superior to 1 g/24 h.

Table 2. The following examinations are required for appropriate diagnosis of arterial hypertension in patients with chronic renal failure

Clinical history and physical examination	**Clinical history** Family background of renal disease (polycystic kidney, Alport and Fabry disease) Date of diagnosis of hypertension Background of diabetes mellitus Symptoms of haematuria, oedema, lithiasis Symptoms of peripheral artery disease, ischemic heart disease, cerebrovascular disease Chronic administration of analgesics, NSAID... **Physical examination** Blood pressure, weight, height and waist circumference Neck palpation and auscultation of both carotid arteries Pulmonary and cardiac auscultation Abdomen: abdominal masses and bruits Limbs: pulse palpation, oedema Fundoscopy: retinopathy degree
Complementary examinations	**Renal function** Determination of serum creatinine; cystatin C, creatinine clearance, MDRD or Cockcroft-Gault formulas Urine: quantification of proteinuria; micro- or macro-albuminuria; protein/creatinine ratio Urine sediment, microhaematuria, casts **Renal morphology:** renal ultrasonography **Renal morphology and function:** urography, scintigraphy and isotopic renal flow **Blood sample determinations:** haemoglobin, leukocytes, platelets, sugar, lipids, uric acid, calcium, phosphorus, transaminases, ionogram and acid-base measurements **Systemic and viral disease with renal involvement markers:** complement, cryoglobulins, ANA anti-DNA, immunoglobulins, ANCAS, viral B and C, and HIV serology **Renal vascularization:** scintigraphy, renal arteriography **Renal histological study:** renal biopsy

Table 3. Non-pharmacological treatment

Sodium intake < 60 mmol/day	Cholesterol intake restriction
Protein intake 0.8–1.2 g/kg/day	Potassium intake restriction
Phosphorus intake < 750 mg/day	Smoking cessation and alcohol restriction
Caloric intake > 35 calories/kg/day	Moderate physical activity
Increased calcium intake	Weight loss

Table 4. Pharmacological treatment

Angiotensin converting enzyme inhibitors (ACEI)	Combination therapy
Angiotensin II receptor blockers (ARB)	ACEI, ARB or RI + diuretics
Renin inhibitors (RI)	ACEI, ARB or RI + calcium-antagonist
Diuretics	ACEI or ARB + RI
Calcium antagonists	Beta-blockers + diuretics
Beta-blockers	Antihypertensive + statins + + antiplatelet treatment
Alpha-blockers	

Non-pharmacological treatment

Non-pharmacological treatment is very important to control blood pressure in chronic renal failure; the indications are listed in Table 3. The strictness of the diet depends on the degree of renal failure. Sodium intake should be reduced to less than 60 mmol/day, and daily intake of proteins will depend upon renal function, but an average of 0.8–1.2 g/kg/day is recommended. Phosphorus intake is related to protein intake and must be less than 750 mg/day. Total caloric intake should never be less than 35 calories/kg/day, with carbohydrates around 50–60%, and saturated fats should be between 30–40% of total calories as long as plasma lipids are not elevated, in which case cholesterol should be reduced in the diet. Other dietary treatments are an increase in calcium intake, weight loss, moderate physical activity and tobacco/alcohol restriction [9].

Pharmacological treatment

The principal drugs used in the treatment of arterial hypertension in chronic renal failure are shown in Table 4. When a glomerular injury is present, especially with elevated proteinuria, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are used most often, both in diabetic [10] and non-diabetic patients [11]. A new class of drugs, renin inhibitors (RI), have been introduced in the treatment of hypertension in chronic renal failure, either alone [12] or in combination with an ARB [13]. They have a vasodilator effect on efferent arteriole reducing intraglomerular pressure and the mesangial fibrotic process. In significant renal failure these drugs produce hyperkalaemia, especially when they are associated with distal tubule diuretics or eplerenone. ACEI and RI doses should be reduced in advanced renal failure (GFR < 15 ml/min), but this is not necessary with ARB. The three drugs have foetal toxicity and are contraindicated during pregnancy.

Calcium antagonists have been recommended in chronic renal failure treatment due to their important antihypertensive and natriuretic effects. Dihydropiridines can cause vasodilatation of the afferent arteriole producing an increase in intraglomerular pressure [14]. Diltiazem and verapamil seem to provide greater kidney protection. Manidipine has demonstrated the greatest reduction of proteinuria due to its vasodilatory effect on both the afferent and efferent arterioles [15]. The most important side effects of calcium antagonists are local ankle oedema, headaches, flushing, tachycardia, and gingival hyperplasia.

Diuretics are widely used medications in these types of patients since they are characterized by sodium and water retention [16]. When GFR is greater than 50 ml/min, thiazide diuretics alone, or in association with distal diuretics such as amiloride, triamterene, and spironolactone, can be administered. However, when GFR is less than 30 ml/min loop diuretics such as furosemide, bumetanide, ethacrynic acid, or torasemide should be administered, but not distal diuretics due to the possible increment of serum potassium. The most prominent side effects of diuretics are hypokalaemia, hyperuricaemia, dyslipidaemia, glucose intolerance, insulin resistance, hyponatraemia, and hypomagnesaemia. Distal diuretics may cause hyperkalaemia, skin rash, and gynaecomastia.

Beta-blockers can be administered in order to counteract activation of sympathetic nervous system, but they can accumulate in advanced phases of renal failure. They should be carefully used in type 1 diabetic patients because they might inhibit hypoglycaemic signs and increase blood glucose levels [17]. In patients with severe peripheral vascular disease, they should be avoided. A significant side effect is bradycardia, especially in combination with other drugs like verapamil, diltiazem, and digoxin. Asthaenia, dyslipidaemia, glucose intolerance, impotence, and hyperkalaemia are other possible side effects.

Alpha-blockers can be used not only for their vasodilator properties but also for their antiproliferative, platelet antiaggregant, and antiatherogenic effects. They are indicated in benign prostatic hypertrophy. The side effects are orthostatic hypotension, headache, mouth dryness, fatigue, and weakness.

Combinations of two, three, or even more drugs are the rule in chronic renal failure, especially in diabetic patients. The most frequent combination is ACEI, ARB or RI with diuretics. If this is not sufficient, a calcium antagonist or a beta-blocker can be added. Combination therapy of ACEI and an ARB has been published with very good results, especially in patients with heavy proteinuria [18]. Combining an ACEI, ARB, or RI with a calcium antagonist has been recommended for a recent reappraisal of the European Society of Hypertension Guidelines [19]. ARB alone can be given in high doses [20].

Recently it has been demonstrated that the addition of a selective vitamin D receptor activation in patients with RAAS inhibition lowers the residual albuminuria and reduces renal risk in patients with diabetic nephropathy [21].

In many circumstances of chronic renal failure, an integrated treatment (antihypertensive, statin and anti-platelet therapy) should be considered.

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HOW TO HANDLE RENOVASCULAR HYPERTENSION?

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Renovascular hypertension (RVH) is defined as the elevation of arterial pressure precipitated by a haemodynamically significant stenosis of a renal artery or arteries (that is, a stenosis greater than 75% of the vessel lumen or 50% with post-stenotic dilation). When the lesion affects both renal arteries, or a single functioning kidney, and is accompanied by renal failure (plasma creatinine concentration above 1.5 mg/dl), it is called ischaemic nephropathy or ischaemic renal disease [1, 2].

The rate of renovascular hypertension is less than 1% when a mild-moderate hypertension population is assessed, but this increases according to the severity of the hypertension and with population age [3].

Two well-differentiated renal artery lesions have been described. Fibromuscular dysplasia is a non-inflammatory lesion that affects young women between 15 and 20 years of age, and its incidence is less than 10% of all RVH cases. Progression of lesions from the angiographic point of view is defined by the appearance of new focal lesions, or a worsening of the existing stenosis grade, and is produced when the intima layer of the artery is affected [4, 5].

The most prevalent mechanism underlying lesions of the renal arteries (90%) is atherosclerosis (ARAS). This increases with age, especially in elderly patients with diabetes, hyperlipidaemia, aortic occlusive disease, and lesions in the coronary artery. Atherosclerosis of the renal artery is a progressive disease that may cause ischaemic renal disease, also known as ischaemic nephropathy. The prevalence of ischaemic nephropathy is poorly quantified, and may vary from 30% in patients with coronary disease to 50% in those with diffuse arteriosclerotic disease [5]. It has been estimated that it may be responsible for 5% to 22% of cases of end-stage renal failure in dialysis programs [6].

Diagnosis

The signs and symptoms that suggest RVH include sudden onset of hypertension, especially in young women (fibrodysplastic lesions), existence of hyperkalaemia, abdominal vascular murmurs, and asymmetry in renal size (> 1.5 cm) according to ultrasonography criteria. When the lesion is due to atheroma plaque in the ostium of the renal artery it affects men over the age of 60 and is accompanied by lesions in other vascular territories. Table 1 shows the most frequent clinical characteristics according to our experience [7–9] in renal arterial lesions due to atherosclerosis.

Screening tests

According to the recommendations of the American College of Cardiology/American Heart Association [10], the following techniques are recommended:

- **magnetic resonance angiography (MRA):** MRA is being increasingly used as the first-line screening test for RVH. The test specificity increases with three-dimensional MRA with gadolinium. The sensitivity and specificity of the technique are 97% and 93%, respectively, in the diagnosis of stenosis greater than 50%. A recent concern regarding the use of gadolinium is the possibility to produce nephrogenic systemic fibrosis in patients with renal failure [11];
- **computed tomography angiography (CTA):** Advances in CT technology allow spiral multi-detector acquisitions that provide accurate anatomic images of small renal arteries. The median sensitivity and specificity of CTA are 94 and 93%, respectively [12]. The need to administer 100 to 150 ml of iodine contrast may cause nephrotoxicity in patients with kidney failure. Furthermore, severe renal artery calcification may obscure luminal narrowing, and the technique does not provide physiological assessment of the stenosis;
- **duplex Doppler ultrasonography (DDU):** in addition to evaluating renal size, it also assesses the morphology of the renal artery and the characteristics of intrarenal flow. The mayor drawbacks of DDU are operator-dependence and lack of uniformity in diagnosis. To asses the ability of the measured parameters associated with DDU to detect renal artery stenosis, a meta-analysis was performed on 88 studies that involved 9974 arteries in 8147 patients [13]. Peak systolic velocity was more accurate than the renal aortic ratio and acceleration index [14] (peak systolic velocity > 200–320 cm/s), with a sensitivity and specificity of 85 and 92 %, respectively. Rademacher et al. [15] reported that the resistance index (IR > 0.80) by DDU provides a measure of parenchymal disease that can predict improved kidney function or blood pressure control after stenting, but others have doubts about these findings [16];

Table 1. Clinical findings consistent with atherosclerotic renal artery stenosis (ARAS)

Abrupt onset at age > 60 years old
Severe hypertension
Smoking
Occlusive vascular disease (cerebrovascular, coronary, peripheral)
Abdominal bruit, flank bruit or both
Unexplained azotaemia
Discrepancy in kidney sizes by more than 1,5 cm with cortical scarring (for unilateral RVH)
Azotaemia induced by treatment with ACEI/ARB
Flash pulmonary oedema

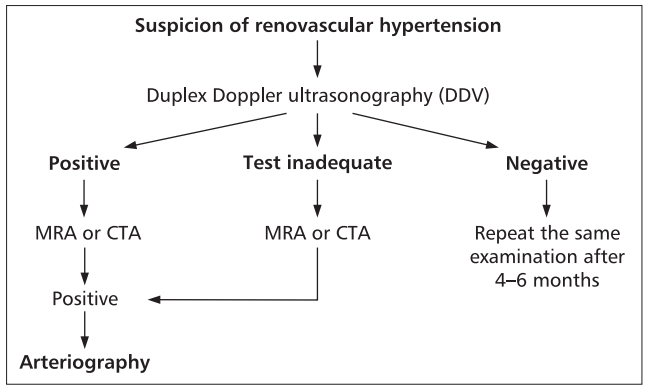

Figure 1. Algorithm for the diagnosis of patients with renovascular hypertension

- **renal arteriography:** This is the technique to confirm the diagnosis of RVH, evaluate the extent of intra-renal vascular disease, and identify associated aneurysmal or occlusive aortic disease. A major advantage of this technique is that the lesion can be measured directly and treated immediately. It has the disadvantage of being an invasive technique with possible complications due to the iodine contrast and due to the risk of atheroembolism.

Figure 1 shows the algorithm for the diagnosis of patients with renovascular hypertension.

Other screening tests

Renal scintigraphy following ACE inhibitor: The sensitivity and specificity of this test are 78–90% and 88–98%, respectively. This decreases when the lesion is bilateral and in kidney failure. In patients with ischaemic nephropathy, only renal scintigraphy is used to demonstrate kidney viability.

Renal vein renin measurements: This is used on rare occasions in patients with lesions in both renal arteries.

In our experience, when there is a high clinical suspicion of RVH due to fibrodysplasia, renal arteriography can be used directly to confirm the lesion and perform a possible angioplasty. When suspicion is moderate, Doppler duplex should be used, followed by MRA or CTA, depending on the results and experience of each centre.

Treatment

The fundamental purpose of the treatment of renovascular hypertension is to control blood pressure and preserve or improve kidney function. Given the different aetiologies and courses of the vascular lesions, both diseases, fibromuscular dysplasia and atherosclerosis, should be analysed separately.

Fibromuscular dysplasia

Blood pressure can be controlled with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), or rennin inhibitor, together with thiazide diuretics. If blood pressure control is not optimal, a calcium antagonist or beta-blocker may be added [10]. The use of ACEI/ARB in patients with severe and bilateral lesions may cause haemodynamic intraglomerular alterations that deteriorate the glomerular filtration rate. This makes it necessary to monitor plasma creatinine and serum potassium.

Renal revascularization (angioplasty and surgery) is indicated in severe and refractory hypertension, and fundamentally when there is progression of the lesions with a loss of renal function and mass. Intraluminal angioplasty is the technique of choice: the morphological results according to angiographic criteria show a beneficial grade of dilation between 83% and 100% [17–19]. The percentage of restenosis is 12% to 25%, with an evolution time of two years [17–18]. Hypertension is controlled in 22% to 59% of these patients, improves in 22% to 74%, and is not modified in 2% to 30% of them [17–20]. However, a recent meta analysis on the effect of revascularization in patients with fibromuscular dysplasia included 50 studies of patients treated with angioplasty and 25 with surgery. **Hypertension was cured after angioplasty or surgery in 46 and 55% of patients, respectively** [21].

Revascularization by surgery is limited to cases with aneurysms in the renal artery or angioplasty failure.

Atherosclerotic renal artery

The indications for revascularization of the renal arteries are in constant dispute. However, in spite of controlled blood pressure, atherosclerosis lesions may advance over time. In some series, progression may reach 45% to 60% in a period of less than 10 years [22]. Complete thrombosis of the renal artery has been described in 3% to 15% of cases, when the stenosis was greater than 75%

[23]. Furthermore, cardiovascular disease in this population is very high, the survival rate being very limited (less than 45% in five years of evolution), especially in patients with bilateral lesions [5].

The treatment options include drugs, angioplasty with endoprosthesis (PTRAS), and revascularization surgery. Lowering lipid levels, smoking cessation, and maintaining acceptable glucose levels all require consideration.

Many studies have been published with different types of treatment, non-invasive with antihypertensive drugs and revascularization, fundamentally with angioplasty, in an attempt to find differences in global and renal survival. Balk et al. [24] conducted a review of the literature between 1993 and 2005. They found 357 studies, only two of which were randomized. It can be deduced from the randomized and controlled studies that the cardiovascular mortality at six months was similar with both treatments. The angioplasty treatment improved the control of blood pressure when the lesion affected both renal arteries, or, in some cases, renal function. Due to the methodological differences and the different objectives established in the studies, it was not possible to draw any conclusions that would make it possible to recommend a certain therapeutic option, although initial medical treatment seems to be the most indicated.

The ASTRAL trial [25] compared PTRAS combined with medical therapy to medical therapy alone for improvement in renal function. In 806 patients with ARAs, differences in renal function, blood pressure, kidney and cardiovascular events, and mortality were not definitive. The decline in renal function over time was slightly slower in the PTRAS group, but not statistically significant. The medical management group required a slightly higher number of antihypertensive drugs, but not statistically significant.

Numerous criticisms have arisen lately about the methodology of the ASTRAL trial [26, 27]. The criteria followed to assess the calibre of the artery stenosis were not specified. Additionally, there was no central laboratory that standardized and compared angiographic studies. The methods used to include patients in the revascularization group or in medical treatment depended on the research and were not properly defined.

The CORAL study [28] is a randomized clinical trial contrasting optimum medical therapy alone to PTRAS with optimum medical therapy on a composite cardiovascular and renal endpoint: cardiovascular and renal death, myocardial infarction, hospitalization for congestive heart failure, stroke, doubling of serum creatinine, and the need for renal replacement therapy.

The primary entry criteria are: 1) an atherosclerotic renal stenosis of > 60% with a 20 mm Hg systolic pressure gradient or > 80% with no gradient necessary; 2) systolic hypertension of > 155 mm Hg on > 2 antihypertensive medications.

RADAR is another [29] prospective, multi-centre study to evaluate the clinical impact of PTRAS on impaired renal function in patients with ARAS > 70%. Three hundred patients will be randomized to best medical treatment versus PTRAS plus medical treatment.

The CORAL and RADAR studies should shed some light on the existing doubts and the potential benefits of revascularization with PTRAS.

The indications to perform revascularization in atherosclerotic renal artery stenosis are shown in Table 2 [9, 10, 27, 30, 31], focusing on three different parameters: renal function, hypertension, and cardiac syndrome. In acute renal failure secondary to aortic and renal artery thrombosis, where the kidneys have an important collateral circulation (non-functioning kidneys), surgical treatment would have a clear indication [32, 33].

Patients with established renal ischaemic disease with long evolution (creatinine > 3.0 mg/dl) and decrease of renal parenchyma with triggering fibrosis would not benefit from any type of revascularization.

Revascularization techniques

Angioplasty with endoprosthesis: in order to improve the efficacy of the angioplasty and decrease the incidence of restenosis in ostial lesions, it is essential to place an endoprosthesis (balloon-expandable intravascular stents) [34]. The specific complications of the technique include bruises in the puncture zones (20%), cholesterol atheroembolisms (10%), contrast-induced nephropathy, and dissection of the renal and iliac arteries [34].

Surgery: This is considered to be the technique of choice 1) in patients with pathology in the aorto-iliac arteries who require a combined revascularization, 2) in very severe ostial lesions, and 3) in complete renal artery thrombosis.

Table 2. Indications for revascularization in atherosclerotic renal artery stenosis

Renal function
Progression of renal artery stenosis
Loss of renal mass
ACEI/ARB induced azotaemia
Hypertension
Refractory hypertension
Cardiac syndrome
Congestive heart failure
Flash pulmonary oedema

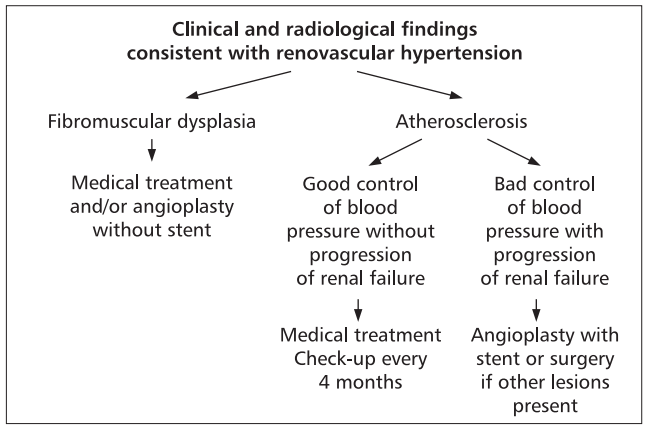

Figure 2. Algorithm for the treatment of patients with renovascular hypertension

The results published describe improvement or stabilization of the renal function in 79% to 90%, and progressive deterioration in 10% to 20%, of these cases [22, 27]. Global mortality was 4.6% and was associated with older age and symptoms of heart failure [35]. Some authors describe good results with surgical revascularization in cases of acute thrombosis of the renal artery (non-functioning kidneys) as long as some minimum criteria are fulfilled for the surgery and it is possible to place a bypass [32, 33].

Figure 2 shows the algorithm for the treatment of patients with renovascular hypertension.

In conclusion, ischaemic renal disease is a complex disease with extrarenal vascular lesions that increase cardiovascular morbidity and mortality. Most of the time, renal artery lesions are due to atherosclerosis and it is recommended to begin with noninvasive techniques. Initially, excellent medical therapy with blockade of the renin–angiotensin system and statin must be used. Revascularization is indicated if there is a progression of the lesions with loss of renal mass and function.

Decisions should be based on individualized analysis of each patient, according to the complexity of their lesions and the experience of each centre.

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ISOLATED SYSTOLIC HYPERTENSION: CARDIOVASCULAR RISK AND TREATMENT BENEFITS

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Introduction

The definition of isolated systolic hypertension (ISH) according to 2007 ESH/ESC guidelines, reappraised in 2009 [1, 2], is: a systolic blood pressure (SBP) > 140 mm Hg, diastolic blood pressure (DBP) < 90 mm Hg. Accordingly, the different grades of ISH are defined as follows:

- Grade 1: SBP < 160 mm Hg,
- Grade 2: SBP > 160 < 180 mm Hg,
- Grade 3: SBP > 180 mm Hg.

Pathogenetic factors

Important factors leading to the development of hypertension and particularly of ISH are age-related vascular and neuro-humoral changes with an endothelium-dependent NO deficiency and/or reduced NO bioavailability. Arterial compliance deteriorates because of structural and functional changes and increases in collagen, extracellular protein matrix, ground substance, and elastin, which occur with age. These changes create structural and mechanical alterations in the vessel intima and media. Calcium binds to the elastin, and undifferentiated muscle cells of the media proliferate and migrate through the elastic laminae to the intima. The proliferation of the connective tissue results in intimal thickening and fibrosis, and increases the stiffness of the vessels with partial loss of contractility. Consequently, arterial compliance diminishes, and the so-called "windkessel" of the large arteries decreases. Pulse pressure and pulse wave velocity increase with an earlier reflection of pressure waves from the periphery, leading to a disproportionate increase in systolic pressure, while diastolic blood pressure does not change, or decreases — particularly over the age of 60. Cardiac output, stroke volume, intravascular volume, and renal blood flow decrease; plasma renin activity may increase. As a consequence of these changes, left ventricular mass (prevalence of left ventricular hypertrophy — LVH), circulating catecholamines (particularly noradrenaline), and total peripheral vascular resistance increase. Baroreceptor sensitivity to blood pressure changes also decreases, resulting in higher blood pressure variability [3–5].

ISH as cardiovascular risk

ISH (using the old definition of ISH: systolic blood pressure > 160 mm Hg and diastolic blood pressure < 90 mm Hg) increases with age, and becomes the most common type of hypertension among people over 60 years of age [6]. According to the cumulative 24-year data from the Framingham Study (with old definition), the incidence of ISH is high both in women (533/1,000) and in men (418/1,000) over the age of 65 years. ISH was the most common type of diagnosed hypertension (57.4% in men, 65.1% in women) in those over 65 years [7]. Subjects with Grade-1 ISH were at increased risk of progression to definite (Grade 2) hypertension or the development of cardiovascular disease [8]. Several studies have shown that ISH increased the risk for cardio- or cerebrovascular diseases or death (including sudden death). In the MRFIT study of 316,099 men, systolic blood pressure was a stronger predictor of outcome than diastolic blood pressure, with an excess risk of cardiovascular diseases in subjects with stage I ISH [9–12]. On the other hand, the 24-year follow-up of 1,207,141 Swedish men revealed a stronger association of total mortality with SBP than DBP, with the lowest risk at a SBP of about 130 mm Hg. Total mortality continuously increased above SBP of 120 mm Hg [13].

Untreated ISH patients showed a high prevalence of LVH with concentric remodelling [14], which has been shown to have a poor cardiovascular prognosis [15]. The meta-analysis of 8 outcome trials involving 15,693 patients with ISH (median follow-up 3.8 years) showed that the relative hazard rates associated with a 10 mm Hg higher initial systolic blood pressure were 1.26 for total mortality, 1.22 for stroke, but only 1.07 for coronary events. Independent of systolic blood pressure, diastolic blood pressure was inversely correlated with total mortality, stressing the role of pulse pressure as a risk factor [16].

Treatment benefits

Randomised clinical trials provide compelling evidence that treatment of ISH results in significant benefits. The landmark trial of Systolic Hypertension in the Elderly Program (SHEP) in 4,716 patients first proved the benefit on CV morbidity and mortality of antihypertensive treatment with chlorthalidone (with the option of adding atenolol or reserpine). Non-fatal stroke was reduced by 37%, non-fatal myocardial infarction by 33%, and left ventricular failure by 54%. There were strong trends towards a decrease in transient ischaemic attacks (25%), and in total (13%), cardiovascular (20%), cerebrovascular (29%), and coronary (20%) mortality [17]. This trial also pointed out that serum uric acid independently predicted cardiovascular events in patients with ISH. These patients experienced the same benefit from diuretic-based treatment as those with low baseline serum uric acid levels [18]. The Systolic Hypertension in Europe (Syst-Eur) study was the first large (4,695 patients with ISH) study of the effect of a longer-acting calcium antagonist, nitrendipine (with optional add-on enalapril and/or hydrochlorothiazide), on long-term morbidity and mortality risks. Total strokes were reduced by 42% [19]. In the Syst-Eur study the rate of vascular dementia was also reduced by 50% [18], while it was not changed by the chlorthalidone-based therapy in the SHEP study [20]; therefore a specific neuroprotective effect of dihydropyridine-type calcium antagonist, nitrendipine, was hypothesized. The Syst-China trial confirmed the beneficial effect of nitrendipine in patients with ISH as it reduced total strokes by 38%, stroke mortality by 58%, all-cause mortality by 39%, cardiovascular mortality by 39%, and fatal and non-fatal CV events by 37% [21]. Subgroup analysis of the INSIGHT trial showed that patients with ISH were slightly more responsive than those with ordinary hypertension to treatment by long-acting nifedipine-GITS, as significantly less patients required addition of a second drug. This study also showed that patients with ISH whose diastolic blood pressure significantly decreased with increasing therapy were smokers with existing evidence of atherosclerosis [22]. Staessen's meta-analysis [16] also showed that active treatment reduced total mortality by 13%, cardiovascular mortality by 18%, all cardiovascular complications by 26%, stroke by 30%, and coronary events by 23%. The absolute benefit was larger in men, in patients aged 70 years or more, and in those with previous cardiovascular complications or wider pulse pressure. Therapy prevented strokes more effectively than coronary events.

Thiazide-based treatment was superior to beta-blockers for reduction of blood pressure and prevention of cardiovascular complications [23–25]. Recent investigations with newer antihypertensive agents, such as ACE-inhibitors and angiotensin AT_1 receptor antagonists, have also demonstrated improved blood pressure control of patients with ISH [26, 27]. In the ISH subgroup of the Losartan Intervention for Endpoint Reduction (LIFE) trial, losartan or atenolol reduced blood pressure by 28/9 mm Hg, but losartan (as compared to atenolol) reduced the primary outcome (cardiovascular death stroke, myocardial infarction) by 25% (unadjusted $p = 0.02$), total mortality by 28% ($p < 0.046$), cardiovascular mortality by 46% ($p < 0.01$), nonfatal and fatal stroke by 40% ($p < 0.02$), and new onset diabetes by 38% ($p < 0.04$) [28]. In the ISH subgroup of the Study on Cognition and Prognosis in the Elderly (SCOPE) candesartan reduced the relative risk of stroke by 42% ($p < 0.050$) with a 2/1 mm Hg BP difference as compared to the control group [29].

ESH Guidelines for management of ISH

Lifestyle modifications are advised as first-line therapy for patients with ISH (physical exercise, reduction of salt intake, weight reduction in obese patients, cessation of smoking). The recommended target systolic blood pressure is equal to or below 140 mm Hg, and in the very elderly (age > 80 years) to below 150 mm Hg. If lifestyle modifications fail to reach the target, drug therapy is advised to control blood pressure. Diuretics, long-acting dihydropyridine-type calcium antagonists, ACE-inhibitors, and angiotensin AT_1 receptor antagonists are advised for treatment of patients with ISH [1, 2].

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PATIENT ADHERENCE AND PHARMACOLOGICAL TREATMENT OF ARTERIAL HYPERTENSION

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Introduction

Former US Surgeon General C. Everet Koop stated that 'drugs don't work in patients who don't take them', a virtue that describes very well the problem of medication-taking behaviour in hypertension. Despite the fact that an increasing number of patients are being treated with antihypertensives, target blood pressures (BP) are reached in only one third of patients in clinical practice [1, 2].

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has identified poor medication-taking behaviour (referred to as non-compliance or non-adherence) as one of the main causes of failure to control BP in patients with hypertension [3]. Results from a systematic review of electronic monitoring studies, for example, indicated that 9% to 37% of patients had inadequate adherence to antihypertensive medication [4]. In turn, non adherent patients remain at high risk for cardiovascular disease including a higher risk of stroke [5], and can be expected to account for a significant cost burden through avoidable hospital admissions, premature deaths, work absenteeism, and reduced productivity [6].

Definitions

The European Society of Hypertension guidelines published in 2001 state that compliance could be defined as 'the degree to which the patient conforms to medical advice about lifestyle, keeping appointments, and taking prescribed medication' [7]. Over the last decade, the term **'compliance'** has acquired a somewhat negative connotation, merely implying 'obedience to physician's orders'. Therefore, nowadays the term adherence is preferred to compliance, although the use of compliance is still widely embedded in daily practice as well as in the medical literature. Medication **adherence** can be defined as 'the extent to which a patient's behaviour, with respect to taking medication, corresponds with agreed recommendations from healthcare providers' [8].

Adherence can be divided into two main components: persistence and execution. **Persistence** is defined as the accumulation of time from initiation to discontinuation of therapy whereas the **execution** refers to the comparison between the prescribed drug dosing regimen and the patient's drug history while on treatment. The latter definition includes **dose omissions** (missed doses) and the so-called **'drug holidays'** (three or more days without drug intake) [9]. Persistence is usually expressed in time, execution is generally reported as the percentage of prescribed doses taken over a certain period of time. Different definitions of 'adequate' adherence have been used in clinical studies, with 'good' adherence corresponding to execution rates between 80––100%, and insufficient adherence to execution rates lower than 70–80% [4]. Of note, adherence (execution) can be more than 100%, since patients can take more than the prescribed dose. However, the best level of adherence varies largely from one patient to another. Therefore, thresholds do not have much clinical significance in daily practice but adherence and blood pressure should be monitored simultaneously and repeatedly to evaluate the impact of adherence on blood pressure and other long-term outcomes.

Detection

The ability of physicians to recognize non-adherence has a low sensitivity (< 40%) but good specificity (90%), suggesting that physicians are good at detecting good adherence but not at detecting poor adherence [10].

Methods helping physicians to detect non-adherence can be grouped into three categories: subjective methods (e.g. patient interviews, patient diaries), direct methods (e.g. analysis of drug levels or biological markers in bodily fluids), and indirect methods (e.g. assessment of a patient's clinical response, physiological markers (heart rate with beta blockers), pill counts, prescription refills, electronic monitoring of medication use). Each method has its advantages and disadvantages. For example, pill counts and patient diaries tend to overestimate medication consumption [11], prescription refill records are only a valid source of information about medication-taking behaviour when the database is complete, and drug dosing methods only provide information about the most recent doses. Besides, it is very difficult to diagnose poor execution with these traditional methods. More insight in specific drug intake patterns of antihypertensives has been gained by electronic pill box monitors (e.g. Medical Event Monitoring System, MEMS®; Intelligent Drug Administration System, IDAS II®), which enable monitoring of the execution on a daily basis by recording the time of each opening of the pill container or taking a tablet out of a blister pack [12]. Despite several shortcomings (indirect method, relatively expensive, requires know-how for packaging and for generating accurate results), electronic pill box monitoring is actually considered as the best way to diagnose non-adherence, and has advanced our knowledge of medication-taking behaviour and its risk factors [13].

Risk factors for poor adherence

First of all, it is important to realize that medication adherence is a dynamic parameter, meaning that phases of good adherence can alternate with phases of poor adherence in the same patient, depending on life circumstances. For example, medication adherence tends to improve around the time of a scheduled clinical visit, but declines thereafter, a phenomenon known as 'white coat adherence' [14].

Second, persistence decreases progressively over time, with about half of patients interrupting their antihypertensive treatment within one year [15]. Of note, patients who have poor execution (omitting doses, drug holidays, variability in hour of intake) are at highest risk of quitting early [15].

The most commonly reported risk factors for non-adherence are shown in Table 1. Unfortunately, no risk factor or combination of risk factors has allowed physicians so far to identify with certainty non-adherent patients [16]. Moreover, two promising patient self- report scales (the 'Hill-Bone Compliance to High Blood Pressure Therapy Scale' and Morisky's 'Self-Reported Measure of Medication Adherence') recently failed to predict low adherence [17]. Taken together, when risk factors as shown in Table 1 are diagnosed, physicians should have heightened awareness for the possibility of non-adherence, but even in the absence of any risk factor, low adherence is possible [18].

Adherence according to antihypertensive drug classes

Several studies have compared medication adherence of different drug classes. The largest trials are outlined in Table 2. Most of these data are retrospective and derived from prescription databases that give insight in persistence but not in execution. Despite differences in design, these studies show the same tendency, namely that AT-II blockers and ACE-inhibitors have a slightly higher persistence than calcium antagonists and beta-blockers, and that persistence with diuretics is the lowest. The main reported reasons for drug discontinuation are perceived treatment failure and side effects [19]. In summary, Table 2 shows that rates of persistent patients decline with time in all drugs until around 50%; most non-persistent patients are lost early during the first years of follow-up. Large randomized, prospective clinical trials have shown higher persistence rates. On average, drug interruptions occur in 15% of patients taking ACE-inhibitors and in 20% of patients taking beta--blockers, diuretics, or calcium antagonists in these trials [20]. However, randomized clinical trials are probably biased since they tend to select the more adherent patients for participation, and lack generalizability to the population treated in community-practice settings.

Independently of the drug class used, some medication-related aspects merit attention. It has been shown that adherence is higher in patients who take their medication in the morning as compared to the evening, the latter leading to more dose omissions [15]. Moreover, a recent meta-analysis

Table 1. Risk factors for non-adherence to antihypertensive treatment [13, 27, 28]

Disease related	Patient related	Physician related	Treatment related
Chronic condition Asymptomatic No immediate consequences of non-persistence or poor execution	Denial of disease state Particular beliefs Young age Social isolation Psychiatric illness Male gender Low education level Lack of knowledge of disease Lack of involvement in treatment plan Missed appointments	Lack of time Failure to increase therapy to reach treatment goal Long waiting time in office Lack of communication and integrated care between physician, patient and pharmacist Lack of specific education in adherence	Complexity of dosing regimen Duration of treatment Non-managed side effects Costs of treatment

Table 2. Studies comparing persistence rates of different antihypertensive drugs [20, 29, 30]

Sstudy	n	Outcome (persistence)	AT-II blockers	ACE-inhibitors	Calcium antagonists	Beta-blockers	Diuretics
Jones, 1995	10,222	6-month persistence	ne	45%	41%	49%	41%
Blooms, 1998	21,723	1-year persistence	64%	58%	50%	43%	38%
Caro, 1999	22,918	4.5-year persistence	ne	53%	47%	49%	40%
Morgan, 2004	82,824	1-year persistence	56%	56%	52%	54%	49%
Perreault, 2005	21,011	3-year persistence	59%	58%	58%	57%	48%
Polluzzi, 2005	6,043	3-year persistence	52%	43%	39%	47%	23%
Simons, 2008	48,690	33-month persistence	84%	84%	72%	ne	ne

ne — not evaluated

including 9 studies (of which 4 were retrospective studies in patients with hypertension) and 20,242 patients found that therapy with fixed-dose combinations decreases the risk of non-adherence by 24% (odds ratio 0.76, 95% confidence interval 0.71–0.81; $p < 0.0001$) in the hypertensive population [21].

Recommendations to improve medication adherence

Since many factors influence adherence, it is not a surprise that no single intervention has been shown to robustly enhance medication-taking behaviour. Of note, most studies in this field are observational; randomized controlled trials are difficult to perform (for example, cannot be blinded), and are sparse. Strategies that have proven to be effective are often complex and thus not easily feasible in the long term [22]. One exception might be the COM99 study, a randomized multicentre trial comparing a low-intensity intervention group (combination of pill count, educational information, and a designated family member to support adherence) with a control group in 877 patients aged > 50 years with uncontrolled hypertension. Patients in the intervention group were less likely to have uncontrolled BP and more likely to be adherent (monitored with electronic pillboxes) after 6 months of follow-up; differences of ~ 2 mm Hg in SBP persisted after 5 years of follow-up, but disappeared after 18 months for DBP [23]. Tailoring adherence-improving methods to each patient is important since a method that works in one patient might not be convenient or successful in another. In our personal experience, the most important point for the clinician is to consider the possibility of non-adherence in case of apparent inefficacy of a drug before raising the dose, and to evaluate adherence when in doubt. In case of confirmed non-adherence, one should search for underlying reasons and possible strategies to improve long-term adherence, and one should establish treatment goals in mutual agreement with the patient [24].

However, patients naturally minimize non-adherence issues in order to please their physician, especially when they feel negatively controlled. To decrease the risk for non-adherence, physicians should talk about it with their patient when starting the first antihypertensive drug and should address the topic repetitively at selected encounters. Moreover, healthcare systems should evolve and address this long-term issue interdisciplinarily by reinforcing seamless care between all involved health-care givers, who should be educated in the clinical domain of medication non-adherence and in communication skills [25]. In fact, patients experience individual or cultural beliefs about their antihypertensive treatment, which make sense in their life and which need to be addressed specifically by trained healthcare professionals. Based on current literature and clinical experience, the following recommendations can be given, mainly consisting of optimizing all factors involved in non-adherence [13, 15, 18, 26].

Patient-related factors:

- Educate patients about their disease and the impact of treatment, and encourage their participation to information sessions.
- Involve the patient in decision making and monitoring (home blood pressure readings).
- Encourage emotional and practical support from friends and family.
- Encourage non-drug therapies such as lifestyle changes.

Physician-related factors:

- Be aware of the possibility of non-adherence at all times in case of non--effectiveness of prescribed drugs.
- Establish treatment goals.
- Tailor treatment and adherence support to the patient's needs.
- Share responsibilities for drug management and get insight into the patient's daily organization.
- Keep in contact with patients who miss appointments.
- Cooperate closely with pharmacists.

Medication-related factors:

- Encourage the use of medication-taking systems.
- Select drugs with a favourable side-effect profile and long plasma half--life, the latter to maintain pharmacological action for one or two dosing cycles after omitted doses.
- Start at a low dose, and increase the dose slowly.
- Privilege combination therapy to high-dose monotherapy.
- Schedule dosing individually; morning doses are often preferred by patients.
- Complex dosing regimens (several times a day) should be avoided.
- Take into account costs and reimbursement.

Healthcare system related factors:

- Organize convenient care for patients.
- Promote seamless care between all healthcare providers, especially physicians and pharmacists in ambulatory care.
- Improve education of healthcare professionals in medication adherence and communication skills.

Conclusions

Good medication adherence is important to achieve optimal blood pressure control, and is associated with reduced risk of adverse cardiovascular outcomes and reduced hypertension-related costs. Patients with hypertension who have poor medication-taking behaviour remain largely unrecognized, and the development of programs to detect these individuals and support long-term adherence is an important issue. Moreover, there is a need for comprehensive interventions that use cognitive, behavioural, and affective strategies tailored to the patient's particular needs. These interventions should be based on objective and reliable assessment of medication-taking behaviour, and should be tested in well-designed clinical trials.

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CYCLOSPORIN-INDUCED HYPERTENSION

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Introduction

Hypertension has emerged as a serious adverse effect of immunosuppression with cyclosporin, which has become the mainstay of immunosuppression in organ transplantation. Improved survival rates with cyclosporin compared to previous regimens based on corticosteroids and azathioprine were established and have led to an expansion of solid organ transplantation. Cyclosporin has also been used at lower dosages for the treatment of autoimmune disease.

Cyclosporin is a macrolide antibiotic structurally different from the newer immunosuppressive agent tacrolimus, although both share final pathways that inhibit cytokine release from lymphocytes. Both cyclosporin and tacrolimus induce widespread vasoconstriction of systemic circulation and an increase in arterial blood pressure. Vasoconstriction in the kidney results in a decreased renal blood flow and is the basis for the nephrotoxicity observed with both agents. The consequence is newly developed hypertension or deterioration of existing hypertension. The prevalence of post-transplant hypertension with cyclosporin and tacrolimus is similar one year after transplantation.

Incidence of hypertension associated with cyclosporin therapy

The introduction of cyclosporin increased the prevalence of hypertension in all indications (Table 1).

The prevalence rates in patients receiving cyclosporin for non-transplant indications such as psoriasis or uveitis range from 23 to 54% while the rates for heart, liver, or kidney transplant recipients treated with the combination of cyclosporin and corticosteroids range from 65 to 100%.

Clinical features of cyclosporin-induced hypertension

Blood pressure rises within days of cyclosporin administration, before changes in renal function or sodium balance can be detected. When corticosteroids are added, blood pressure may further increase to levels requiring antihypertensive therapy within the first weeks or months.

In patients after heart transplantation, hypertension is nearly universal. It is associated with a high incidence of left ventricular hypertrophy. Allograft vasculopathy leads to accelerated coronary injury. A subgroup of patients may develop progressive renal failure.

In liver transplant recipients there is a clinically significant rise in blood pressure, usually over a period of several weeks.

Approximately 50% of kidney transplant candidates have hypertension before the procedure. Transplant-related complications such as rejection, organ preservation injury, or transplant renal artery stenosis can impair renal function and worsen hypertension.

Bone marrow recipients usually develop severe hypertension during acute cyclosporin administration, which later resolves. Total body irradiation may accelerate renal vascular injury. There were some complications reported like intracerebral haemorrhage, encephalopathy, or seizures.

Cyclosporin in non-transplant indications increases blood pressure less rapidly, and progression to hypertension is less common.

Cyclosporin-induced hypertension appears to be dose-related, and early on will be reversed if the drug is discontinued. Hypertension has usually been mild to moderate in nature except in bone marrow transplant recipients and paediatric transplant recipients, in whom it has often been severe. Hypomagnesaemia has been reported; magnesium replacement, however, does not seem to reverse the hypertension seen in adults.

Table 1. Hypertension before and after introduction of cyclosporin

Indication	Hypertension (%)	
	Before cyclosporin	After cyclosporin
Transplant		
Bone marrow	5–10	33–60
Cardiac	10	71–100
Liver	NA	65–85
Renal	45–55	67–86
Non-transplant		
Rheumatoid arthritis	NA	42–45
Uveitis	NA	23–29
Myasthenia gravis	NA	81
Psoriasis	NA	30

NA — not applicable

Complications

Hypertension after organ transplantation is characterized by a disturbed circadian rhythm with the absence or reversal of the normal nocturnal fall in blood pressure. Nocturnal headaches and increased nocturnal urination are commonly noted by patients. The highest blood pressure values within a 24-hour period may be recorded at night occasionally producing retinal haemorrhages and CNS symptoms. Early studies in cardiac transplant recipients raised the possibility that changes in the circadian rhythm of blood pressure reflect cardiac denervation. However, there is an identical loss of normal pressure variation after cardiac transplantation, and also a smaller fall in cardiac output and a rise in systemic vascular resistance during the night. The loss of the nocturnal blood pressure fall is associated with a higher incidence of left ventricular hypertrophy, lacunar stroke, and microalbuminuria. Nocturnal blood pressure elevations may predispose transplant recipients to accelerated atherosclerotic complications. Corticosteroids have also been associated with a loss of the nocturnal blood pressure fall in other situations such as in Cushing's syndrome.

Cyclosporin and renal dysfunction attributable to cyclosporin commonly co-exist. Cyclosporin nephrotoxicity alone does not explain cyclosporin-induced hypertension. Several studies indicate that cyclosporin-induced hypertension is sodium-sensitive and may be modulated by sodium intake.

Remarkably, hypertension persists later after transplantation despite reductions both in cyclosporin and corticosteroid dosages. Occasionally, there is a reversal of post-transplant hypertension to normal levels of blood pressure during long-term follow-up.

Pathogenesis of hypertension after transplantation

The precise mechanism remains to be elucidated. During cyclosporin administration, there is an increased systemic vascular resistance. The activity of the renin-angiotensin system is suppressed by cyclosporin even during restriction. This explains why ACE inhibitors have a limited antihypertensive efficacy early after transplantation.

Microneurographic studies of adrenergic nerve traffic in cardiac transplant recipients and myasthenia gravis indicate that cyclosporin enhances nerve activity although circulating catecholamine levels are normal. Studies in liver transplant recipients report a decrease in sympathetic nerve activity during cyclosporin administration. Some data support impaired endothelium-dependent vasodilation mediated by nitric oxide pathways in cyclosporin-induced vasoconstriction.

Management of hypertension during cyclosporin administration

The choice of antihypertensive therapy should take into account the reduced glomerular filtration rate and renal vasoconstriction universal-

ly present in all patients treated with cyclosporin. The patients usually have elevated uric acid, and cyclosporin partially inhibits renal potassium and hydrogen ion excretion predisposing to hypokalaemic metabolic acidosis. To prevent worsening of azotaemia and hyperuricaemia, diuretics are often avoided. Potassium-sparing agents must be used with caution. ACE inhibitors and angiotensin II antagonists, when used alone, have limited efficacy early after transplant, and may aggravate both hyperkalaemia and acidosis. The gradual increase in plasma renin activity after transplantation provides clinical support to use ACE inhibitors later. Dihydropyridine calcium antagonists are preferred, mostly due to their ability to reverse cyclosporin-mediated vasoconstriction. Verapamil is a less potent vasodilator potentiating immunosuppression, thereby allowing cyclosporin doses to be reduced. Beta-blockers have also been successfully used, either alone or in combination with dihydropyridines. Labetalol, an α-β-blocker, is effective both intravenously and orally.

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HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

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In hypertension, left ventricular hypertrophy (LVH) is initially a useful compensatory process that represents an adaptation to increased ventricular wall stress; however, it is also the first step toward the development of overt clinical disease. The Framingham Study has shown that the prevalence of LVH, according to EKG criteria, is quite low in a general population sample (about 3%).

Using the echocardiographic technique it has been demonstrated that the prevalence of LVH in the Framingham population increases from 5% in subjects younger then 30 years to 50% in those older than 70 years. The Framingham study has also shown that the prevalence of echocardiographic LVH is 15–20% in mild hypertensive patients and further increases in patients with more severe hypertension [1].

The increase of LV mass with age might reflect the influence that other risk factors exert with time on the development of LVH. The relationship between echocardiographic LV mass and clinical blood pressure is usually weak. Twenty-four-hour blood pressure recordings have shown a much closer correlation between LV mass and average daily blood pressure [2]. Non-haemodynamic factors, such as age, sex, race, body mass index, diabetes, and dietary salt intake, may contribute to determine who among hypertensive patients develop LVH and to what degree LVM is increased.

LVH seems to be associated with an inflammatory state (as indicated by elevated CRP levels), although the relationship appears to be mediated by comorbid conditions [3]. In fact, the coexistence of hypertension with diabetes increases the prevalence of LVH. Moreover, insulin resistance and high insulin levels are associated with the development of LVH in hypertensive patients. Other major cardiometabolic risk factors, notably hypercholesterolaemia and hyperglycaemia, may also modify the extent of LVM and the prevalence of LVH in the hypertensive population.

Genetic factors might also exert a powerful modulation of LV mass; in fact monozygotic twins have more similar LV mass values then dizygotic twins [4].

Diagnosis of LVH

Several diagnostic criteria for LVH diagnosis can be used. Electrocardiography has a low sensitivity for LVH detection, but LVH diagnosed by the Sokolow--Lyon index or the Cornell voltage-duration product has been shown to be an independent predictor of cardiovascular events [5]. The voltage of R wave in AV_L has been shown to best correlate with LV mass index [6].

Electrocardiography can also be used to detect patterns of repolarization abnormalities and arrhythmias, including atrial fibrillation.

Echocardiography is a specific, repeatable, and far more sensitive measure of LVH in comparison with EKG.

Proper evaluation includes calculation of LV mass according to M--mode measurements, under two-dimensional control, of LV internal diameter and wall thicknesses, according to ASE Recommendations or the "Penn Convention". These methods have been validated with measurements obtained at necroscopic examination. Measurements of LV wall thicknesses and internal dimensions from 2D images can be also performed.

Although the relationship between LV mass and incidence of cardiovascular events is continuous [7], ESH/ESC guidelines indicate that the thresholds of 125 g/m^2 BSA in men and 110 g/m^2 in women may be used for conservative estimates of LVH [8].

An assessment of LV mass reproducibility, one of the major technical limitations of echocardiography, has shown that LV mass changes of 10 to 15% may have true biological significance in the individual patient [9]. Geometric adaptation of the left ventricle to increased cardiac load may be different among patients. Concentric hypertrophy is characterized by increased mass and increased relative wall thickness, whereas eccentric hypertrophy is characterized by increased mass and relative wall thickness < 0.42; concentric remodelling occurs when there is increased thickness with respect to radius, in the presence of normal LV mass [10]. These LV geometric patterns are associated with different haemodynamic characteristics, and peripheral resistances are greater in patients with concentric geometry, while cardiac index is increased in those with eccentric hypertrophy.

It has been proposed that LV mass increase may be evaluated taking into account gender and cardiac loading conditions, in order to discriminate the amount of LV mass adequate to compensate the haemodynamic load (adequate or appropriate) from the amount in excess to loading conditions (and therefore inappropriate or non-compensatory). LV mass is inappropriate when the value of LV mass measured in the single subject exceeds the amount needed to adapt to stroke work for the given gender and body size [11].

In addition, echocardiography can measure other parameters (regional and global LV systolic and diastolic function, left atrium dimensions and volume), all associated with an increased incidence of major CV events.

LV mass measurement may be obtained by cardiac magnetic resonance, with a higher reproducibility than echocardiography; the improvement in reproducibility has relevant practical implications such as more precise detection of serial changes in individual patients in a shorter time interval and smaller sample size design in clinical trials targeting LVH regression during antihypertensive treatment

Table 1. LVH and risk of cardiovascular (CV) events

Reference	No. patients	Average follow-up (yrs)	CV events
Levy et al. 1994	524 Framingham population	36 EKG bi-annual examination	Decrease in voltage vs. no change OR 0.46 (95% CI 0.26–0.84) ♂ OR 0.56 (95% CI 0.30–1.04) ♀ Increase in voltage vs. no change OR 1.86 (95% CI 1.14–3.03) ♂ OR 1.61 (95% CI 0.91–2.84) ♀
Matthew et al. 2001	8281 High CV risk patients	2.8	12.3% in patients with LVH regression/absence 15.8% in patients with LVH persistence/development
Fagard et al. 2004	4159 Older patients with systolic hypertension	6.1	14% decrease in cardiac events for 1 mV change in EKG voltage
Okin et al. 2004	9193 Patients with EKG LVH	4.8	20.4% decrease in composite endpoint for 10.5 mm (1 SD) Sokolow Lyon Index 15.4% decrease in composite endpoint for 1050 mm × × msec (1SD) Cornell product

Prognostic value of LVH and its regression by treatment

A large number of studies have reported on the relationship between LVH at baseline examination, measured either by EKG or by echocardiography, and the risk of subsequent morbid or mortal cardiovascular and renal events in clinical or epidemiological populations [5].

Despite the fact that electrocardiography has a low sensitivity for LVH detection, LVH diagnosed by the Sokolow-Lyon index or the Cornell voltage--duration product is an independent predictor of cardiovascular events [5].

Direct measurement of LV mass by echocardiography (M-mode, under two-dimensional control) has proven to be a strong predictor of the risk of cardiovascular morbidity and mortality; subjects with LVH consistently have 2 to 4 or more fold higher rates of cardiovascular complications, independent of other risk factors such as hypercholesterolaemia, age, and blood pressure measured in the clinic or by 24-hour blood pressure monitoring [5]. Concentric hypertrophy appears to carry the highest risk and eccentric hypertrophy an intermediate risk. The presence of inappropriate LV mass is also associated with an increased number of cardiovascular events, even in hypertensive patients without LVH [12].

The prognostic significance of changes in EKG criteria of LVH has been demonstrated in the Framingham population [13], in high CV risk patients [14], and in hypertensives with isolated systolic hypertension [15] or with EKG--LVH [16] (Table 1).

Other observational, prospective studies have examined the potential clinical benefits of regression of echocardiographic detectable LVH, and have demonstrated that changes in LV mass during treatment may imply an important prognostic significance in hypertensive patients (Table 2) [17–20]. The results of these studies have also been analysed in a meta-analysis [21]. They have clearly shown that subjects who failed to achieve LVH regression or in whom LVH developed during follow-up were much more likely to suffer morbid events than those in whom LVH regressed or never developed. In these studies LV mass changes during antihypertensive treatment and age were the most important factors related to the occurrence of cardiovascular fatal and non-fatal events in hypertensive patients. Further information was obtained in the LIFE echocardiographic substudy, performed according to a prospective, interventional, controlled design. In this study, which included 930 patients with EKG LVH, a decrease of 25 gr/m^2 (i.e. one standard deviation) of LV mass index was associated with a 20% reduction of the primary end-point, adjusting for type of treatment, basal and treatment BP, and basal LV mass index [22].

The information obtained in the meta-analysis and in the LIFE study should be considered complementary. In fact, while the observational prospective studies have analysed younger patients with and without LVH at baseline, followed by their family doctors, in the LIFE study all patients had EKG LVH, were older, at higher cardiovascular risk, were randomized to receive

Table 2. Regression of LVH during antihypertensive treatment (yes/no) and occurence of non-fatal cardiovascular events

Reference	No. patients	Average follow-up (yrs)	CV events		
Prospective studies in hypertensive patients with and without LVH, no randomized treatment			LVH regression	No LVH regression	Never LVH
Muiesan et al., 1995	151	10.1	12.5%	37%	5.1%
Verdecchia et al., 1998	430	2.8	6%	13%	5.4%
Cipriano et al., 1992	311	7.9	9.6%	13%	4.8%
Koren et al., 2001	172	11.6	6.2%	28.6%	9.6%
Muiesan et al., 2004	436	10	7.4%	28.6%	12.3%
Prospective study in patients with EKG LVH, randomized treatment					
Devereux et al., 2004	930	4.8	HR 0.80 (95% CI 0.70–0.95) of CV events for a change in LVMI of 25 g/m^2, p = 0.009 20% reduction of		

antihypertensive treatment, and were followed according to a clinical prospective protocol.

The prognostic significance of LVM changes in subgroups of patients at higher CV risk (diabetics, patients with previous stroke or MI) deserves further investigation. Changes in geometric adaptation seem to imply a prognostic value, independent of changes in LV mass. The persistence or the development of a concentric geometry during treatment has been found to be associated with a greater incidence of cardiovascular events, independent of changes in LV mass [23]. The LIFE study has provided results that confirm the prognostic influence of LV geometry, in addition to changes in LV mass [24].

The better prognosis associated with regression of LVH may be related to the improvement of systolic and diastolic function, to the increase of coronary flow reserve, and to the decrease of cardiac arrhythmias.

ESC/ESH guidelines suggest that echocardiography should be performed in patients at low or intermediate CV risk in order to better identify the global cardiovascular risk, and to more appropriately start pharmacological treatment [8]. In fact, it has been shown that an increase of echocardiographic LV mass can be identified in 25–30% of hypertensive patients with a low or moderate CV risk (based on risk factor evaluation and EKG), thus substantially changing the original risk stratification [25, 26]. There is no evidence that an echocardiographic study can modify the therapeutic strategy in patients at high or very high CV risk.

In patients at high CV risk, and in particular in patients with aortic valve disease or in patients with asymptomatic LV dysfunction, echocardiography may be useful to better define and follow cardiac anatomic and functional alterations.

Regression of echocardiographically determined inappropriate LVM during treatment is associated with an improvement in prognosis, and the evaluation of changes in LVM appropriateness may add prognostic information, in particular in patients with persistence or development of traditionally defined LVH

At this time the echocardiographic instrumentation for LV mass measurements is largely available in most western countries, and hopefully with reduction of price its use will be expanded worldwide. Among other diagnostic procedures, usually reserved for specific indications, nuclear magnetic resonance provides the most precise measurements of LV mass and cardiac tissue constitution; however, the cost of NMR prevents large-scale use in hypertension. Techniques based on reflectivity of cardiac ultrasound imaging have been used in order to assess the degree of cardiac fibrosis and to improve the ability of increased LV mass to predict outcome, together with the use of new biomarkers, such as circulating markers of collagen tissue composition.

It has been demonstrated that an effective, long-term antihypertensive treatment, inducing a gradual, constant, and homogeneous control of 24-hour blood pressure values, may determine a significant reduction, and even a normalization of LVH [27]. However, available studies have also suggested that regression of LVH may be more rapidly or more completely obtained by the use of some classes of antihypertensive drugs, such as Angiotensin receptor blockers, ACE-inhibitors, and calcium antagonists [28, 29]. The most recent meta-analysis of comparative studies evaluating the effect of treatment with different classes of antihypertensive drugs on LV mass changes has shown a superiority of Angiotensin II blockers versus beta-blockers [30].

Some recent studies have documented, by cardiac magnetic resonance, the effect of treatment on LV mass changes in hypertensive patients [31, 32].

Echo-reflectivity studies have suggested that tissue composition of the left ventricle may vary and that drugs favouring LVH regression may differently affect myocardial fibrosis.

Conclusions

Patients with LVH at baseline and in whom LV mass reduction has not been reached during antihypertensive treatment should be considered at high risk for cardiovascular events and therefore should undergo frequent and accurate clinical controls for blood pressure and other risk factor assessment. At the present time regression of LVH represents the most clinically useful intermediate end-point, together with proteinuria, for the evaluation of the efficacy of antihypertensive treatment.

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ASSESSMENT OF PRECLINICAL TARGET ORGAN DAMAGE IN HYPERTENSION: CAROTID INTIMA-MEDIA THICKNESS AND PLAQUE

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Carotid intima-media thickness and plaque

High-resolution ultrasound of the carotid arteries may allow the measurement of intima-media complex in the arterial wall.

Population studies, such as the Vobarno [1], the Rotterdam [2], and the Cardiovascular Health Study [3] have clearly demonstrated that systolic blood pressure is a major determinant of the increase of intima media thickness in the carotid arteries, particularly in hypertensive patients.

Methods of measurement

There are different methods for measuring IMT. The three most frequently used measurements in clinical trials are as follows [3–6]: 1) Mean of the maximum IMT of the four far walls of the carotid bifurcations and distal common carotid arteries (CBM max); 2) Mean maximum thickness (M max) of up to 12 different sites (right and left, near and far walls, distal common, bifurcation, and proximal internal carotid); and 3) Overall single maximum IMT (T max). Analysis may be performed by manual cursor placement or by automated computerized edge detection. In order to optimize reproducibility with the last method, IMT measurement is restricted to the far wall of the distal segment of the common carotid artery, thus providing about 3% of relative difference between two successive measurements [7, 8]. A new echo tracking technology based on 128 radiofrequency lines may allow a more rapid and precise measurement of IMT and the investigation of the carotid wall mechanical properties; the circumferential and longitudinal stress may exert a direct action on carotid plaque stability and composition [9].

Clinical and epidemiological studies have given useful information on the reproducibility of IMT repeated measurements. Salonen and Salonen have indicated that between observers and intra-observers variation coefficients were 10.5% and 8.3%, respectively [10]. In the ACAPS study [5] the mean replicate difference was 0.11 mm and in the MIDAS study [11] it was 0.12 mm. In the MIDAS study the arithmetic difference in replicate scans mean max IMT was calculated as 0.003 ± 0.156 mm. More recently, the ELSA (European Lacidipine Study of Atherosclerosis) included more than 2000 patients in whom the cross sectional reproducibility of ultrasound measurements at baseline was calculated: the overall coefficient of reliability (R) was 0.859 for CBM max, 0.872 for M max, and 0.794 for T max; intra- and inter-reader reliability were 0.915 and 0.872, respectively [5].

Data collected in the VHAS (Verapamil in Hypertension and Atherosclerosis Study) [6] and the ELSA studies have shown a high prevalence of carotid wall structural changes in hypertensive patients; in the VHAS study 40% of the patients had a plaque (i.e. an intima-media thickness > 1.5 mm) in at least one site along the carotid arteries, and only 33% of patients had normal carotid artery walls. In the ELSA study 82% of 2259 essential hypertensives had a plaque (i.e. an intima media thickness > 1.3 mm). Moreover, in the RIS study (Risk Intervention Study) patients with severe essential hypertension and high cardiovascular risk had a significantly higher prevalence of atherosclerotic lesions compared to control subjects [12].

The normal IMT values are influenced by age and sex. IMT normal values may be defined in terms of statistical distribution within a healthy population; however, it may be better defined in terms of increased risk, and available data indicate that IMT > 0.9 mm represents a risk of myocardial infarction and/or cerebrovascular disease [2, 3, 12–16].

Furthermore, plaque volume assessment by three-dimensional reconstruction of ultrasound or NMR images has been proposed to better evaluate atherosclerotic lesions changes, and stratify patient risk.

Ultrasonic plaque morphology may add useful information about plaque stability and may correlate with symptoms. In addition to the visual judgment of plaque echolucency and homogeneity, the use of non-invasive methods that may quantify tissue composition of vascular wall (such as videodensitometry or the analysis of integrated backscatter signal) has been proposed for the assessment of cellular composition of atherosclerotic plaque, particularly of earlier lesions [17, 18].

Relationship to cardiovascular risk and to clinical events

Traditional risk factors, including male sex, ageing, being overweight, elevated blood pressure, diabetes, and smoking, are all positively associated with carotid IMT in observational and epidemiological studies. Hypertension, and particularly high systolic BP values, seems to have the greatest effect on IMT [19]. About 30% of hypertensive subjects may be mistakenly classified as at low or moderate added risk without ultrasound for carotid artery thickening or plaque, whereas vascular damage places them in the high added risk group [20].

Also some new risk factors, including various lipoproteins, plasma viscosity, and hyperhomocysteinaemia have demonstrated an association with increased IMT. Patients with metabolic syndrome have higher IMT than patients with individual metabolic risk factors. Carotid IMT has also been found to be associated with preclinical cardiovascular alterations, in the heart, in the brain, in the kidney, and in the lower limb arteries.

Several studies have demonstrated and confirmed the important prognostic significance of intima-media thickness, as measured by ultrasound. In their prospective study, Salonen et al. [13] observed in 1288 Finnish male subjects that the risk for coronary events was exponentially related to the increase of intima-media thickness in the common carotid and in the carotid bifurcation. In a larger sample of middle-aged subjects (13,780) enrolled into the ARIC (Atherosclerotic Risk In the Communities) study [14] intima-media thickness, measured by ultrasound, was associated with an increased prevalence of cardiovascular and cerebrovascular diseases. In the Rotterdam study [2] the intima-media thickness was shown to predict the risk of myocardial infarction and cerebrovascular events during a mean follow-up period of 2.7 years. The CHS [3] has prospectively evaluated 4400 subjects aged more than 65 years for a follow-up period of 6 years; the annual incidence of myocardial infarction or stroke increased in the highest quintiles of intima-media thickness measured in the common and the internal carotid arteries.

A recent meta-analysis of data collected in 8 studies in general populations, including 37,197 subjects who were followed up for a mean of 5.5 years, has demonstrated that for an absolute carotid IMT difference of 0.1 mm, the future risk of myocardial infarction increases by 10% to 15%, and the stroke risk increases by 13% to 18% [16] (Table 1).

It has not been demonstrated whether a decrease of IMT progression is associated with a reduction of cardiovascular events and an improvement in prognosis; the retrospective analysis of some studies has given conflicting results. No data are available on the prognostic significance of plaque composition characteristics.

Table 1. Hazard ratio (HR) for 0.1 mm difference in common carotid IMT (modified from ref [15])

Event	HR	(95% confidence intervals)	No. patients
Adjusted for age and sex			
Myocardial infarction	1.15	1.05–1.17	30,162
Stroke	1.18	1.16–1.21	34,335
Adjusted for age, sex, and other cardiovascular risk factors			
Myocardial infarction	1.1	1.08–1.13	30,162
Stroke	1.13	1.10–1.16	34,335

Effect of treatment

Therapeutic double blind trials have shown that antihypertensive drugs may have a more or less marked effect on carotid IMT progression. A recent metaregression analysis [21] including 22 randomized controlled trials has evaluated the effects of an antihypertensive drug versus placebo or another antihypertensive agent of a different class on carotid intima-media thickness. The results have shown that compared with no treatment, diuretics/± beta-blockers, or ACE inhibitors, CCBs attenuate the rate of progression of carotid intima-media thickening. In the prevention of carotid intima-media thickening, calcium-antagonists are more effective than ACE inhibitors, which in turn are more effective than placebo or no treatment, but are not more active than diuretics/ /± beta-blockers (Table 2). The odds ratio for all fatal and nonfatal cardiovascular events in trials comparing active treatment with placebo reached statistical significance (p = 0.007).

The results of the PHYLLIS study have reported that in hypertensive and hypercholesterlaemic patients, the administration of pravastatin prevents the progression of carotid intima media thickness seen in patients treated with hydrochlorothiazide, but the combination of pravastatin and the ACE-inhibitor Fosinopril had no additive effect [22].

Few studies, including a relatively small number of patients, have shown a lower thickness of intima-media during treatment with angiotensin II antagonists in respect to patients treated with beta--blockers [23].

A recent study (MORE, Multicentre Olmesartan Atherosclerosis Regression Evaluation) assessing the effect of long-term treatment with an AT1 receptor antagonist (olmesartan) and with a beta-blocker (atenolol) on carotid atherosclerosis, with the use of the non invasive 3D plaque measurement, has confirmed the greater reduction of plaque volume with the Angiotensin II blocker in respect to the beta-blocker [24].

No significant changes in plaque composition were observed after 4 years of treatment with either lacidipine or atenolol in patients participating into the ELSA study, suggesting that treatment with a calcium antagonist may slow IMT progression without influencing the characteristics of plaque tissue [25].

Table 2. Effect of antihypertensive treatment on changes in IMT in trials with antihypertensive drugs (modified from ref [20])

Antihypertensive treatment	Comparison	Change IMT μm/year (95% confidence intervals)
All trials (n = 1780)	Placebo (n = 1549)	–7 μm (–12 to –2) p = 0.01
ACE inhibitors (n = 1161)	Placebo (n = 929)	–6 μm (–12 to 0.4) p = 0.41
Beta-blockers (n = 428)	Placebo (n = 434)	–10 μm (–33 to 13) p = 0.02
All trials (n = 2285)	Diuretics/β-blockers (n = 2279)	–3 μm (–5 to –0.3) p = 0.03
Calcium-antagonists (n = 1811)	Diuretics/β-blockers (n = 1808)	–5 μm (–9 to –1) p = 0.007
ACE inhibitors (n = 319)	Diuretics/β-blockers (n = 321)	–1 μm (–5 to 2) p = 0.52
ACE inhibitors (n = 142)	Calcium-antagonists (n = 145)	–23 μm (–42 to –4) p = 0.02

Conclusions

An ultrasound examination of the common, bifurcation, and internal carotid arteries should be performed in hypertensive patients with concomitant risk factors, such as smoking, dyslipidaemia, diabetes, and family history for cardiovascular diseases. However, before widely proposing routine measurement of IMT in clinical practice for stratifying cardiovascular risk, methodological standardization for IMT measurement needs to be further implemented.

Quantitative B mode ultrasound of carotid arteries requires appropriate training. In the presence of increased IMT or plaque in the carotid arteries an aggressive approach to risk factor modifications should be considered.

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HOME BLOOD PRESSURE MONITORING

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Introduction

Home blood pressure (BP) monitoring is more and more frequently employed in clinical practice to assess a subject's BP status in hypertension diagnosis and follow-up. This increasing use is due to a number of advantages of home BP over conventional office BP measurement, and to the rapid technological development in the field leading to accurate and cheap automated BP monitoring devices that are easy to use in the patient's home (Table 1) [1]. The growing interest in this approach is testified by the almost simultaneous publication in 2008 of updated ESH guidelines for home BP monitoring [2] and the US recommendations on the same topic [3].

Features of home blood pressure monitoring and its reference values

The main advantages of home BP over office BP monitoring are related to the ability of the former approach to provide a much larger number of measurements [4], obtained automatically by validated devices over extended periods of time in subjects' daily life conditions. The average values derived from repeated home BP measurements are more reproducible than office BP [5, 6], are not affected by observer bias or end digit preference [7], and are devoid of a systematic error related to the presence of the white coat effect [8]. In general, home BP tends to be lower than office BP and similar to daytime ambulatory BP. In fact, based on both epidemiological and outcome studies, the commonly accepted threshold for hypertension diagnosis with home BP monitoring (corresponding to an office BP threshold of 140/90 mm Hg) is ≥ 135/85 mm Hg, which is the same as with average daytime ambulatory BP [2, 9–11]. More longitudinal and outcome studies are still needed, however, to determine the home BP targets for antihypertensive treatment, as well as the home BP diagnostic thresholds to be used in high-risk subjects, such as those with diabetes and kidney disease.

Table 1. Advantages and limitations of home blood pressure monitoring ([2] modified by permission)

Advantages
A number of measurements during the day and over several days, weeks, or months are possible
Assessment of treatment effects at different times of the day and over extended periods
No alarm reaction to BP measurement
Good reproducibility
Better prognostic value than isolated office BP readings
Relatively low cost
Patient-friendliness (with semi-automated and automated devices)
Involvement of patient in hypertension management
Possibility of digital storage, printout, PC download, or tele-transmission of BP values (in some devices/systems)
Improvement of patient compliance to treatment
Improvement of hypertension control rates
Limitations
Need for patient training (short for automated devices)
Possible use of inaccurate devices (need to check their validation)
Measurement errors
Limited reliability of BP values reported by patients
Induction of anxiety, resulting in excessive monitoring
Treatment changes made by patients on the basis of casual home measurements without doctor's guidance
Normality thresholds and therapeutic targets still debated
Lack of night BP recordings

BP — blood pressure

Prognostic significance

Recently, a number of studies have been published which document the prognostic value of home BP in terms of cardiovascular events [12–17]. All these studies have demonstrated that home BP may be a better risk predictor than office BP. Moreover, the results of PAMELA suggest that home BP might provide additional prognostic information independent of that provided by 24-hour ambulatory BP monitoring (ABPM) [12].

When proper diagnostic thresholds are considered, the classification of subjects such as hypertensive or normotensive BP based on home monitoring is not always in accordance with that based on office BP, a finding in line with previous observations based on a comparison between office BP and ABPM. While some subjects can be classified as "true" normotensive (both office and home BP normal) or sustained hypertensive (both office and home BP elevated), in other subjects either an association between elevated office BP and normal home BP (isolated office hypertension or "white coat hypertension") or between normal office BP and elevated home BP (masked hypertension) can be observed. As shown by several studies, isolated office hypertension may, if anything, only moderately increase cardiovascular risk compared with true normotensive subjects, while masked hypertension is associated with a cardiovascular risk close to that of sustained hypertension [8, 12, 17, 18]. Thus, unless home BP (or ABPM) is used, in the latter case, a high BP-related cardiovascular risk will not be identified, with the consequent inability to adequately manage subjects with masked hypertension, who constitute 10–20% of the general population (Figure 1).

Usefulness of home blood pressure monitoring

In the diagnosis of hypertension, home BP monitoring does not substitute office BP but is a useful complementary tool in defining BP-related cardiovascular risk more accurately, especially in patients in whom office BP provides questionable results (high BP variability, pronounced "white coat" effect, inconsistent relation with organ damage, etc.) [1, 2]. In this regard, home BP monitoring may be used as a first line tool, being cheaper than ABPM. Home BP monitoring is even more useful in the follow-up of treated hypertensive patients. This is because of its prognostic value, low cost, and additional advantages related to the

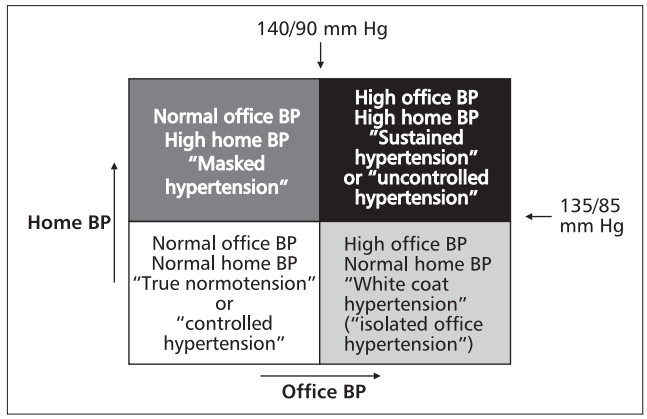

Figure 1. Classification of subjects based on office and home blood pressure (BP) being above or below the respective accepted thresholds for hypertension diagnosis (modified from [2], by permission). Sustained hypertensives are at greatest risk of cardio-vascular events, and true normotensive subjects at lowest risk. White coat and masked hypertensives lie in-between, subjects with isolated office hypertension having a risk closer to that of true normotensives, and subjects with masked hypertension carrying a risk closer to that of true hypertensive patients

Table 2. Methodological requirements for the correct implementation of home blood pressure measurements

Measurements obtained over ≥ 5 minutes, after a period ≥ 30 minutes without smoking or ingesting caffeine
Patient seated for at least 5 min, with his/her back supported and the arm resting on the table
The lower edge of the cuff being about 2.5 cm above the bend of the elbow and the cuff itself being positioned at heart level
Patient immobile and not talking during the measurement
Repeated readings taken 1–2 minutes apart
Measured blood pressure values recorded immediately on log-book and/or stored in device memory) [2]

fact that home BP monitoring may, by itself, improve BP control [19] probably by promoting patients' involvement in the management of their high BP condition and thus favouring their adherence to prescribed antihypertensive treatment [20]. Therefore, home BP monitoring may be particularly valuable in refractory hypertension, often caused by poor compliance [1, 2]. Home BP monitoring may also be useful in clinical research [21]. In clinical trials, home BP measurements, being more reproducible and free from the "white coat" effect, improve the statistical power and minimize or eliminate the placebo effect and may thus facilitate the detection of differences in BP between treatments [22, 23]. Moreover, morning and evening home BP values may be used for assessing the duration of action of a given drug or drug combination, and for evaluating the effects of different dosing patterns [24]. Home BP is also an interesting option for obtaining information on BP levels in outcome studies with large populations and long follow-up, where it may be considered a particularly suitable tool, being more precise than office BP and less expensive and easier to implement on a large scale than ABPM [2].

Practical issues

A number of methodological requirements have to be fulfilled in order to maximize the clinical value of the information obtained by home BP monitoring. Measurement conditions should be standardized similarly as with office BP (Table 2).

Only fully automated oscillometric upper arm devices, validated according to internationally acknowledged protocols, are currently recommended (lists of validated devices are available at dedicated websites, e.g. www.dableducational.org) [2]. The auscultatory technique is not recommended with home BP monitoring because it is difficult for patients and is associated with problems of device accuracy (especially in the case of aneroid devices), with the possible exception of patients with significant arrhythmias (atrial fibrillation), in whom the oscillometric technique is inaccurate. Finger devices should not be used at all. Validated wrist devices might be considered but only in selected cases (e.g. obese subjects with conical arm shape, elderly subjects with motor impairment), although their routine use is not recommended at the present time [2]. For clinical decisions, the average value of a number of home BP measurements should be used. While even a few home BP readings may provide information of prognostic significance, a larger number of them provide information that is more reproducible and more closely associated with risk of events [4]. Therefore, it is proposed that an average of measurements obtained over 7 days (two in the morning — before drug intake if treated — and two in the evening) before each doctor's visit should be used, discarding the values of the initial day, which are higher and less stable [2, 4]. Patient education is crucial for the correct performance of home BP monitoring [25]. It should include information about hypertension and cardiovascular risk, training in BP measurement, advice on the equipment, and information about measurement protocol and interpretation of BP readings. In particular, self-modification of treatment by patients based on home measured BP values should be discouraged, and home BP monitoring should always be performed under the supervision of the physician in charge of the patient. Special training for doctors and nurses might be needed as well.

When care is taken to ensure that the above requirements are fulfilled, the vast majority of subjects are expected to be able to perform good quality and clinically valuable home BP readings [26].

Finally, home BP may be very useful in special populations such as pregnant women, high-risk subjects (e.g. those with diabetes or renal disease), children, and elderly subjects although further studies are still needed to define diagnostic thresholds for home BP in these groups, and only a few devices validated to be used in these special conditions are currently available [2].

Recent evidence emphasizes two additional advantages associated with use of Home BP monitoring. First, use of self BP measurements at home over a prolonged follow-up time allows not only mean Home BP levels to be assessed, but also the variability in Home BP between days to be quantified. This may be clinically relevant because data from the Ohasama study have provided evidence that an enhanced day to day variability in Home BP carries an increased risk of cardiovascular mortality [27]. Second, in a few recent studies, the addition of telemonitoring of home BP to routine patient management was shown to improve the rate of hypertension control. This was largely due to better patient compliance with treatment, and/or to patients' active cooperation in titrating their ongoing drug therapy following instructions by their physicians. [28–32]. This is an advantage of paramount importance because in real life low compliance to treatment is an extremely common phenomenon, which can be held as majorly responsible for the poor rate of BP control that characterizes the hypertensive population [33].

Conclusions

Home BP monitoring offers many advantages over clinic BP measurements, and may improve the overall management of hypertension [28––32, 34]. Its use in clinical practice is currently supported by robust scientific evidence, but proper methodology, adequate patient training, and correct data interpretation are indispensable for the safe and effective use of this method in hypertension diagnosis, monitoring, and treatment.

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HYPERTENSION IN CHILDREN AND ADOLESCENTS

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Introduction

The incorporation of blood pressure (BP) measurement into routine paediatric healthcare and the publication of norms for BP in children [1] has not only enabled detection of significant asymptomatic hypertension secondary to a previously undetected disorder, but it has also confirmed that mild elevations in BP during childhood are more common than was previously recognized, particularly in adolescents.

The roots of hypertension in adulthood extend back to childhood. Indeed, childhood BP has been shown to track into adulthood. That is to say, children with elevated BP are more likely to become hypertensive adults [2–4], an observation emphasizing the importance of BP control in children and adolescents. Importantly, both the use of repeated measurements (aiming at the reduction of measurement error) in the identification of those children with elevated BP [2], as well as the assessment of co-morbidities (in particular obesity) and family history of cardiovascular disease, critically improve accuracy of the prediction of hypertension later in life.

Diagnosis

Diagnostic criteria for elevated BP in children are based on the concept that BP in children increases with age and body size, making it impossible to utilize a single BP level to define hypertension, as done in adults.

Extensive paediatric normative data on auscultatory clinic measurements have been provided for the United States, based on more than 70,000 children [5]. Blood pressure percentiles have been calculated for each sex, age group, and for seven height percentile categories (www.pediatrics.org/cgi/content/full/114/2/S2/555). Height percentiles are based on the growth charts of the Centre for Disease Control and Prevention (www.cdc.gov/growthcharts). According to the criteria of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [5], criteria shared by the ESH Guidelines in Children, normal BP in children is defined as systolic and diastolic BP < 90th percentile for age, gender, and height, while hypertension is defined as systolic and/or diastolic BP persistently ≥ 95th percentile, measured on at least three separate occasions with the auscultatory method. Children with average of systolic or diastolic BP ≥ 90th but < 95th percentiles are classified as having high-normal BP. Adolescents with BP ≥ 120/80 mm Hg, even if < 90th percentile, are also considered as having high-normal BP (Table 1).

The diagnosis of hypertension should be based on multiple office BP measurements, taken on separate occasions over a period of time. Office BP measurement has provided the basis for the present knowledge of the potential risk associated with hypertension [6] and has guided patient management for many years. Although office BP should be used as reference, BP values obtained out of office may improve the evaluation in untreated and treated subjects.

Ambulatory BP measurement (ABPM) is now increasingly recognized as being indispensable to the diagnosis and management of hypertension [7], and it has contributed significantly to our understanding of hypertension by "unmasking" BP phenomena that were not readily apparent using office BP, the non-dipping patterns of nocturnal BP ([8], white-coat [9], and masked hypertension [10]. Recommendations for the use of 24-hour ABPM are **during the process of diagnosis** (confirm hypertension before starting antihypertensive drug treatment, type 1 diabetes, chronic kidney disease, renal, liver, or heart transplant); **during antihypertensive drug treatment** (evaluation of refractory hypertension, assessment of BP control in children with organ damage, symptoms of hypotension); **clinical trials; other clinical conditions** (autonomic dysfunction, suspicion of catecholamine-secreting tumours). Concerning home BP measurements, evidence in children and adolescents is promising but limited.

Table 1. Definition and classification of HTN in children and adolescents (modified from: Task Force on High Blood Pressure in Children and Adolescents. *Pediatrics* 2004 [5])

Class	SBP and/or DBP percentile
Normal	< 90 th
High-normal	≥ 90th to < 95th
	≥ 120/80 even if below 90th percentile in adolescents
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mm Hg
Stage 2 hypertension	> 99th percentile plus 5 mm Hg

Evaluation

Several steps should be followed, from screening to confirmation, to rule out secondary causes of hypertension, if indicated. The proposed diagnostic algorithm is found in Figure 1 [11]).

Once hypertension is confirmed, organ damage evaluation should include heart and kidney due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease. Subsequently, the evaluation is useful not only as an assessment for cardiovascular risk, but also as an intermediate endpoint for monitoring treatment-induced protection.

Left ventricular hypertrophy remains to date the most thoroughly documented form of end-organ damage caused by hypertension in children and adolescents. The role of microalbuminuria assessment in paediatric essential hypertension, however, has gained ground. Consequently, echocardiography and testing for microalbuminuria should be performed in all hypertensive children and adolescents. The assessment of carotid-intima media thickness is not recommended for routine clinical use. The presence of organ damage is an indication to initiate or to intensify antihypertensive therapy.

Preventive measures

As most cases of high normal blood pressure and hypertension in childhood are now known not to be cases of secondary hypertension to be detected and specifically treated, efforts should be made to understand conditions associated in order to return BP within the normal range or to avoid high normal BP in youth developing into full hypertension in adulthood.

Considerable advances have been made in recent years in identifying conditions often associated with, and considered responsible for, high BP in children and adolescents, while more limited evidence has been accumulated on the results of corrective interventions.

Overweight is probably the most important of the conditions associated with elevated BP in childhood [12] and accounts for more than half the risk for developing hypertension [13–15]. Fatter children are known to be more likely to remain fat, and adiposity is the most powerful risk factor for higher BP. In addition to body mass index, waist circumference (abdominal obesity) has been shown to play a role [16]. Birth size and postnatal growth have also been recently implicated in the development of high blood pressure and adult cardiovascular disease [17–19]. Finally, dietary habits early in life, and particularly high salt intake, have been implicated as factors favouring higher BP values [20, 21].

Data about BP reduction from randomized intervention trials for reducing weight are limited. Lifestyle trials are currently underway in many settings but until these are finished, evidence-based recommendations are limited [11]. Most, however, are obvious and common sense. From reviews, it appears that "40 minutes of moderate to vigorous aerobic-based physical activity 3–5 days/week is required to improve vascular function and reduce BP in obese children" [12].

Thus, any interventions which not only reduce energy intake, but also increase physical activity in these children are likely to be helpful in keeping BP lower. In general, such interventions should be global policy in schools and as 'advice' to parents, not just advice directed at individual children. Group activities, a whole new ethos of outdoor lifestyle promotion, wherever and whenever possible, as part of school curricula, and regular vigorous activity sessions for boys and girls are regarded as essential components in helping children and parents (re-)learn that these are the foundation of what we currently know of how to keep BPs low through childhood and adolescence.

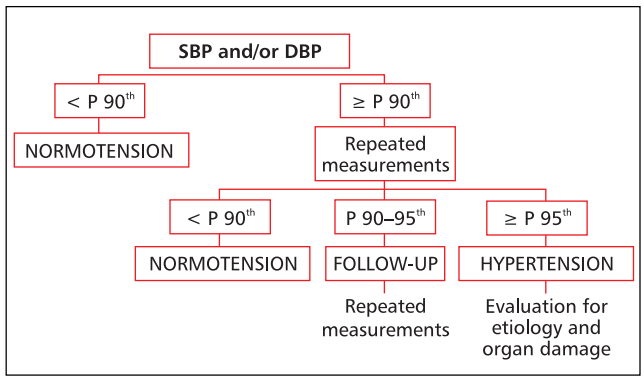

Figure 1. Diagnostic algorithm of hypertension; SBP — systolic blood pressure; DBP — diastolic blood pressure; P — percentile

Evidence for therapeutic management

Cardiovascular end-points such as myocardial infarction, stroke, renal insufficiency, or heart failure are extremely uncommon in childhood, and their rarity has thus far prevented event-based randomized therapeutic trials. Despite this, clinical experience shows that reduction of high BP in life-threatening conditions, such as acute heart failure, hypertensive encephalopathy, and malignant hypertension, improves survival and reduces sequelae in children. Because of the rarity of events, most of the limited evidence available so far is based on the use of organ damage markers, including left ventricular hypertrophy and increased urinary albumin excretion as surrogate endpoints.

In children, as in adults, the decision to initiate antihypertensive treatment should not be taken on BP levels alone, but should also consider the presence or absence of target organ damage, other risk factors or diseases such as obesity, renal diseases or diabetes [11]. In children with proven secondary hypertension, specific treatment of the underlying disease must be initiated immediately after detection. In children with primary hypertension, antihypertensive therapy should first target the risk factors for BP elevation (i.e. overweight, increased salt intake, low physical activity).

Non-pharmacological therapy should be continued even after starting pharmacological therapy as it can improve the overall cardiovascular risk profile in hypertensive children.

In the absence of prospective long-term studies linking children's BP levels to cardiovascular outcomes, paediatric BP targets are commonly defined in relation to the distribution of BP in the normal population. The 95th percentile is commonly used as a cut-off for defining hypertension in children and adolescents. This provides a rationale for targeting children and adolescents with essential hypertension to a BP below the 95th age-, sex-, and height-specific percentile, but it is probably wise and safer to aim at a BP below the 90th percentile [11].

In children with chronic kidney disease, there is preliminary evidence from the prospective randomized ESCAPE trial that strict BP control aiming for a 24-hour target below the 50th percentile of mean arterial pressure by the addition of other antihypertensive agents to ACEI inhibitor therapy results in a better 5-year renal survival, despite a return of proteinuria toward pre-treatment values [22]. Analysis by achieved BP levels shows similar renal outcomes with any 24-hour BP below the 75th percentile, contrasting with significantly reduced 5-year renal survival in patients exceeding this cut-off level. A poorer renal survival is associated with an attained 24-hour BP above the 90th percentile. Proteinuria appears to be an important modifier of the renoprotective efficacy of intensified BP control. Despite the dissociation in time of the renoprotective and antiproteinuric effects, an improved renal survival is associated with targeting BP to lower levels only in children with even mild baseline proteinuria, whereas no benefit of more intense BP lowering is found in children with non-proteinuric disease.

Therapeutic strategies

It should be reiterated here that lifestyle measures should not only precede but also accompany pharmacological treatment.

Monotherapy

It is reasonable that in children treatment should be started with a single drug, administered at a low dose, in order to avoid rapid fall in BP. If BP does not decrease sufficiently after a few weeks, usually 4 to 8, an increase to the full dose should be initiated. When BP does not respond adequately or significant side effects occur, switching to another antihypertensive drug of a different class is recommended. This procedure allows the patient's best individual response to the drug to be found in terms of efficacy and tolerability. Since the response rate is often not sufficient in single drug treatment, particularly in moderate or severe hypertension, combination therapy is often necessary.

As in adults, choice of antihypertensive agents can include ACE-inhibitors, angiotensin receptor antagonists (ARB), calcium antagonists, beta-blockers, and diuretics. A few placebo-controlled studies are available, but there are almost no head-to-head studies directly comparing the efficacy and safety of different antihypertensive drugs in children or adolescents.

Combination therapy

In children with renal disease, monotherapy is often not sufficient to achieve adequate BP control. Therefore, early combination therapy is required. Early dose combination of antihypertensive agents is more efficient and has a lower rate of adverse drug reaction compared to that of high dose monotherapy. Antihypertensive drugs of different classes have complementary effects, resulting in a higher degree of BP reduction and a lower rate of adverse drug reaction. The best choices of antihypertensive drug combinations are those recommended in the ESH 2009 reappraisal of Guidelines [23]. Fixed-dose combinations of two drugs are rarely used in children, since individual-based contributions are preferred, but fixed combinations may have a place in treating adolescents to improve compliance.

Treatment of associated risk factors: lipid lowering agents and glycaemic control

The new guidelines of the American Academy of Paediatrics (AAP) recommend measuring lipoproteins starting at age 2 in overweight, hypertensive, or diabetic children or in those with a family history of dyslipidaemia or early coronary artery disease [24]. If lipid values are within age- and gender-specific normal ranges, children should be retested in 3 to 5 years. For those out of normal ranges, initial treatment should be focused on recommending a diet low in cholesterol (< 200 mg/day) and saturated fat (< 7% of calories) supplemented with plant sterols and dietary fibres (child's age + 5 g/day up to 20 g at 15 years of age) [25]. Increased physical activity may be useful for modifying HDL-C and triglycerides. According to the AAP, statins should be considered for children 8 years and older if any of the following conditions exist: a) LDL-C remains ≥ 190 mg/dl (4.94 mmol/L); b) LDL-C remains ≥ 160 mg/dl (4.16 mmol/L) and there is a family history of early coronary artery disease or the presence of other risk factors as obesity, hypertension, or smoking; or c) LDL-C remains ≥ 130 mg/dl (3.38 mmol/l) in children with diabetes mellitus. The Food and Drug Administration (FDA) and European Medicines Agency (EMEA) has approved the use of pravastatin for children with familial hypercholesterolaemia who are 8 years and older. It should be noted, however, that AAP recommendations are controversial: they are not evidence based and the long-term effects of statins on children are unknown. The use of ezetimibe is approved in the USA (but not in Europe) only for those rare children with familial homozygous hypercholesterolaemia or with sitosterolaemia. Bile-acid sequestrants are difficult to tolerate over the long term. Fibrates may be used in adolescents with triglycerides ≥ 500 mg/dl who are at increased risk of pancreatitis [24, 25].

The increasing prevalence of paediatric type 2 diabetes coincides with increasing obesity in children. Most obese children have insulin resistance (60%), 5% have impaired glucose tolerance (IGT), 1% impaired fasting glucose, and 0.2% type 2 diabetes [11]. Reducing overweight and impaired glucose tolerance may help prevent or delay the development of type 2 diabetes in high-risk youths. Behavioural modification (dietary changes and ≥ 60 minutes daily of physical activity), using techniques to motivate children and families [11], is effective at reducing insulin levels and reverting impaired glucose tolerance to normal. Metformin is the only oral medication that has been adequately studied in children and approved by the FDA and some European Agencies for use in children over 10 years of age with type 2 diabetes. In obese insulin-resistant children, metformin has been shown to have favourable effects on body composition, fasting insulin, and fasting glucose [26].

Conclusions

It is clear that paediatric high BP will further contribute to the current epidemic of cardiovascular disease unless it is given the attention it deserves by policy makers, health care providers, schools, parents, caregivers, and society as a whole. The role of learned societies, particularly the European Society of Hypertension, is crucial not only for spreading the guidelines throughout all European Countries, but also for obtaining their acceptance by national hypertension societies and leagues.

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HYPERTENSION AND CORONARY HEART DISEASE

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Introduction

Hypertension (HT) is a major risk factor for coronary heart disease (CHD). Among the numerous risk factors associated with CHD, HT plays a major role given its high frequency and its physiopathogenesis. Thus, roughly 20% of the general adult population manifest HT with a net male predominance, and 25% of patients with CHD have HT [1]. CHD is the first cause of morbidity and mortality in hypertensive patients.

Numerous other risk factors for CHD, such as dyslipidaemia, diabetes, insulin resistance, obesity, lack of physical exercise and certain genetic mutations, are frequently associated with HT [2]. Furthermore, hypertensive patients have a greater number of cardiovascular risk factors than normotensive patients. In the INTERHEART study, history of hypertension was significantly (odds ratio 1.91) related to acute myocardial infarction [3].

Epidemiological studies have shown that smoking and hypercholesterolaemia increase the risk for CHD associated with HT in a multiplicative rather than in an additive manner [4]. Furthermore, although HT alone is weakly predictive of individual risk for the occurrence of CHD, the association between the level of blood pressure (BP) and the risk of CHD is independent of other factors.

Level of BP and risk of CHD

Numerous epidemiological studies have shown that the presence of HT increases the risk of CHD, not only in at risk populations but also in the general population. The prevalence of CHD is closely related to the BP level, especially systolic BP. This has been shown in studies of clinical BP and also in studies using ambulatory BP measurements (ABPM) [5]. Otherwise, the increase in pulse pressure is a predictive factor of coronary mortality [6]. The relationship between BP level and CHD seems linear, continuous, and independent [7]. Indeed, the J-shaped curve of the relationship between BP level and the risk of CHD comes from retrospective studies in patients with cardiovascular antecedents before anti-hypertensive treatment was instituted. Prospective therapeutic trials did not show an increase in risk of CHD in the lower levels of BP. After a myocardial infarction the risk of a subsequent fatal or non-fatal coronary event is greater if BP is raised [8]. In reference to ABPM studies, it has been reported that non-dipper hypertensive patients (night-time fall in BP < 10%) have a cardiovascular risk, in particular a CHD risk, multiplied by three [9].

The fall in BP under treatment is associated with a reduction in cardiovascular events, more so for stroke than for coronary events. Thus, a reduction by 5 mm Hg in diastolic BP reduces by one fifth the risk of CHD, and a reduction of 10 mm Hg leads to nearly a one third reduction in CHD risk [1]. According to a meta-analysis of 37,000 patients followed up over 5 years, treatment of moderate HT reduced by 14% the coronary morbidity and mortality by primary prevention [10]. Likewise, the meta-analysis by MacMahon et al. showed that a fall in BP in hypertensive subjects over 60 years reduced major coronary events by 19% [11].

Physiopathogenesis of myocardial ischaemia in HT

There is a multiplicity of mechanisms related to HT that lead to the development of myocardial ischaemia. These act by leading to an inequality between the transport and consumption of oxygen by the myocardium.

Acceleration of atherosclerosis

HT is an important risk factor for atherosclerosis and in particular in the coronary bed. The reduction in the lumen of the coronary arteries by atheromatous plaques reduces myocardium blood flow, thereby favouring ischaemia. These plaques may eventually break and thus form peripheral emboli or especially thrombus in situ by means of platelet aggregation that is responsible for acute coronary syndromes.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is one of the most important risk markers for CHD and sudden death independent of the level of BP [12]. This is the case whether LVH is diagnosed by ECG or by echocardiography. LVH reduces coronary flow reserve and favours the development of ventricular arrhythmias. This reduction in coronary flow reserve is secondary to structural and functional modifications in the myocardium (myocardial component) and in the arteries (vascular component), and also to anomalies in the control of coronary blood flow (nervous component) [13]. LVH increases metabolic and oxygen demands of the myocardium, increases coronary flow and coronary vascular resistances, but diminishes coronary flow reserve. This is associated with disturbance of diastolic function of the left ventricle that leads to a fall in perfusion of the myocardium. Furthermore, LVH is responsible for dysfunction of the mechano-receptors in the left ventricle, thereby leading to anomalies in coronary vascular tone.

Anomalies of the microcirculation

HT is associated with anomalies of the coronary microcirculation with a perivascular fibrosis, a thickening of the media, a reduction in the number of capillaries per gram of muscular tissue, and a diminution of the vascular lumen [14].

Endothelial dysfunction

The endothelium-dependent vascular relaxation is altered in HT [15]. This has been well demonstrated by the reduction in the vasodilator response after an intra-arterial injection of acetylcholine in the hypertensive subject while the response to nitrate derivatives is not altered [16]. This endothelial dysfunction brings into function numerous mediators such as nitric oxide, prostacyclins, factors acting on the differentiation and the growth of vascular smooth muscle cells, or cyclo-oxygenase dependent contraction factor. The anomalies in endothelial function explain in part the increase in the risk of CHD in HT since they favour vasoconstriction, thrombogenesis, and the action of proliferative substances.

Insulin resistance

Insulin resistance is frequently found in essential HT. This leads to hyperinsulinism that is an independent predictive factor of CHD. This insulin resistance is often associated with low levels of HDL cholesterol and elevated levels of triglycerides. These may result in an acceleration of the atherosclerotic process.

Sympathetic activation

The regulation of myocardial blood flow is, in part, mediated by the sympathetic nervous system. HT is accompanied by an exaggerated sympathetic response to physiological stimuli that favours myocardial ischaemia.

Detection of CHD in the hypertensive patient

Repolarisation anomalies are frequently found on the ECGs of hypertensive patients, in particular negative T waves in the lateral leads indicating systolic overload of the left ventricle, frequently associated with LVH. The exercise ECG is difficult to interpret in HT since a ST depression in V5 and V6 is frequent especially in the presence of LVH. These findings are of low specificity for myocardial ischaemia. Myocardial scintigraphy is also often abnormal in HT because of LVH and anomalies of coronary microcirculation [17]. Stress echocardiography can also be performed in hypertensive subjects to detect myocardial ischaemia. If diagnostic doubt persists after a non-invasive test in hypertensive subjects with chest pain, coronary angiography is often necessary.

It has been shown that roughly 30% of hypertensives have silent episodes of myocardial ischaemia due to a reduction in coronary flow reserve, endothelial dysfunction and anomalies in the autonomic nervous system.

Treatment of HT and CHD

An isolated fall in BP with treatment does not completely reduce the risk of CHD in essential HT. This confirms the complexity of the relationship between CHD and HT since numerous factors other than HT are implicated, as previously discussed. Treatment of HT in patients with

CHD must be more aggressive than in the absence of CHD. Indeed, the risk of a recurrent coronary event in this population is very high, and all efforts should be expended in order to lower BP, especially since we may expect a better compliance with treatment after a coronary event.

In primary prevention, successive studies have shown the benefit of thiazide diuretics and beta-blockers on cardiovascular events. Subsequently, calcium-channel blockers and angiotensin converting enzyme (ACE) inhibitors have been shown to be effective in the same situation, just as angiotensin 2 receptor antagonists (ARBs) have been [18]. All these treatments have an identical effect on the fall in BP and on the percentage of responders [19, 20]. The thiazide diuretics, beta--blockers, calcium-channel blockers, and ACE inhibitors have a similar effect of reduction in cardiovascular morbidity and mortality. The same drugs lead to a modest reduction in coronary events, of the order of 20%. Although it has not been definitively proven, the regression in LVH by antihypertensive treatment allows improvement in myocardial perfusion thereby reducing the risk of CHD. In this context, ACE inhibitors and ARBs may have a more marked effect than the other therapeutic classes as regards regression in LVH [21, 22].

As regards secondary prevention, there are no studies of diuretics. The therapeutic classes which have been proven to prevent recurrence of coronary events, whether associated with HT or not, are beta-blockers [23–25], ACE inhibitors [26–29], ARBs [30], and calcium-channel blockers such as verapamil in case of contraindication of beta-blockers or in association with trandolapril [31, 32]. In patients surviving a myocardial infarction, early administration of beta-blockers, ACE inhibitors, or ARBs reduce the incidence of recurrent myocardial infarction and death [33]. Antihypertensive treatment is also beneficial in HT patients with chronic CHD [33]. The benefit appears to be related to the degree of BP reduction. Reappraisal of European guidelines on hypertension management indicate that it is reasonable to lower systolic BP down to the 130–139 mm Hg range in patients with concomitant CHD [34]. Intensive lipid management and antiplatelet therapy are also indicated [33].

Conclusions

The prevalence of HT is very high in the general population and more so in patients with CHD. The mechanisms by which HT favours the development of CHD are multiple and are not simply limited to the presence of atheroma in the coronary arteries. Non-invasive diagnostic tests for CHD are often inadequate in HT. HT, as a major risk factor for CHD, can be partially reversed by anti-hypertensive treatment that has a vital role both in primary and secondary prevention.

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RESISTANT HYPERTENSION

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Definition and prevalence

Hypertension is a major health problem affecting approximately 30% of people by the age of 60 years. Some patients with hypertension are difficult to control despite the use of combinations of antihypertensive drugs, and are considered as resistant to treatment. Hypertension is usually defined as resistant or refractory (RH) to treatment when a therapeutic plan that includes attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) at correct doses has failed to lower systolic (SBP) and diastolic blood pressure (DBP) to goal levels, excluding isolated office hypertension [1]. The estimated prevalence of RH in large prevention-of-morbidity-and-mortality trials in hypertension, such as the ALLHAT, VALUE, ASCOTT, and CONVINCE trials, is 7–15% [2–6]. Older studies estimated the prevalence of RH in tertiary care centres as 5–18% [7–12], whereas a large cohort study by Alderman et al. found that only 2.9% were resistant to antihypertensive therapy [13]. Several clinical trials suggest that RH is increasingly common. In the Systolic Hypertension in Europe (Syst-Eur) study, 43% of patients were reported to be resistant [14], but isolated systolic hypertension in the elderly is a different condition usually not included in the estimates of prevalence of RH. In other studies in high-risk hypertensive patients, such as the LIFE (Losartan intervention for Endpoint Reduction in Hypertension) study [15], which enrolled hypertensive patients with left ventricular hypertrophy, 26% were estimated as resistant, but not all fulfilled the strict criteria of RH [1]. However, these figures overestimate the prevalence of RH in the overall hypertensive population as they are limited to older or high-risk patients. Finally, a recent position paper by the American Heart Association on resistant hypertension suggests that patients with controlled BP requiring ≥ 4 medications should be considered as resistant to treatment [16].

Causes and therapeutic approaches in resistant hypertension

The first step to a correct diagnosis in a patient resistant to antihypertensive therapy is to rule out apparent or false RH due to the white-coat effect, pseudohypertension or non-compliance with treatment [1, 16]. Assessment of 24-hour ambulatory blood pressure monitoring (ABPM) is crucial for the diagnosis of white-coat hypertension [17, 18]. In addition, ABPM has an important prognostic value in patients with true RH. It has been shown that patients with RH with a mean daytime DBP ≥ 95 mm Hg have a significant five-year increase in cardiovascular events [17]. As shown in Table 1, the appropriateness of the therapeutic regimen, the use of illicit drugs, possible drug interactions, high salt or alcohol intake, volume overload, obesity, and sleep apnoea should be carefully investigated. The most-common exogenous substances/drugs compromising hypertension control are NSAIDs, alcohol, recreational and illicit drugs such as cocaine, oral contraceptives, psychotropics, and weight-loss drugs. There is wide individual variation in the effects of drugs, and a minority of patients may be particularly sensitive; therefore, withdrawal from potentially interfering medication facilitates better BP control. Patient compliance is undoubtedly a major component of successful BP control and can only be confirmed by patient self-report. Lack of BP control has been attributed to poor adherence to the prescribed regimen in approximately 50% of patients [19–22]. One study in patients with RH, in which compliance was assessed by the Medication Event Monitoring System (MEMS) for two months, found a BP reduction < 140/90 in about 30% of patients, attributable only to patient self-perception of "being observed", without any changes in medication [20].

Pseudohypertension, which has been suggested to be more common in the elderly, is defined as a condition in which cuff pressure is inappropriately high compared to intra-arterial pressure due to vascular stiffening. Lack of target organ involvement despite high auscultatory BP levels or symptoms of hypotension in a patient with apparent RH may indicate pseudohypertension. Osler's manoeuvre, which was proposed as a screening method, proved to have little predictive value [23, 24]. Thanks to ABPM studies, isolated office (white coat) hypertension is an increasingly important form of spurious hypertension. A recent study by Oikawa et al. demonstrated the importance of the white coat effect as a cause of false RH [25].

Plasma volume expansion, which can be measured using I^{125} radiolabeled albumin, is common in patients with RH [26]. A study of 279 patients with RH found higher aldosterone and natriuretic levels in comparison with controls [27]. Population-based studies suggest a linear relationship between dietary salt intake and BP [28, 29]. Excessive sodium can blunt the antihypertensive effects of ACE-inhibitors and diuretics: therefore, dietary salt restriction should be strictly recommended to all patients with RH. The results of the Framingham Study indicate an association between BMI (> 25–30 kg/m^2) and treatment resistance. The close relationship between obesity and RH is a result of complex mechanisms in obese patients, including increased sympathetic nervous system activation [30–32], baroreflex dysfunction and sleep apnoea syndrome [33], increased renal and cardiac sympathetic activity [34], the direct effects of adipose tissue, and abnormalities in the renin-angiotensin system [35, 36]. Each 10% increase in weight is associated with a 6.5 mm Hg increase in SBP [37, 38]. For this reason, weight reduction should be recommended to all overweight hypertensive patients. A significant association between hypertension, especially RH, and sleep apnoea has been demonstrated [39, 40]. In a recent study [41] obstructive sleep apnoea (OSA) (apnoea/hypopnoea index > 5) was found in 79.6% of patients with true RH, while moderate-severe OSA was diagnosed in 53.7% and was more frequent in men than in women (77.4% vs. 21.7%).

After all these possible causes of RH have been reasonably ruled-out, secondary causes should be considered. Recently, stimulated renin profiling, the so-called "physiologic tailoring" of management, has been suggested in cases of RH [42]. Reports suggest that hyperaldosteronism is the most-common secondary cause (8–32%) followed by renal failure and renal artery stenosis [43–45]. Recognition that most patients do not have low serum potassium levels, which had been seen as a prerequisite for the diagnosis of primary hyperaldosteronism, has led to increased detection of the disease [46]. In patients with low renin resistant hypertension, screening for aldosteronism is mandatory. Primary hyperaldosteronism responds well to appropriate surgical or medical treatment. In renovascular disease, revascularization preserves renal function but the effect on blood pressure control is limited [47]. Renal failure should be treated according to the aetiology. After eliminating all the previously-mentioned causal factors, "true essential RH" is a rare finding, estimated to affect less than 5% of people with hypertension [48].

Table 1. Underlying causes of resistant hypertension

Causes of resistant hypertension
Poor adherence to therapeutic plans
Failure to modify lifestyles, including:
• weight gain
• high alcohol intake (NB: binge drinking)
Continued intake of agents that raise blood pressure (liquorice, cocaine, glucocorticoids, non-steroidal anti-inflammatory drugs, etc.)
Obstructive sleep apnoea
Unsuspected secondary cause
Irreversible or minimally-reversible organ damage
Volume overload due to:
• inadequate diuretic therapy
• progressive renal failure
• high sodium intake
• hyperaldosteronism
Causes of spurious resistant hypertension
Isolated office (white-coat) hypertension
Failure to use large cuff on large arm
Pseudohypertension

The pharmacological approach to RH patients already treated with three antihypertensive drugs may be guided by non-invasive haemodynamic studies assessing the cardiac index, systemic resistance, and intrathoracic volume by bioimpedance. Depending on the haemodynamic evaluation, vasodilators, diuretics, or beta-blockers may be added or eliminated, and doses increased or reduced [49]. The close relationship between the aldosterone status and RH has provided a rationale for the recommendation of adding low-dose spironolactone as the first step in reducing and controlling blood pressure in RH. Recent trials have shown the benefit of adding spironolactone to the baseline strategy of an ACE inhibitor or ARB associated with a calcium channel blocker and a thiazide diuretic in RH patients [50–55]. Low--dose spironolactone (12.5 mg/d with the possibility of up-titration to 50 mg/d) should be considered in all patients whose BP remains above desired levels despite medication with three drugs [56].

Recent research on the pathogenesis of hypertension has lead to new treatment concepts involving the neurohumoral regulation of BP [57]. Electrical carotid baroreceptor stimulation by devices permanently placed around the bifurcations of the carotid arteries reduces BP through sympathetic inhibition [58–60]. Baroreceptor stimulation may have benefits in BP reduction in conditions with sympathetic nervous system predominance such as obesity [61], obstructive sleep apnoea [62], and isolated systolic hypertension [63]. The Device-Based Therapy in Hypertension Extension Trial (DEBut-HET) showed that carotid receptor stimulation by an implantable device reduced office SBP and DBP, and heart rate in 21 RH patients [64], although the findings require confirmation in clinical studies including large numbers of patients. Detailed data on the long-term effects of the procedure are also required.

The pivotal role of the kidney in BP regulation is due mainly to its afferent and efferent innervations and to renin release. Denervation of renal afferent nerves by radiofrequency catheter-based treatment resulted in significant blood pressure reduction in animals [65] and in hypertensive patients [66–68]. The additional benefits of the procedure are a systemic reduction in norepinephrine spillover, an increase in renal perfusion, improvements in the halving of circulating plasma renin levels, and a reduction in insulin resistance [69].

Conclusions

"True resistant hypertension" should be diagnosed only after the above--mentioned contributing factors have been reasonably ruled-out. Multiple exogenous factors may make blood pressure control difficult, in addition to the less-frequent secondary causes of hypertension. The treatment of resistant hypertension includes the elimination of exogenous factors and the use of the maximum tolerated doses of combined antihypertensive agents, including rennin-angiotensin system blockade with an ACEI or ARBs, a calcium-channel blocker, a long-acting thiazide diuretic, and low dose spironolactone. Increasing understanding of the pathophysiology of hypertension may allow the development of new interventional and pharmaceutical therapies for resistant hypertension.

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MICROALBUMINURIA IN TYPE-1 DIABETES MELLITUS

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Introduction

The prevalence of type-1 diabetes had increased in most European populations and it may also be rising among US youths [1]. In persons with diabetes, compared to those without diabetes, the prevalence, incidence, and mortality of end-stage renal disease (ESRD) [2] and all forms of cardiovascular disease (CVD) [3] are strikingly increased. In all likelihood, an earlier onset of diabetes will lead to an earlier onset of CVD complications. The presence of diabetic nephropathy, which appears many years before the development of clinically relevant cardiac and arterial damage, further increases the risk of CVD diseases. Indeed, one of the major goals is to prevent development of diabetic nephropathy.

The onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several interventions, but these interventions have their greatest impact if instituted at a point very early on in the course. Microalbuminuria, i.e. small amounts of urinary albumin excretion (UAE), is the best predictor of high risk of developing diabetic nephropathy [4]. Thus, the detection of microalbuminuria has played a key-role in the management of type-1 diabetes.

Assessment and clinical value of microalbuminuria

Microalbuminuria is defined as the appearance of low but abnormal levels of albumin in the urine (30–300 mg/24-hour). In microalbuminuric patients not receiving antihypertensive treatment, 80% progress to an increase in UAE rate of 6% to 14% per year and a risk of developing overt diabetic nephropathy of 3% to 30% per year. Microalbuminuria rarely occurs shortly after a patient develops type-1 diabetes. Therefore, screening in these individuals should begin after 5 years of disease duration. A sensitive method of dipstick or enzymoimmunoassay for albumin should be used and repeated every year if the result is negative. If the result is positive, microalbuminuria can be confirmed and quantified by measuring the ratio of albumin to creatinine in a morning urine sample or by measuring the rate of albumin excretion in overnight urine. Overnight samples can also be used to distinguish true microalbuminuria from postural or exercise proteinuria, which are common in young patients. Since short-term hyperglycaemia, exercise, urinary tract infection, and acute febrile illness can cause transient elevations in UAE, and there is also marked day-to-day variability in UAE, at least two of three collections done over a 3–6 month period should show elevated levels before designating a patient as having persistent microalbuminuria [5]. Although isolated microalbuminuria usually indicates the presence of early diabetic nephropathy, the presence of other abnormalities upon urinalysis may suggest another renal disease [6]. The potential role of combining microalbuminuria and NAG excretion, a marker of tubular dysfunction, early in type 1 diabetes may identify individuals susceptible to future diabetic nephropathy and may yield a better predictive model than either one alone [7].

Significance of microalbuminuria

The relationship between microalbuminuria and renal functional and structural abnormalities has been analysed. Glomerular hyperfiltration, increments in renal plasma flow, and nephromegaly have been recognized for many years in Type-1 diabetes, and an enhanced risk of developing microalbuminuria has been proposed in these patients. A clear relationship between hyperfiltration and microalbuminuria, however, has not been demonstrated [8]. Likewise, structural abnormalities correlate poorly with isolated microalbuminuria. Mauer et al. [9] observed that in patients with microalbuminuria in the lower range and otherwise normal glomerular filtration rate (GFR) and BP, the mesangial volume fractions completely overlapped with those in patients whose renal function was normal. In contrast, patients with microalbuminuria and either hypertension, decreased GFR, or both had more advanced mesangial expansion. Microalbuminuria also indicates the presence of more generalized structural or functional abnormalities outside of the kidneys. Endothelial dysfunction, estimated for a reduction in the vasodilatory capacity to reactive ischaemia or to acetylcholine infusion in isolate arm, or for an impairment of insulin-mediated skeletal muscle blood flow, has been demonstrated. Furthermore, microalbuminuria has been associated not only with other microvascular lesions, incipient neuropathy, and proliferative diabetic retinopathy, but also with macrovascular disease and coronary heart disease [10]. Asymptomatic patients with long-lasting type 1 diabetes may have disturbances in myocardial perfusion, especially those with microalbuminuria [11].

Risk factors for microalbuminuria

Identification of factors related to the development of microalbuminuria leads to the development of strategies to reduce the occurrence of new cases. Several main factors have been identified. Among them, metabolic control, blood pressure levels and genetic factors are the most studied although some others have also been implicated.

A large body of evidence implicates poor metabolic control with the risk of developing microalbuminuria. Elevated levels of glucose increase the risk, not only for the short term, through the generation of advanced glycated proteins, activating an isoform of the protein kinase C and increasing the sensitivity to angiotensin II. Likewise, the variability of HbA1c predicts the development and progression of incipient and overt renal disease [12]. Intensive glucose-lowering treatment reduces the risk of developing microalbuminuria [13]. What is controversial is whether or not there is a glycaemic threshold for risk. Data coming from cross-sectional, follow-up, and intervention studies has not supported the existence of a threshold, and efforts to reduce HbA1c should, therefore, be continued at all levels [14].

Several studies have reported that systemic blood pressure is not raised prior to the onset of microalbuminuria. Using ambulatory blood pressure monitoring, however, it has become evident that in Type 1 diabetics with microalbuminuria, nocturnal blood pressure is already higher than in Type 1 diabetics with normoalbuminuria or in age-matched control subjects [15]. Consequently, these studies have shown that in Type 1 diabetics the presence of microalbuminuria is often associated with subtle alterations in blood pressure, characterized by a "non-dipping status" [16]. The relationship between night-time BP and urinary albumin excretion has been previously documented, and the BP parameter which best correlated with urinary albumin excretion was night-time BP. High BP during sleep leads to renal damage due to the transmission of systemic BP into glomerular and tubulointerstitial structures and is facilitated by the low preglomerular tone during recumbence and resting conditions that is more marked in diabetic subjects than in normal subjects. Although there is a potential role for systemic BP transmission to act as a renal damage-inducing mechanism, other evidence supports the thesis that higher sleep BP may be a consequence of the incipient renal damage itself leading, consequently, to higher sleep BP. Neither the cause nor the consequence interpretation of these data is mutually exclusive. The impact of lowering nocturnal BP on reducing the development of nephropathy and/or cardiovascular damage remains to be confirmed in the future.

Familial clustering of diabetic nephropathy suggests the presence of genetically transmissible factors that modulate the risk of nephropathy. The Insertion/Deletion of angiotensin converting enzyme (ACE) gene has been one of the first, and it is the most studied gene due to the influence of the polymorphism on the activity of ACE, a key enzyme in angiotensin II generation [17]. Association with the polymorphism of other candidate genes is less consistent and the studies of genome wide-scan (GWAS) have not provided more precise information yet.

Other factors associated with the development of microalbuminuria are inflammation, obesity, and smoking [18], although their interaction with the three main factors is difficult to assess.

Treatment of microalbuminuria

Glycaemic control is the first goal to be achieved in diabetic subjects [19]. Although randomized studies comparing the renal effect of intensified blood glucose control to conventional treatment did not demonstrate significant differences, long-term intensified therapy in the Diabetes Control and Complications Trial (DCCT) [20] reduced the risk of

proteinuria by 54%. Achieving HbA1c < 7% is a reasonable target, but a lower goals should be pursued in the absence of clinical atherosclerosis.

Based on well-conducted clinical trials, angiotensin-converting enzyme inhibitors (ACEI) are recommended for all patients with Type 1 diabetes and microalbuminuria, regardless of BP values [21]. In a meta-analysis based in 698 individual data from studies which had a placebo or a non-intervention group and at least 1 year of follow-up, ACEI was shown to prevent progression of albumin excretion rate from the microalbuminuric to the clinically proteinuric range and normalize albumin excretion rate in patients with microalbuminuria [22]. The effect of ACEI does not differ according to sex, age, disease duration, glycaemic control, or baseline blood pressure, but the effect seems to be partially independent of the BP lowering effect. If abnormal urinary albumin excretion values are high and persist for more than a year, only long-lasting treatment with ACEI seems able to induce persistent remission, especially when associated with good metabolic control and high HDL cholesterol levels [23].

Experience with angiotensin receptor blockers (ARBs) also reflected the potential to reduce microalbuminuria. Although a significant reduction in UAE with losartan has been observed, one similar to those observed with enalapril, no evidence exists in terms of its advantages over ACEI. Thus, ACEI is still the recommended drug in these patients, unless ACEI intolerance exists.

Prevention

There are two main strategies that have been evaluated to avoid the progression from normoalbuminuria to microalbuminuria: improvement of glycaemic control; and administration of blood pressure lowering agents which blockade the renin–angiotensin–aldosteron system (RAAS) [24]. Concerning the impact of improving glycaemic control, Wang et al. published a meta-analysis of 12 studies comparing the effect of intensive versus conventional blood glucose control on the risk of progression to nephropathy in patients with normoalbuminuria and microalbuminuria. The risk, defined as an increment in UAE, decreased with the intensified treatment, with an odds ratio of 0.34 [25]. Likewise, in the DCCT intensified therapy reduced the occurrence of microalbuminuria by 39%, but the effect does not occur for at least three years.

ACEI also significantly reduces the albumin excretion rate below the threshold to define microalbuminuria, even in patients with a relatively low albumin excretion rate. Although the magnitude of the effect in such patients is not as great as in those with higher rates, it is nonetheless of statistical and probably clinical significance. The EUCLID study, a randomized placebo control trial, demonstrated that lisinopril is able to reduce the occurrence rate of microalbuminuria by 30%. Indeed, ACEI was recommended in treating normoalbuminuric subjects at high risk of developing an increase in the urinary albumin excretion rate.

More recently, however, two studies introduced a word of caution about the potential role of RAAS blockade to prevent the development of persistent microalbuminuria [26, 27]. Mauer et al [26] studied the effect of losartan or enalapril in renal damage assessed by glomerular mesangial fraction volume in kidney biopsies. The occurrence of microalbuminuria was equal in placebo control subjects to that in those receiving enalapril. The losartan treated subjects had higher rates of microalbuminuria compared to those receiving placebo. In the DIRECT study [27], Candesartan, 32 mg/d, for 4.7 years did not prevent microalbuminuria in 3329 mainly normotensive patients with type 1 diabetes.

It is still likely that progression to microalbuminuria will occur in a substantial proportion of patients, and therefore there is a need to explore the role of risk factors other than glycaemic control, reducing BP, or decreasing angiotensin II activity, which may provide further clues for interventions. Looking for early markers of risk can help a selective and prompt therapy to protect the patient from the development of microalbuminuria and the likelihood of diabetic nephropathy. Until these markers can be identified, detection of urinary albumin excretion in the high normal range needs to be considered for early intervention due to the risk of progression and because it is now clear that the significance of microalbuminuria extends beyond nephropathy being a marker for generalized vascular dysfunction and cardiovascular risk.

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INTERACTIONS BETWEEN ANTIHYPERTENSIVE AGENTS AND OTHER DRUGS

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Introduction

The vast majority of hypertensive patients are treated with antihypertensive drugs for many years. Other therapeutic agents are frequently used simultaneously, thus giving rise to the possibility of drug-drug interactions. It is estimated that 6–10% of adverse drug events are associated with drug–drug interactions [1]. The potential for drug––drug interactions increases with rising age, since elderly patients a receive larger number of drugs, but also because the renal excretion of several therapeutic agents is impaired in the elderly as a result of diminishing kidney function [2–3]. The interactions between **antihypertensive drugs and other therapeutic agents** will be discussed and summarized in the present issue after a brief general explanation of the various mechanisms underlying drug-drug inter-actions. The combination and mutual interactions between various categories of antihypertensive agents will be dealt with by us in a separate issue of this newsletter.

Mechanisms

There are several mechanisms by which drugs may interact [4–6], and most of these mechanisms can be categorized as pharmacokinetic (involving intestinal absorption, distribution, metabolism, and elimination), as pharmacodynamic, or as additive toxicity, respectively.

Table 1. Interactions between antihypertensive and other drugs

Drugs (class)	Interaction with	Mechanism	Effect
Beta-blockers	Verapamil diltiazem	Additive effects	A-V conduction impaired; risk of A-V block
	Oral antidiabetics	$Beta_2$-receptor blockade	Symptoms of hypoglycaemia are suppressed
	Broncho-spasmolytic agents	$Beta_2$-receptor blockade	Suppression of the bronchospasmolytic effect
	Dobutamine	$Beta_1$-receptor antagonism	The inotropic action of dobutamine is inhibited
Metoprolol	Propafenone, amiodarone, dronedarone	Enzymatic inhibition (CYP-450)	accumulation of metoprolol
Thiazide diuretics	Digoxin	Hypokalaemia	Digoxin becomes more toxic (arrhythmogenic)
	Lithium ions	Renal excretion of lithium ions impaired	Accumulation of lithium ions
Alpha-blockers	Noradrenaline	$Alpha_1$-receptor blockade	Noradrenaline shows less vasoconstrictor activity
	Alcohol	$Alpha_1$-receptor blockade potentiates alcohol induced hypotension [11]	Orthostatic hypotension
	PDE5-inhibitors (sildenafil, tadalafil, vardenafil)	Increased cGMP availability	Severe hypotension
Calcium antagonists			
Verapamil, diltiazem	Beta-blocker	Additive effect	A-V conduction impaired; risk of A-V block
	Azole antimycotics	Enzymatic inhibition (CYP-450)	Accumulation of DHP Ca-antagonist
	Digoxin	Renal excretion of digoxin	Digoxin may accumulate; arrhythmogenic effect
	Protease inhibitors (HIV-treatment)	Inhibition of hepatic degradation	Accumulation of verapamil or diltiazem
	Cimetidine	Ibid.	Ibid.
Dihydropyridine Ca-antagonists	Beta-blocker	Beta-receptor blockade	Suppression of reflex tachycardia (favourable)
Felodipine, verapamil	Grapefruit juice	Enzymic inhibition (CYP-450 system)	Accumulation of felodipine, verapamil
ACE inhibitors	Diuretics (thiazide)	Additive effect	Strong hypotensive action
	Diuretics (K^+-sparing)	Reduced renal excretion of K^+	Hyperkalaemia
	NSAID's including **high** dose ASA	Retention of Na^+ and H_2O	Reduced antihypertensive effects
	Lithium ions	Reduced excretion of lithium ions	Lithium ions accumulate
	DPP4-inhibitor (vildagliptin)	Inhibition of substance-P degradation [12]	Increased risk of angioedema
AT_1-receptor antagonists	Virtually the same as ACE-inhibitors (except of DPP4-inhibitor)	Interactions as ACEIs (see above)	Described before
Centrally acting antihypertensives			
Alpha-methyl-DOPA	Fe^{2+}-ions	Enteral absorption of α-methyl-DOPA	Reduced antihypertensive action
Clonidine	Tricyclic antidepressants	Antagonism of central α_2-adrenoceptors	Ibid.
	Beta-blockers	Unknown	The clonidine rebound phenomenon is more frequent
Both clonidine and α-methyl-DOPA	Centrally acting depressant agents (hypnotics, tranquillizers, aneuroleptics, anti-epileptics, some anti-depressants, H1-anti-histaminic agents, alcohol)	Additive effect, non-specific	Sedation, fatigue

Pharmacokinetic interactions

The interaction in **intestinal absorption** is best illustrated by an example: tetracylines and other broad-spectrum antibiotics may impair the absorption of oral contraceptives (in particular those with low-dose progestogens and/or oestrogens) and hence render contraception unsafe. Several drugs are subject to inactivation via **metabolic degradation** in the liver, catalysed by various liver enzymes. The formation of these enzymes can be induced or enhanced by drugs such as rifampicin, griseofulvin, and several anti-epileptics (carbamazepine, phenytoine, phenobarbital), but also by regular alcohol consumption. This process, which requires several weeks of treatment and which is indicated as enzyme induction, enhances the metabolic degradation of several drugs. In practice, enzyme induction may play a relevant role for oral anticoagulants (coumarin type), corticosteroids (glucocorticoids), oral contraceptives, or quinidine. Accordingly, these categories of drugs are metabolized/inactivated more rapidly and their doses should therefore be increased. A comparable but opposite problem is the **inhibition of liver enzymes** involved in the biotransformation by a variety of drugs, such as cimetidine, erythromycin, metronidazole, tricyclic anti-depressants, phenothiazine-neuroleptics, and sulphonamides (also in co-trimoxazole). Enzyme inhibitors of this type impair the biodegradation of certain drugs and hence increase their effect. A well-known problem is the enhanced effect of anticoagulants (as reflected by bleeding) induced by additional treatment with co-trimoxazole. Certain drugs may **impair the renal excretion** [3–5] of other agents, usually at the renal tubular level. A well-known relevant example is the rise in the plasma level and toxicity of digoxin, provoked by verapamil, amiodarone, or quinidine. Similarly, thiazide diuretics may decelerate the renal elimination of lithium salts and hence reinforce their toxicity. A beneficial effect of such an interaction is the impaired excretion of penicillin antibiotics induced by simultaneously administered probenecid.

Pharmacodynamic interactions and additive toxicity [4–6]

Pharmacodynamic interactions between similarly acting drugs may lead to additive or even over-additive effects (potentiation). A well-known example is the combination of IV verapamil and a β-blocker, which may cause additive impairment of cardiac A-V conduction and the risk of A-V block. Another possibility is the inhibition of the therapeutic effect of a drug by an additional agent. Over-additive adverse reactions are illustrated by the following example: an important interaction, probably caused by non-specific mechanisms, is the mutual enhancement of the central nervous depressant effect of all drugs that are known to dampen the activity of the central nervous system. This interaction holds for hypnotics, anxiolytics (minor tranquillizers), antipsychotics (neuroleptics, major tranquillizers), anti-epileptics, and opioids but also for drugs with central nervous depressant adverse reactions, such as antihistamines, centrally acting antitussives (codeine etc.), and scopolamine [3–5, 9]. Furthermore, alcohol enhances the central nervous depressant effect of all of the aforementioned therapeutics. Accordingly, enhanced sedation, impaired psychomotor skills (driving), but also respiratory depression may occur.

Antihypertensive agents and other drugs

The most relevant interactions between antihypertensive and other drugs have been listed in Table 1, and the effect of these interactions on blood pressure are listed in Table 2. A few comments may be made: it goes without saying that a combination of two or more anti-hypertensive agents may be expected to cause an additive blood pressure lowering effect, which is to be discussed in more detail in a forthcoming issue of this newsletter. The central nervous depressant effect of all drugs suppressing the activity of the central nervous system enhances the side--effects of centrally acting antihypertensives (reserpine, alpha-methyldopa, guanfacine, clonidine) [4–6, 10]. More recently, a great deal of attention has been paid to the interaction between antihypertensive drugs and NSAIDs. As an example: indomethacin and other non-steroidal anti-inflammatory drugs (NSAIDs) may counteract the antihypertensive effect of thiazide diuretics, β-blockers, ACE-inhibitors, and AT_1-receptor antagonists as a result of sodium and fluid retention as well as of decreased formation of vasodilatory prostaglandins [7–8]. It has been clearly demonstrated, however, that low-dose acetylsalicylic acid (ASA; Aspirin®, 75 mg daily) does not interfere with the antihypertensive activity of ACE-inhibitors and other types of antihypertensive drugs [9].

Table 2. Effect of drug interactions on blood pressure

Drugs	Mechanism of action	Increase in BP	Interferes with anti-hypertensive effect
Sympathomimetics	Nasal decongestants (α-rec.)	YES	NO
Ergot alkaloids	Anti-migraine drugs (5HT) Bronchodilators (β_2 rec.)	YES	NO
NSAIDs	Sodium retention Inhibition of vasodil. PGs	YES	YES
Oral contraceptives	Estrogens and progesterone	YES	NO
Corticosteroids	Sodium retention	YES	YES
Psychotropes	Chlorpromazine, tricyclics, MAO-inhibitors etc.	YES	NO
Erythropoietin	Increase in blood viscosity	YES	NO
Cyclosporine	Hypothetical (via NO)	YES	NO
Resin	Inhibition of GI, absorption of anti-HT drugs	YES	YES
Anabolic steroids	Sodium retention	YES	NO

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BENEFICIAL COMBINATIONS OF TWO OR MORE ANTIHYPERTENSIVE AGENTS

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Introduction

In a preceding communication we described the most relevant interactions between antihypertensive drugs and other therapeutics [1]. In the present paper we will deal with the combination of different types of antihypertensive drugs. Approximately half of hypertensive patients can be satisfactorily controlled with a single drug, with the usual advice for appropriate changes in lifestyle. This means that the other 50% of patients require two or even more antihypertensive drugs for the adequate control of their blood pressure. The need for drug combination therapy has long been neglected or dismissed in academic medicine. In particular the use of tablets containing two or three different drugs in a fixed dose has been strongly criticized. This view has clearly reverted towards an appreciation of combined treatment, as expressed in more recently issued guidelines (2007 ESH–ESC [2] and JNC VI [3]). In these guidelines, combination therapy is advocated more explicitly for certain types of hypertensive disease, such as:

- isolated systolic hypertension (ISH);
- accelerated hypertension;
- in patients where blood pressure (BP) values lower than 140/90 mm Hg are required to prevent target organ damage (e.g. in diabetes mellitus: < 130/85 mm Hg, chronic parenchymatous nephropathy: < 125/75 mm Hg).

The combination of two or more drugs may be expected to offer a more pronounced lowering of increased blood pressure, and this has indeed been observed in numerous, usually rather small, clinical studies. For very few drugs, their combination has been included deliberately in large randomised intervention studies (e.g. the combination of diuretics and β-blockers [4, 5]). Furthermore, the use of a **fixed combination**, in a single tablet, is increasingly appreciated since it significantly reduces the number of tablets to be taken daily, thus improving patient compliance, a most relevant source of insufficient therapeutic efficacy in hypertensive patients. Fixed dose combinations have been enriched by **very low dose combinations**, which may now be considered as first-line therapy.

Effective combinations of two different antihypertensive drugs

Over the years, several combinations of antihypertensive drugs have been studied and these have shown to be effective in lowering elevated blood pressure. In this chapter we will discuss a series of combinations which are assumed to be effective and probably beneficial in certain groups of patients. Although not all are based on large intervention studies required for evidence-based decisions, we have chosen these combinations on the basis of haemodynamic and pathophysiological considerations, mostly supported by studies as well as by our own experience.

Thiazide-diuretics + beta-blockers

This combination has long been favoured by guidelines for patients with uncomplicated hypertension without target organ damage and in patients with congestive heart failure (CHF). This combination has been included in several large-scale intervention studies (e.g. STOP [4]; MRC [5], ALLHAT [12]) and can be considered as firmly established, but evidence is now available that these drugs have dysmetabolic effects and facilitate new-onset diabetes in predisposed patients, such as those with metabolic syndrome or prediabetes, which may be even more pronounced when they are administered together. However, it should not be ignored that beta-blockers are not a homogeneous class, and that vasodilating beta-blockers, such as celiprolol, carvedilol, and nebivolol, appear not to share some of the negative properties described for other compounds.

Thiazide-diuretics + ACE-inhibitors

Useful in patients with hypertension and CHF, ISH, as well as hypertension in the elderly (which is frequently ISH) and in p. This combination is considered to be a very potent antihypertensive medication, and the addition of an ACE--inhibitor to a diuretic (or vice versa) should be performed cautiously, in order to prevent a too rapid decrease in BP. Furthermore, both ACE-inhibitors and diuretics are considered as standard therapy in CHF.

Diuretics + AT_1-blockers (ARB)

This is proven to be a more effective combination for the treatment of hypertension with left ventricular hypertrophy than beta-blockers + + diuretics [10]. ISH is also a condition in which this combination could successfully be applied [11]. It may also be beneficial for those with hypertension and CHF.

Diuretics + imidazoline (I_1) receptor agonists

This combination, which has not been studied on any large scale, can be considered if a beta-blocker cannot be added to a diuretic agent because of contraindications.

Diuretics + calcium antagonist (dihydropyridines)

Dihydropyridine calcium antagonists, known to be potent vasodilators, can concomitantly be administered with diuretics in ISH-patients, who are usually elderly. There exists evidence both for diuretics [4, 5] and for dihydropyridine calcium antagonists [6] (although not so clearly for their combination) that they are effective in lowering BP in ISH, as well as for protective activity towards complications of hypertensive disease. Importantly, the association of a calcium antagonist with a diuretic has been used in the FEVER, ELSA, and VALUE trials [20–22] to great benefits.

Alpha-blockers + beta-blockers

This combination may be used in accelerated hypertension. There is little evidence for the efficacy of this combination. Accelerated hypertension is probably based on sympathetic hyperactivity and its sequelae. For this reason, sympatholytic activity, as caused by both drugs of the combination, appears to be a logical therapeutic approach. For sympathetic overactivity, centrally acting antihypertensives (clonidine, imidazoline I_1 receptor stimulants) and non-dihydropyridine calcium antagonists may also be considered.

Beta-blockers + ACE-inhibitors

Although the antihypertensive effect of this combination is less than that of diuretics + beta-blockers [12], it could be used in hypertensive patients after myocardial infarction (MI) in those with coronary heart disease (CHD) or with CHF [8].

Calcium antagonists (dihydropyridine-type!) + beta-blockers

Patients with hypertension and CHD can be treated by this combination. Both types of drugs, as well as being efficacious antihypertensives, are known to display beneficial activity in CHD patients. The fixed combination of the two types of drugs can help improve patients' therapeutic compliance [17].

Calcium antagonists + ACE-inhibitors

This combination can be suggested for the treatment of hypertensive patients with nephropathy, CHD, or established atherosclerosis. The combination displays pronounced antihypertensive activity. Ca-antagonists are known to have anti-ischaemic activity in CHD. ACE-inhibitors are proven to be renoprotective, particularly in patients with diabetic nephropathy. Calcium antagonists, as shown for lacidipine in the ELSA study [9], amlodipine in the PREVENT study [13], and nifedipine-GITS in the INSIGHT study [14], are proven to display anti-atherogenic activity. For ACE-inhibitors this effect has also been revealed (SECURE study) [15]. The combination amlodipine–perindopril was widely used in the ASCOT study, being more effective in lowering BP and cardiovascular events than the combination of a beta-blocker with a thiazide [18]. In the ACCOMPLISH trial the incidence of the primary endpoint (a composite of several cardiovascular fatal and nonfatal events) was 20% less in patients on benazepril–amlodipine combination than in the group receiving the benazepril–hydrochlorothiazide combination, with a significant reduction also in cause-specific events such as myocardial infarction, although not heart failure [19].

Calcium antagonists (dihydropyridines) + AT_1-blockers

The presumed beneficial effects of this combination are globally the same as for the combination calcium-antagonists + ACE-inhibitors [16]. The renoprotective activity in diabetic (type 2) nephropathy appears to be well established [9]. Dihydropyridine-type calcium antagonists and the AT1-blocker losartan are known to display uricosuric activity, which may be advantageous also in patients with gout.

ACE-inhibitors + AT_1-blockers

This combination can be considered in hypertensive patients with diabetic nephropathy as well as with glomerulonephritis, since both types of drugs have been shown to decrease proteinuria more than the individual components, so they may display renoprotective activity. The widespread use of this combination has now been questioned by the results of ONTARGET [23––24], in which the combination of full doses of telmisartan and ramipril reduced the initial BP values slightly more than the reduction seen with the administration of one or the other drug alone, without, however, any further reduction in cardiovascular or renal endpoints (except proteinuria), and indeed with a greater number of renal side effects and a more frequent discontinuation of the initial treatment.

ACE-inhibitors + imidazoline receptor agonists

Theoretically this combination could be considered if it were desirable to simultaneously suppress the activities of both the renin–angiotensin aldos-

terone system (RAAS) and the sympathetic nervous system (SNS). The metabolic syndrome has been proposed as a target for SNS-suppressant drugs such as moxonidine or rilmenidine, since this syndrome is believed to be partly the result of SNS-hyperactivity.

AT_1-blockers+ direct renin inhibitors
Preliminary findings using the direct renin inhibitor aliskiren in the AVOID trial have demonstrated further reductions in proteinuria when combined with valsartan [25].

Triple combinations

A few suggestions have been put forward for triple combinations involving different antihypertensive drugs. These combinations are put together on merely theoretical grounds, virtually without formal clinical evidence. Arguments in favour of the use of one particular category of drugs are the same as those discussed above for the components of combinations of two different drugs. The following drug combinations are conceivable:

Diuretics + beta-blockers + calcium antagonists
A very potent combination which could be used in the treatment of accelerated hypertension.

Diuretics + calcium antagonists + ACE-inhibitors
Potentially beneficial in the treatment of diabetic hypertensive patients, of those with accelerated hypertension or ISH.

AT_1-antagonists + calcium antagonists + diuretics
This triple combination may help reach the target BP (< 130/85 mm Hg) in hypertensive patients with type-2 diabetes mellitus or with ISH.

ACE-inhibitors + alpha1-adrenoreceptor antagonists + imidazoline agonists
Potentially beneficial in the treatment of diabetic hypertensive patients or for those with metabolic syndrome, in particular when beta-blockers are contra-indicated or not well tolerated.

ACE-inhibitors + Ca-antagonists + beta-blockers
Potentially beneficial in hypertensive patients with coronary heart disease.

Conclusions

Combination therapy has become widely accepted for the management of hypertensive disease and a substantial fraction of patients is best treated by two or frequently three antihypertensive drugs. Tablets with fixed combination of two drugs will facilitate the therapeutic schedule and thus improve patient compliance. Use of fixed dose combinations of two drugs can directly follow initial monotherapy when addition of a second drug is required to control BP, or it can be the first treatment step when a high cardiovascular risk makes early BP control desirable. This approach is now facilitated by the availability of different fixed dose combinations of the same two drugs, which minimizes one of its inconveniences, i.e. the inability to only increase the dose of one drug but not that of the other.

The choice of drug combinations is mainly based upon haemodynamic and metabolic criteria, and for most combinations formal evidence has not (yet) been put forward.

Drugs	Potential use
Beta-blockers + diuretics	Hypertension + congestive heart failure (CHF)
Diuretics + ACE-inhibitors	Hypertension + CHF, Isolated systolic hypertension (ISH), hypertension in the elderly
Diuretics + AT_1-blockers	ISH + CHF, ISH
Diuretics + imidazoline (I_1)-receptor agonists	To be used when a β-blocker (contraindications) cannot be added to a diuretic
Diuretics + calcium-antagonists (dihydropyridines)	ISH (usually elderly patients)
Beta-blockers + α-blockers	Accelerated hypertension
Beta-blockers + ACE-inhibitors	Hypertensives: post MI (sec. prevention) CHD, CHF
Ca-antagonist + β-blockers	Hypertension + CHD
Ca-antagonist + ACE-inhibitors	Hypertension + nephropathy, CHD or atherosclerosis
Ca-antagonists+AT_1-blockers	Hypertension+ nephropathy, CHD or atherosclerosis
ACE-inhibitors + AT_1-blockers	Hypertension + proteinuric nephropathy
ACE-inhibitors + imidazoline (I_1)-receptor agonists	Patients with activated RAAS and SNS
Diuretics + β-blockers + calcium antagonists	Accelerated hypertension
Diuretics + calcium antagonists + ACE-inhibitors	Accelerated hypertension ISH, hypertension + diabetes mellitus
Diuretics + calcium antagonists + AT_1-antagonists	Ibid.
ACE-inhibitors + α_1-blockers + imidazoline (I_1)-receptor agonists	Hypertension + diabetes mellitus, metabolic syndrome
ACE-inhibitors + Ca-antagonists + β-blockers	Hypertension + CHD

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THE CLINICAL VALUE OF AMBULATORY BLOOD PRESSURE MONITORING

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Introduction

Initially reserved for research purposes, ambulatory blood pressure (BP) monitoring (ABPM) has gradually entered the standard medical practice and is now a widely used clinical tool both for diagnostic purposes and for assessment of treatment efficacy [1, 2].

Technical aspects

The number of devices available for ABPM continues to increase. Devices based on auscultatory and those based on oscillometric methods are available, although in most cases the oscillometric approach is now preferred. In order to be acceptable for practical use, a device must have been validated [3] according to international protocols [4, 5]. One of these protocols has been described by the Working Group on ABPM of the European Society of Hypertension [6] and has recently been updated to facilitate its implementation in different laboratories [7].

All ABPM devices available for practical use allow BP to be only intermittently sampled. Different sampling intervals can be adopted, although it is recommended not to exceed 20–30 minutes to avoid incorrect estimates of 24h-day- or night-time BP values, while intervals no longer than 15 minutes are required to reliably assess 24-h BP standard deviation, a measure of BP variability [8]. The current routine using sampling intervals longer at night than during the day, to avoid disturbance of night sleep, has little scientific background [9] and may lead to errors in estimating the average of night-time BP. Before starting the ambulatory monitoring it is advisable to perform two auscultatory measurements on the contralateral arm in parallel with the first automated readings, aimed at ensuring that differences do not exceed ± 5 mm Hg due to local mismatch between arm and cuff size, or due to incorrect cuff application. Patients must also be instructed to live their usual life during the recording, avoiding unusual strenuous exercise. They should also be instructed to fill in a diary, by recording unusual events and quality/duration of night sleep [10].

Diagnostic use

Evidence is available that 24-h, day- or night-time average BP values correlate with sub-clinical organ damage more closely than office values [11]. Evidence is also available that 1) in the general population and in hypertensive patients ambulatory BP values are more predictive of cardiovascular risk than office values [12–15], and 2) in hypertensive patients the regression of clinically important organ damage (such as left ventricular hypertrophy) is more closely predicted by treatment-induced changes in average ABP than in office BPs [16]. This has justified the increasing use of ABPM for diagnostic purposes [17]. However, it should be kept in mind that in the general population ABPM values are much lower than the equivalent office values. Based on cross-sectional population studies [18] the threshold values to diagnose hypertension for 24-h average BP are 125/80 mm Hg [1] while the equivalent office values are 140/90 mm Hg.

Isolated office (white coat) hypertension

Continued use of office and ambulatory BP measurements has allowed the identification of a condition characterized by persistently elevated office BP and persistently normal ambulatory BP [19]. Most data indicate that this condition (which occurs in about 10% [20] of the population) is associated with a lower cardiovascular risk than the condition characterized by both office and ambulatory BP elevation. Conflicting data about the prevalence of organ damage, cardiovascular risk, and proneness to future hypertension make it still uncertain whether it represents a truly innocent phenomenon as compared to other BP categories [20–35].

This suggests that caution should be exercised when deciding whether these patients should or should not be treated. Non-drug treatment should always be implemented and drugs prescribed in case of organ damage or for high-risk profile patients. If treatment is not started, a close follow-up is recommended.

Masked hypertension (reverse white coat hypertension)

When comparing office with ABPM and home BP measurement, it is possible to identify patients whose BP values are normal in the office and abnormal outside the office, a condition termed as "masked hypertension" [36]. In terms of prevalence, there are important differences according to the studied population, with values between 10 and 40%. Cross-sectional studies have shown that masked hypertension is associated with increased left ventricular mass and carotid intima-media thickness, and with impaired large artery distensibility [37–40]. Epidemiological prospective studies suggest that masked hypertension is an independent predictor of cardiovascular morbidity and a strong predictor of cardiovascular risk [31, 35, 41––51]. Several factors can raise ambulatory BP, increasing the likelihood of having masked hypertension, either because of stressful events during daytime or because of disturbance of night sleep, as in the case of obstructive sleep apnoea [47, 52].

Clinical relevance of 24-h ABP profiles and BP variability within the 24 hours

Several components of the 24-h BP profile have been shown to have clinical importance. The possible prognostic value of BP increase in the morning, on going from sleep to wakefulness and daytime activities, known as **morning BP surge**, has been investigated in many studies, based on the reports that a pronounced morning BP surge might predict cardiovascular events [53]. However, there is no solid demonstration yet of the occurrence of a cause-effect relationship between morning BP surge and cardiovascular events, most of the available evidence being only in favour of an association of morning BP rise with a morning peak incidence of coronary heart disease and stroke [54–56]. Indeed, other factors, in addition to morning BP rise, might explain the higher rate of cardiovascular events during this time period, including a concomitant increase in platelet aggregability and reduction in fibrinolytic activity. It seems nevertheless advisable for the physician to ensure that antihypertensive treatment lowers BP also in the morning after arousal with no escape from the reduction seen in the remaining 24-h. **Night-time BP reduction ("dipping")** — BP falls at night but more so in some subjects than in others. This led to the classification of hypertensive patients into dippers and non-dippers, based on a nocturnal BP fall of more or less than 10% of daytime values, respectively [56, 57]. The main limitations of patient classification based on the nocturnal BP dipping rate are related to poor reproducibility of the magnitude of night-time hypotension [58] (in relation to differences in sleep quality/depth) and to the fact that a cut off value for a nocturnal BP fall of 10% of daytime BP levels to separate dippers from non dippers, is an arbitrary selection [18]. Moreover, the level of nocturnal BP rather than the dipping rate seems to be a stronger predictor of outcome [59]. Indeed, several studies have shown that night-time BP is related to target organ damage and cardiovascular risk [60–69], and some authors have reported a higher prognostic value of nocturnal vs. daytime BP [13]. It should be acknowledged, however, that in most studies day and night BP values and their changes with treatment have been shown to be characterized by a close relationship [16, 58, 70, 71]. In clinical practice a 24-h ABPM should definitely include BP values obtained during the night period, and treatment should ensure that both day- and night-time BP levels are smoothly reduced. Special attention should be paid to patients in whom the night is associated with no reduction (or even an increase) in BP (provided that subjects not sleeping at night are excluded) because this suggests the existence of a marked degree of vascular damage and autonomic dysfunction, as well as a considerable hypertension severity. The possibility of an obstructive sleep apnoea condition should also be considered in these patients [72]. In addition, special attention should be paid to subjects with a very pronounced reduction in night-time BP (> 20%, so-called extreme dippers) because this may lead to brain under-perfusion, particularly if a further BP fall is induced by the treatment [73].

BP variability — evidence is available that for a given increase in BP, organ damage and prognosis are worsened by a greater 24-h BP variability [38, 74–77]. Increasing evidence is accumulating that BP variability might indeed represent an additional risk factor on top of increased mean BP levels, although the size of such an additional contribution to cardiovascular risk and the impact of a treatment-induced reduction in BP variability on patient outcome are still unresolved research issues [78–80].

Efficacy of antihypertensive treatment

ABPM has drastically improved the ability to assess the efficacy of antihypertensive treatment both in clinical studies and in medical practice [81–84], with results often different from those obtained by focusing on clinic visits only [85]. In clinical trials advantages such as a greater reproducibility, the lack of placebo effect, and the absence of an alerting-dependant BP response [84] make ABPM the ideal approach to quantify the antihypertensive effect of new antihypertensive drugs, drug combinations, or non-pharmacological measures. It also allows the study of the extent and the distribution of the BP lowering effect of different antihypertensive drugs, and a comparison between different drugs and/or different doses being quantitatively facilitated by use of indices such as the trough-to-peak ratio and the smoothness

index [80, 84, 85]. To some extent this is also possible in the medical practice, if ABPM is performed before and during treatment. A limitation, however, for such a daily clinical application is the yet incomplete knowledge of the ABP values to be reached by treatment in order to obtain the same degree of cardiovascular protection offered by achieving the office BP targets shown by outcome studies to ensure significant reduction in cardiovascular risk.

Conclusions

ABPM has opened new horizons for hypertension research, and its progressively greater, use has had a positive impact on clinical practice. Its adoption can thus be recommended, when facilities are available, in a larger number of patients, as compared to what was indicated in previous recommendations. The usefulness of ABPM is particularly evident in patients with consistent discrepancies between clinic and home BP levels, in those with elevated clinic BP but no evidence of organ damage, in patients with high cardiovascular risk and in those in whom information on night--time BP levels and on the degree of BP fluctuations may be particularly relevant. However, further research is still needed to collect additional information on a number of important and yet partly unresolved issues, such as the actual role of ambulatory BP variability, the ABP targets to be achieved by treatment, the clinical importance of isolated clinic or white coat hypertension, and the clinical and pathophysiological meaning of specific ambulatory BP patterns within 24 hours.

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HIGH BLOOD PRESSURE, SMOKING AND CARDIOVASCULAR RISK

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Introduction

Tobacco use and high blood pressure have been identified as two major cardiovascular risk factors, accounting for the greatest proportion of total and cardiovascular mortality worldwide. Indeed, according to the latest estimations of the World Health Organization, more than 5.1 million deaths a year are attributable to smoking and no less than 7.5 million to high blood pressure [1]. If current trends persist, tobacco will kill more than 8 million people worldwide each year by the year 2030, with 80% of these premature deaths in low- and middle-income countries.

The prevalence of smoking is estimated at around 33% of the adult population all over the world (in men ~ 35% in high-resource countries, up to 50% in developing countries; among women ~ 22% and 9% in low- and middle-resource countries, respectively) [2], and high blood pressure (≥ 140/90 mm Hg) is found in around 26% of the adult population in most countries, either developed or developing [3].

Cardiovascular effects of smoking

Smoking and hypertension often coexist sharing multiple pathophysiological mechanisms and cardiovascular consequences (Table 1). Furthermore, they interact with other cardiovascular risk factors, as shown in Table 2 [4].

The cardiovascular responses to smoking represent a complex interplay between haemodynamic factors, autonomic nervous system, and multiple vasoactive mediators. Cigarette smoking has been linked to endothelial dysfunction [5], accelerated atherosclerosis, decreased arterial compliance [6], and impaired arterial baroreflex sensitivity [7]. Cigarette smoking increases sympathetic nerve traffic to blood vessels, to the skin, and to the heart [8, 9]. Haemodynamic responses to smoking include increased heart rate and blood pressure, and myocardial contractility [10]. These acute responses occur within one to two minutes of smoking and result in increased myocardial oxygen demand. The pressor and tachycardiac effects of smoking last for at least 30 minutes [11].

Despite the acute pressor effect of cigarette smoking, several earlier epidemiological studies failed to confirm an independent link between smoking and risk of hypertension. However, the vast majority of these studies were based on office measurements in subjects abstaining from smoking. Blood pressure measured in the office is consistently lower than the blood pressure to which subjects are exposed during actual smoking. Indeed, ambulatory daytime blood pressure is higher in hypertensive smokers than in non-smokers with similar office blood pressure (Figure 1) [12–14]. Furthermore, long-term epidemiological studies have shown that cigarette smoking is associated with development of hypertension independently of baseline blood pressure and various other lifestyle factors [15].

Table 1. Cardiovascular consequences of smoking

Cardiac effects

Coronary arteries:
- atherosclerosis in native circulation
- restenosis after angioplasty
- atherosclerosis in bypass grafts
- vasoconstriction

Arrhythmias and sudden death

Left ventricular hypertrophy

Cerebral effects

Stroke

TIA

Recurrent carotid artery stenosis after endarterectomy

Other arterial pathology

Aortic atherosclerosis

Iliofemoral atherosclerosis

Intermittent claudication

Lower limb ischaemia and amputations

Recurrent atherosclerosis of bypass grafts

Abdominal aortic aneurysm

Renal artery stenosis

Failure of skin grafts

Uteroplacental arterial hyperplasia

Diabetic microangiopathy

Smoking cessation strategies in hypertensive patients

Smoking cessation is the only intervention with the potential to reduce tobacco-related morbidity and mortality in the short and medium term. The techniques used for smoking cessation or treatment of tobacco dependence include a range of techniques such as motivation, counselling, telephone or internet support, as well as pharmaceutical aids for patients. The success of these interventions depends on their synergistic use as well as the public-health approach and media support. The effective strategies for smoking reduction include a smoke-free workplace and increasing cigarettes taxation, among others [16].

Every health care worker's responsibility should be monitoring tobacco use and assisting in the process of discontinuing use of tobacco products

Table 2. Interactions between smoking, hypertension, and other cardiovascular risk factors

Blood pressure

Rises with smoking

Hypertensive smokers:
- are harder to achieve optimal BP control in
- have a worse prognosis
- are more likely to have atherosclerotic renovascular hypertension
- are more likely to develop malignant hypertension

Serum lipids

Increased levels of LDL-cholesterol, free fatty acids, and triglycerides

Decreased HDL-cholesterol level

Obesity

As a rule, smokers have lower body weight

Hematorheology

Increased fibrinogen, blood viscosity, leukocyte count, haematocrit, and platelet aggregation

Decreased platelet survival and bleeding time, erythrocyte

Oral contraceptives

Substantial increase in risk of MI, stroke and thromboembolic events

Hormonal and metabolic changes

Increased plasma oestradiol (men) and vasopressin, and impaired glucose tolerance

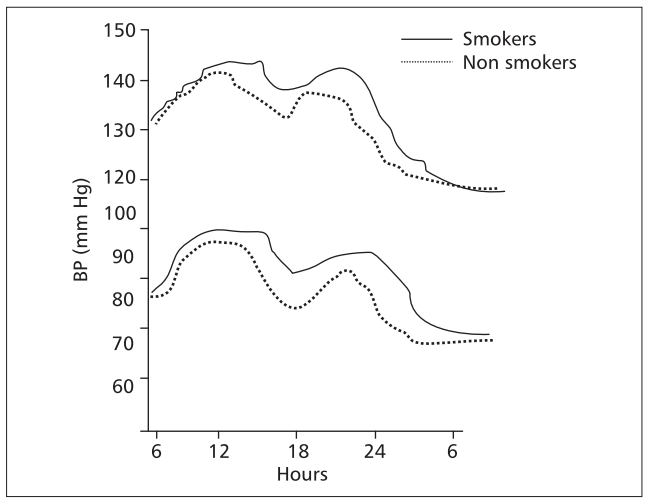

Figure 1. 24-hour blood pressure monitoring profiles in smokers and non-smokers (modified from ref [14])

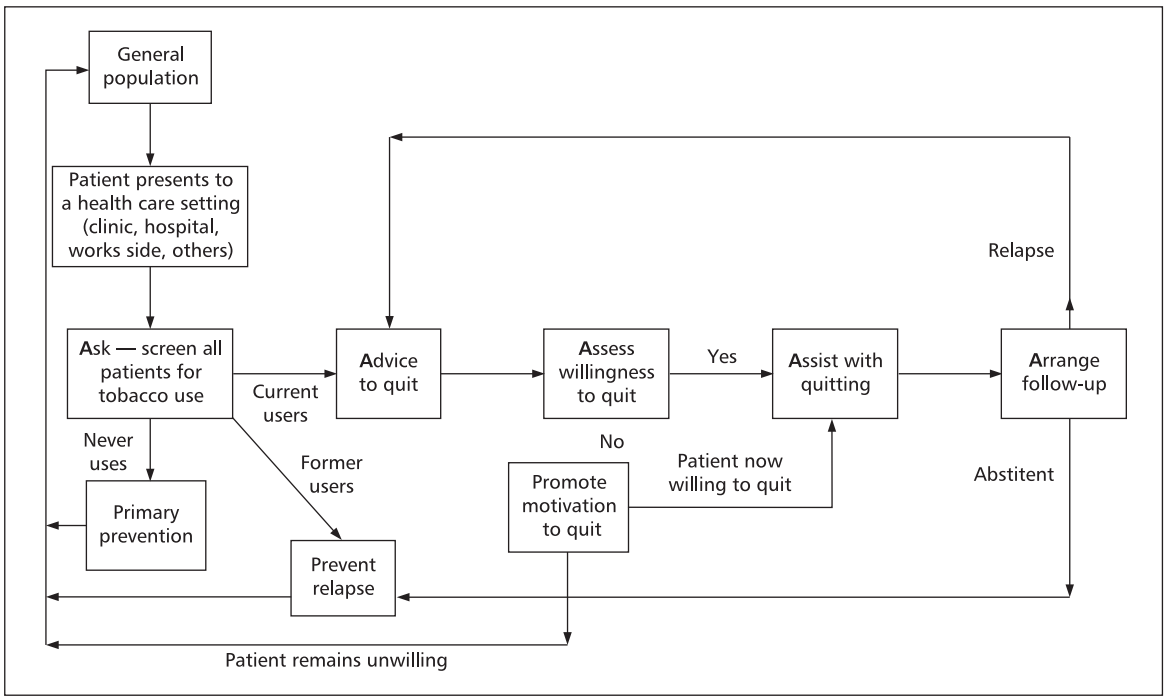

Figure 2. Model for treatment of tobacco use and dependence (modified from ref [16])

in every seen patient. The approach to treatment of tobacco dependence and discontinuing tobacco products use depends highly on the patient's willingness to discontinue smoking. Therefore, it is crucial to asses the readiness of every smoker to take part in the smoking cessation programs. If the patient remains unwilling to quit smoking one should keep on motivating the patient to quit and re-asses the patient's decision (Figure 2). It is important to remember that tailored interventions based on, for example, stages of change, do not consistently produce higher long-term quit rates than non-tailored interventions of the same intensity [17].

Minimal interventions, and other types of counselling strategies delivered by physicians, have a quitting rate of approximately 10.2% (range 8.5–12.0%). Certain types of counselling strategies are especially effective. Practical counselling (problem solving/skills-training approaches) and social support are associated with significant increases in abstinence rates. It is also important that with the growing amount of time spent on a single session as well as with the increase of the number of sessions smoking quitting rates may increase to up to 25%.

The quitting rates may also be improved by pharmacotherapy. The first-line medications include: bupropion SR, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline. Certain combinations of cessation medications may be effective. Therefore, their use should be encouraged for all smokers except in the presence of contraindications or for specific populations for which there is insufficient evidence of effectiveness. In addition, combining counselling and medication increases abstinence rates.

The population of hypertensive and coronary artery disease patients should be aggressively counselled on smoking cessation to lower the total cardiovascular risk [18]. The use of behavioural and counselling schemes should be delivered to those groups of patients to the same extent as to the general population. It was also observed that the application of nicotine replacement therapy or one of the first line therapy drugs for nicotine dependence is not connected with cardio-vascular event rate increases [19– 21].

Two final considerations are related to harm reduction strategy and frequent relapse. Concerning the later, during the following 12 months after an attempt to quit around 70% of abstainers totally or partially relapse. This is similar to the situation in hypertension control (more than 60–70% of hypertensives under treatment remain with their blood pressure figures uncontrolled). Physicians have to be aware of the chronic nature of tobacco dependence and therefore provide their patients with proper support and relapse prevention after the stopping date. The consequence of tobacco dependence as a chronic condition is that the definitive abstinence from smoking very often comes only after several quitting attempts [22]. In relation to the harm reduction strategy, it has been postulated in recent years with the aim of facilitating the integration of smoking cessation interventions in daily clinical practice, assuming that the reduction of risk is an optional objective when the complete abstinence is very difficult or even impossible [23]. Needless to say, full abstinence, like full hypertension control, remains the main goal of the physicians' intervention.

Smoking cessation is probably the single most powerful lifestyle measure for the prevention of cardiovascular disease. The potential benefits of smoking cessation are similar to those of antihypertensive-treatment. Fortunately there is a growing involvement of governments and authorities to implement smoking-banning strategies as well as developing social and medical support for the tobacco use cessation process [24]. Because of the long time delay for the development of tobacco related diseases, the impact of smoking-caused diseases on mortality in low- and middle-income countries — and for women in many regions — will continue to rise for at least two decades, even if efforts to reduce smoking are relatively successful. Therefore, still more intensive efforts are needed to achieve more involvement of physicians and other health professionals in smoking cessation at a clinical level, and in smoking prevention and control at a community level [25].

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TREATMENT OF HYPERTENSION IN DIALYSED PATIENTS

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Introduction

Hypertension is one of the most important risk factors for cardiovascular disease, the leading cause of mortality and morbidity in dialysis. It has been found in 80% of patients at pre-dialysis state, in 60% of patients with haemodialysis, and in 30% of those with peritoneal dialysis [1, 2].

The relationship between hypertension and cardiovascular mortality/ /morbidity is apparently controversial in dialysed patients because of the high prevalence of comorbid conditions, the underlying vascular pathology, and the effects of dialysis on blood pressure. The effects of age, left ventricular hypertrophy/dysfunction (which are also more prevalent in patients with hypertension), and poor nutrition may mask the true relationship between blood pressure and mortality in dialysed patients [3].

Hypertension has been associated with stroke, ventricular dysrhythmias, and progression of atherosclerosis in patients on haemodialysis. Improved survival due to adequate blood pressure control of dialysed patients has been clearly demonstrated, stressing the importance of adequate antihypertensive treatment [4].

The aetiology of hypertension in dialysis patients is multifactorial [5] (Table 1).

Blood pressure measurement in dialysis patients

Pre- or post-dialysis blood pressure measurements in patients with haemodialysis may be misleading for a diagnosis of hypertension. The pre-dialysis systolic blood pressure may overestimate, whereas the post-dialysis systolic blood pressure may underestimate, the mean inter-dialytic systolic blood pressure by 10 mm Hg and the mean diastolic blood pressure by 7 mm Hg [6]. The post-dialysis systolic blood pressure measurement could be more reflective of interdialytic blood pressure [7].

Ambulatory pressure monitoring (ABPM) has shown that blood pressure is frequently high in pre-dialysis, falls immediately after dialysis, and then gradually increases during the inter-dialytic period. ABPM may be useful in determining the 'systolic blood pressure load', which is an important factor in the development of left ventricular hypertrophy. Pre-dialysis blood pressure correlates better with left ventricular hypertrophy than post-dialysis blood pressure measurement does [8]. Dialysed patients usually lose the diurnal variation in blood pressure, and consequently these patients develop nocturnal hypertension.

Home blood pressure measurement, an increasingly popular method, may also be useful for estimating blood pressure control in dialysed patients [9]. One study proposed that blood pressure measurements if made after a midweek dialysis twice a day for four days would be sufficient to detect the presence of left ventricular hypertrophy and outcomes in these patients [10].

Target blood pressure of hypertensive dialysed patients

For most patients on dialysis (mainly in older age) the goal blood pressure is less than an average value below 150/90 mm Hg on no medication. For dialysis patients the recommended goal blood pressure levels should be a pre-dialysis value of below 140/90 mm Hg and a post-dialysis value of below 130/80 mm Hg. The reasonable target goal of mean ambulatory blood pressure is less than 135/85 mm Hg during the day and less than 120/ /80 mm Hg at night [5]. After adjustment for typical demographic and clinical characteristics, including modified comorbidity score (ICED or Charlson), pre-dialysis systolic blood pressure less than 120 mm Hg was associated with increased death risk [11, 12]. The suggested target ranges, need to be set for haemodialysis patients based on their clinical status, diagnosis, age, cardiac condition, neuropathy, and comorbid conditions. Very low systolic blood pressure (< 110 mm Hg) may be associated with enhanced cardiovascular mortality ('J'-or 'U'-shaped curve). An algorithm for blood pressure control is given in Table 2 [13].

Table 1. Aetiology of hypertension in dialysed patients

Sodium and volume excess due to diminished sodium excretory capacity of kidney
Activation of the renin–angiotensin–aldosterone system
Increased activity of the sympathetic nervous system
Increased endogenous vasoconstrictor (endothelin-1, Na-K-ATPase inhibitors, adrenomedullin), and decreased vasodilator (nitric oxide, prostaglandins) compounds
Frequent administration of erythropoietin
Increased intracellular calcium content, induced by parathyroid hormone excess
Hyperparathyroidism and hypercalcaemia
Use of recombinant human erythropoietin
Calcification of arterial tree, arterial stiffness
Pre-existent hypertension
Nocturnal hypoxaemia, frequent sleep apnoea

Non-pharmacological treatment of hypertension in dialysed patients

Control of plasma volume can either normalize blood pressure or help normalize blood pressure in dialysed patients. Multiple clinical defnitions of stable 'dry weight' have been advanced: 1) either the blood pressure has normalized or symptoms of hypervolaemia disappear (not merely the absence of oedema); 2) after dialysis, seated blood pressure is optimal, and symptomatic orthostatic hypotension and clinical signs of fluid overload are not present; and 3) at the end of dialysis, patients remain normotensive until the next dialysis without antihypertensive medication.

Some factors may limit fluid removal by predisposing to episodes of hypotension during haemodialysis treatment because hypotension is one of the important cardiovascular risk factors. Limiting control of volume overload in dialysis patients has been indicated as a lag phenomenon.

To avoid large inter-dialytic weight gains, patients should restrict salt intake (750–1000 mg of sodium/day). This also decreases thirst (an important factor of patient compliance). A fixed low dialysate sodium concentration with a combination of dietary salt restriction or a programmed decrease in sodium dialysate concentration (from 155 to 135 Meq/l) may result in smaller doses of antihypertensive drugs being needed to control blood pressure.

Long, slow haemodialysis treatment (eight hours, three times a week) is associated with the maintenance of normotension without medication in almost all patients because this decreases afferent renal nerve activity and efferent sympathetic activation. Nocturnal haemodialysis treatment (six or seven nights a week during sleep hours) can also normalize blood pressure without medication in most patients.

More frequent haemodialysis treatment (two hours, six times per week) may also be associated with normotension without medication and with regression of left ventricular hypertrophy.

Bilateral nephrectomy may be considered in those rare non-compliant individuals with life-threatening hypertension, whose blood pressure cannot be controlled with any of the above-detailed dialysis modalities.

The clinician must define the dry weight and goal blood pressure for each dialysed patient based upon his or her best judgment.

Lifestyle changes should include increasing exercise, losing weight if overweight, limiting alcohol intake, stopping the use of medications that increase blood pressure, and discontinuation of tobacco use (Table 3) [14, 15].

Table 2. Algorithm for blood pressure control in dialysis patients

Estimate dry weight
Determine Hypertension Severity Index
Initiate non-pharmacological treatment
Attain dry weight
Start or increase the dose of antihypertensives to maintain blood pressure below 150/90 mm Hg
If blood pressure is not controlled or dry weight not attained in 30 days, consider: 24–48-h ambulatory pressure monitoring; increasing time of dialysis to facilitate removal of fluid and attainment of dry weight; discontinuing sodium modelling; increasing the dose or number of antihypertensives
If blood pressure remains uncontrolled, consider: evaluating for secondary forms of hypertension; peritoneal dialysis bilateral nephrectomy (exceptional)

Pharmacological treatment of hypertension in dialysed patients

Antihypertensive drug therapy is necessary in 25–30% of patients. The type of drug or antihypertensive combination depends on the severity of hypertension (Table 4) and comorbidities.

To calculate for an individual dialysis treatment, sum the pre-dialysis systolic and diastolic and post-dialysis systolic and diastolic blood pressure scores. The hypertension severity index can range from 0 to 12.

Nocturnal dosing of once daily antihypertensive medication is preferred in order to try to minimize the occurence of intradialytic hypotension [16].

Table 5 shows the compelling indications of antihypertensive drugs, their specific side-effects, and special important precautions.

Antihypertensive drugs

Calcium channel blockers are very effective and well tolerated in dialysis patients, even in those who are volume expanded. They are useful in patients with left ventricular hypertrophy, diastolic dysfunction, and stabile angina pectoris. Calcium channel blockers do not require supplementary post-dialysis dosing. Calcium channel blockers have a unique feature among dialysis patients — a prospective cohort study from USRDS showed a significant 26% reduction in cardiovascular mortality.

Inhibitors of the renin–angiotensin system ought to be considered as first-line agents for blood pressure control in haemodialysis patients because of their documented beneficial effect on left ventricular hypertrophy, arterial stiffness, and endothelial cell function [16].

Angiotensin-converting enzyme (ACE) inhibitors are effective and well tolerated in dialysis patients. They are useful in patients with left ventricular hypertrophy, and in those with heart failure due to systolic dysfunction. ACE inhibitors reduce mortality in hypertensive patients undergoing maintenance dialysis. Significantly lower mortality was observed among ACE inhibitor-treated dialysis patients (< 65 years of age). This survival benefit was independent of antihypertensive effect. These drugs can reduce the synthesis/ /secretion of endogenous erythropoietin and can trigger an anaphylactoid reaction in patients dialysed with AN69 dialyser.

There is only limited experience with angiotensin II receptor blockers (ARBs) in end-stage renal disease. Losartan does not enhance the risk of anaphylactoid dialyser reactions that may occur with the ACE inhibitors. No dose adjustment is necessary in renal failure in the absence of volume depletion. The KDOQI gudelines suggest that these agents are preferred in dialysis patients with hypertension and significant residual renal function [17]. Aliskiren is the first in the class of direct renin inhibitors, and it has not yet been evaluated in patients on haemodialysis. The use of aldosteron antagonists in haemodialysis patients has not been fully investigated to date. The role of endothelin antagonists in controlling blood pressure in haemodialysis patients has not been tested.

Beta-blockers are indicated in dialysis patients after myocardial infarction. Potential side-effects include central nervous system depression (mainly lipid-soluble drugs), bradycardia, and heart failure. A preferable blocker may be labetalol or carvedilol, which have a lower incidence of bronchospasm and have a neutral effect on plasma lipid levels. Atenolol, administered three times a week post-dialysis, may be effective.

Peripheral alpha-1 adrenergic receptor blocker (prazosin, doxazosin) would help to counteract the increase in sympathetic nerve activity. In long--term treatment, the favourable metabolic effects (on lipids and insulin resistance) might be advantageous. These drugs are preferred in antihypertensive combinations.

Centrally acting drugs (methyldopa, clonidine, guanfacine) have more side-effects than those described above. Newer imidazoline receptor agonists (moxonidine, rilmenidine) are considered to be safe and effective, but only limited experience is available.

The pharmacokinetics of frequently used antihypertensive drugs in dialysis patients are given in the Appendix [18].

Table 3. Non-pharmacological treatment of hypertension in dialysis patients

Aerobic exercise
Control of salt and fluid intake
Cessation of smoking
Weight reduction
Avoidance of alcohol
Long, slow, and more frequent haemodialysis treatment
Bilateral nephrectomy

Table 4. Hypertension severity index (HSI)

HSI score	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
0	< 150	< 90
1	150–159	90–99
2	160–179	100–109
3	> 179	> 109

Special situations

Treatment of refractory hypertension in hypertensive dialysis patients

Use of minoxidil (the strongest direct vasodilator) may be effective in reducing blood pressure. Dialysed patients who are non-compliant, and in whom volume status and hypertension cannot be adequately controlled, may benefit from switching to continuous ambulant peritoneal dialysis.

Treatment of erythropoietin-induced hypertension

An attempt should be made to 1) decrease the actual dry weight; 2) decrease the dose (if possible) or interrupt treatment, and reintroduce later at lower dosage; and 3) introduce or increase antihypertensive medication, preferably calcium channel blockers [19].

Treatment of hypertension in diabetic dialysis patients

The number of dialysis patients with type-2 diabetes mellitus is rapidly increasing, and these patients are generally hypertensive. Exchangeable sodium is increased in diabetic patients, and orthostatic hypotension, due to autonomic neuropathy, and dialysis hypotension, with severe symptoms, coronary artery disease, and vascular atherosclerosis, are frequent. Longer dialysis, slow ultrafiltration rate, haemofiltration, and glucose-containing dialysate can be used to avoid the risk of severe hypotension. ACE inhibitors and ARBs decrease blood pressure and may prevent end-organ vascular diseases. Calcium channel blockers are effective in reducing blood pressure but may result in severe hypotensive episodes. Benefit from blockade is particularly significant in patients with type-2 diabetes mellitus and coronary heart disease.

Conclusions

The progress of dialysis technology leads to better tolerated dialysis treatment and more adequate removal of sodium-water overload. Treatment of hypertension in dialysis patients still remains a careful clinical judgment: adequate evaluation of the dry weight, choice of adequate treatment time, and frequency. For those patients in whom ultra-filtration and maintenance of dry weight do not adequately control hypertension, antihypertensive medications are indicated [20–26]. Randomized clinical trials suggested some benefit from antihypertensive therapy among haemodialysis patients [27], and treatment with agents to lower blood pressure should routinely be considered for individuals undergoing dialysis to reduce the very high cardiovascular morbidity and mortality rate in this population [28].

Table 5. Use of antihypertensive drugs in haemodialysis patients

Drugs	Compelling indication	Specifc side-effects	Special precautions
Angiotensin-converting enzyme inhibitors	Left ventricular hypertrophy Heart failure Diabetes mellitus	Anaphylactic reactions with AN69 dialysator	
Dihydropyridine calcium channel blockers	Associated coronary heart disease		
Non-dihydropyridine calcium channel blockers	Associated coronary heart disease		Avoid combination with blockers
Beta-blockers	Associated coronary heart disease	Excessive bradycardia with liposoluble compounds	Avoid combination with non-dihydropyridine calcium channel blockers
Centrally acting anti-adrenergic drugs $\alpha 2$ or I1 receptor (agonists)	None	Post-haemodialysis hypertensive rebound with methyldopa	Avoid

Appendix. Features of frequently used antihypertensive drugs in haemodialysis patients

	Elimination, metabolism	Dosing	Supplement required with dialysis	Miscellaneous
Diuretics				
Thiazides/chlorthalidone	R	Avoid		
K^+ sparing	R	Avoid		
Acetazolamide	R	Avoid		
Loop agents				
Furosemide	R (H)	Useful in high doses	No	Ototoxicity and augmented aminoglycoside toxicity
Bumetadine	R (H)	Useful in high doses		
Etacrynic acid	R (H)	Avoid		
Beta-blockers				
Acebutolol	H (R)	25–50%	No	Active metabolites accumulation
Atenolol	R	25–50%	Yes	Removed by dialysis
Bisoprolol		25%	Yes	
Betaxolol		50%	Yes	
Carvedilol		Unchanged	No	
Labetalol	H	Unchanged	No	
Metoprolol	H	Unchanged	No	
Nadolol	R	50%	Yes	Removed by dialysis
Pindolol	H (R)	Unchanged	No	
Propranolol	H	Unchanged	No	Active metabolite accumulation interferes with bilirubin dosage
Sotalol	R	30%	Yes	Class 3 anti-arrhythmic properties
Tertatolol	R	Unchanged	No	Active metabolites accumulation
Timolol	H	Unchanged	No	Inactive metabolites accumulation
Alpha1-adrenergic blockers				
Prazosin	H (R)	Unchanged	No	First dose effect
Doxazosin		Unchanged	No	Beneficial effects on insulin resistance and on plasma lipids
Urapidil	H (R)	Unchanged	No	Inactive metabolites may accumulate
Angiotensin-converting enzyme inhibitors				Anaemia, anaphylactoid reactions
Benazepril	R (H)	50%	No	Non-renal clearance of benazeprilate
Captopril	R	25–50%	Yes	Active metabolite accumulation
Cilazapril	R (H)	25%	Yes	
Enalapril	R (H)	50%	Yes	Parent drug accumulation
Fosinopril	R and H	Unchanged	No	50% hepatic elimination
Lisinopril	R	25%	Yes	
Perindopril	R (H)	25–50%	Yes	
Quinapril	R (H)	25–50%	No	
Ramipril	R (H)	25–50%	Yes	
Trandolapril	R (H)	50%	Yes	Trandolaprilat is further metabolized before excretion
Angiotensin II receptor antagonists				
Candesartan	R (H)	Avoid		
Eprosartan	H	Avoid		
Irbesartan	H	Unchanged	No	
Losartan	R (H)	Unchanged	No	
Olmesartan	R H	Unchanged	No	
Telmisartan	H	Unchanged	No	
Valsartan	H	Unchanged	No	
Calcium channel blockers				
Amlodipine	H	Unchanged	No	
Diltiazem	H	Unchanged	No	Risk of conduction disturbance
Felodipine	H	Unchanged	No	
Isradipine	H	Unchanged	No	
Lacidipine	H	Unchanged	No	
Nicardipine	H	Unchanged	No	
Nifedipine	H	Unchanged	No	
Nitrendipine	H	Unchanged	No	

R — renal elimination; H — hepatic elimination; NR — non-renal elimination

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HIGH BLOOD PRESSURE, ALCOHOL, AND CARDIOVASCULAR RISK

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Introduction

Several cross-sectional and prospective epidemiologic studies have established an empiric alcohol and hypertension link. This observation has been made in European, North American, Australian, and Japanese populations and seems independent from adiposity, salt intake, education, cigarette smoking, and other indirect explanations [1–3]. A fairy consistent finding is that heavy drinking (usually defined as > 3 drinks/ /day — > 40 g of ethanol/day) is associated with increased blood pressure (BP) and incident hypertension [4]. However, men who consume 1–2 drinks per day and women who drink half of this amount do not show significant changes in BP or even significant reductions in BP compared to abstainers [5], suggesting that the pressor effects of alcohol may follow a "J" shape curve. Several aspects of the data obtained from different studies suggest a causal relationship between high ethanol intake and an increase in BP. Thus, reduction of alcohol intake lowers BP, whereas continued intake impairs response to antihypertensive treatments [6].

Intervention studies carried out in human subjects in order to confirm epidemiological data have shown inconsistent results with either an increase or a decrease in BP with alcohol administration, even when ambulatory BP monitoring (ABPM) was used for accurate measurement [7, 8]. These conflicting results may be due to differences in rate, dose, route of ethanol administration, time interval to BP pressure measurement, and psychic factors in the reported studies. However, a meta-analysis of randomized controlled trials, in which alcohol reduction was the only intervention difference between active and control treatment groups, showed a significant reduction in mean (95% confidence interval) systolic and diastolic BP of –3.31 mm Hg (–2.52 to –4.10 mm Hg) and –2.04 mm Hg (–1.49 to 2.58 mm Hg), respectively. These reductions in BP would be expected to result in a 6% reduction in the risk of coronary heart disease, and a 15% reduction in the risk of stroke and transient ischaemic attacks [9].

Mechanisms of alcohol-related hypertension

The differences observed in the results of previous studies suggest that pressor effects seem to be heterogeneous. Similar to the effects of salt intake on BP, when the effects of ethanol intake on BP are analysed, two populations may be encountered, one sensitive to ethanol and another resistant to the pressor effects of ethanol. In our experience, half of the normotensive and four-fifths of the alcohol dependent patients with high blood pressure show significant changes in 24-h mean BP and may be classified as sensitive to alcohol, whereas the remainder should be considered resistant to the pressor effects of alcohol [10]. The results of this study and others [11] suggest that genetic factors may play a role in the pathogenesis of ethanol related hypertension.

Although the basis of the association between alcohol intake and hypertension has not yet been established, the following mechanisms have been proposed: 1) activation of the renin-angiotensin aldosterone system; 2) adrenergic nervous system discharge; 3) cortisol secretion; 4) reduction of insulin sensitivity with impairment of glucose tolerance, which may also favour fat storage and dyslipemia; 5) heart rate variability; 6) direct effects of ethanol on peripheral muscle tone via changes in calcium or sodium transport into smooth muscle cells; and 7) endothelial dysfunction due to ethanol that may induce changes in the relaxant capacity of the endothelium and decrease the release of nitric oxide (Table 1) [12–15]. In respect to the last point, some studies have suggested that polyphenols contained in foods (i.e. wine and beer) may exert antihypertensive effects and contribute to the prevention of hypertension due to their vasodilatation properties [16].

Some authors have also suggested that the association of alcohol and hypertension may be due to withdrawal from alcohol. However, in intervention studies, no differences in plasma adrenaline or noradrenaline values were observed when patients did or did not receive ethanol and alcohol withdrawal syndrome was excluded. In addition, if hypertension were related to alcohol withdrawal, BP would be higher when alcohol dependent patients give up alcohol. Finally, epidemiological studies [17] have related changes in BP to obesity, cigarette smoking, coffee, tea, total cholesterol, uric acid, potassium, and calcium, and experimental studies have suggested that alcohol-induced hypertension could be related to magnesium depletion. However, in intervention studies performed to evaluate the pressor effects of ethanol, no significant differences were observed in plasma ionic and metabolic parameters of chronic alcoholics between the measurements obtained when they received ethanol and when they only received the placebo. These data suggest that the short-term effects of ethanol are not related to any change in plasma hormones or ions.

Table 1. Mechanisms involved in the pathogenesis of ethanol related hypertension

Genetic factors
Stimulation of the renin–angiotensin–aldosterone system
Abnormal sympathetic stimulation
Increased cortisol secretion
Reduction of insulin sensitivity with changes in glucose tolerance
Heart rate variability
Effects on peripheral muscle tone via changes in calcium or sodium transport into smooth muscle cells
Endothelial dysfunction

Clinical features

The clinical relevance of the magnitude of changes in BP after ethanol withdrawal should also be considered. In some intervention studies, the average change of 24-hour mean BP was –8.4 mm Hg in the alcohol-sensitive normotensive patients and –12.5 mm Hg in the alcohol-sensitive hypertensive subjects. In epidemiological studies, reductions of only 2 or 3 mm Hg in BP in the whole population have the same effect on mortality as anti-hypertensive treatment. Since the reductions of BP observed in the intervention studies after alcohol withdrawal were between two- to six-fold greater than these figures, the changes should be considered as clinically relevant [10].

On the other hand, ethanol-sensitive alcohol dependent patients have shown a significantly lower left ventricular ejection fraction and a significantly greater left ventricular mass than ethanol-resistant patients (Table 2). In this respect, one may wonder whether the former group of alcohol dependent patients is more sensitive to the effects of ethanol intake on the whole cardiovascular system or whether the changes observed in ethanol-sensitive patients are secondary to a relatively higher BP than ethanol-resistant alcohol dependent patients. Since no significant differences were observed in the BP parameters, alcohol dependent subjects sensitive to the pressor effects of ethanol may also be more sensitive to the effects of ethanol on the myocardium [10]. Thus, an echocardiography and/or radionuclide ventriculography should be performed in all alcoholics with ethanol-induced hypertension in order to rule out left ventricular dysfunction or dilated cardiomyopathy [18].

Alcohol intake in the management of hypertension

The first step in the management of hypertension in alcohol dependent patients should be to give up ethanol [8]. In most of these patients BP will reduce to normal values within the following days and they will not need pharmacological treatment. Because of the high prevalence of myocardial dysfunction and dilated myocardiopathy among chronic alcoholics, angiotensin converting enzymes inhibitors, angiotensin II receptor antagonists, and/or beta-blockers are commonly used to treat these patients. However, the rapid reduction of BP on cessation of alcohol intake makes close monitoring of BP and pharmacological treatment necessary during the first month of abstinence. Non-alcohol dependent patients with hypertension should limit their alcohol consumption to two

Table 2. Clinical and laboratory data of the alcoholic patients classified as sensitive to the pressor effects of ethanol compared to those classified as resistant (non-sensitive) in a series of 35 normotensive chronic alcoholics (from ref [9])

	Sensitive (n = 18)	Non-sensitive (n = 17)
Age (y)	39.8 ± 7.1	39.5 ± 8.0
Daily ethanol intake (g)	219 ± 86	214 ± 72
TLDE (kg/kg)	21.9 ± 13.3	19.3 ± 10.7
SBP (mm Hg)	122 ± 7	121 ± 10
MBP (mm Hg)	92 ± 5	91 ± 7
DBP (mm Hg)	78 ± 6	77 ± 7
End-diastolic diameter (mm)	52.4 ± 2.7*	50.5 ± 3.5
End-systolic diameter (mm)	34.2 ± 3.0	32.8 ± 3.4
Interventricular thickness (mm)	10.4 ± 1.4*	8.2 ± 0.8
Posterior wall thickness (mm)	9.8 ± 1.2*	8.5 ± 0.7
Left ventricular mass (g/m^2)	132 ± 23**	95 ± 17
Shortening fraction (%)	34.8 ± 3.8	35.7 ± 4.7
Ejection fraction (%)	52.6 ± 6.1**	57.8 ± 4.9
m — cortisol (nmol/L)	451 ± 163	513 ± 155
e — cortisol (nmol/L)	206 ± 108	246 ± 138
PRA (pmol of angiotensin h^{-1} ml^{-1})	0.68 ± 0.99	0.68 ± 0.66
Aldosterone (ng/dL)	402 ± 280	460 ± 272
ANP (fmol/mL)	18.1 ± 22.5	14.1 ± 13.4
Noradrenaline (pg/mL)	260 ± 137	246 ± 80
Adrenaline (pg/mL)	71 ± 36	61 ± 33
Insulin (pmol/L)	112 ± 71	120 ± 75
SGOT (U/L)	59.7 (15– 357)*	33.1 (9–101)
SGPT (U/L)	47.9 (15–128)	39.3 (8–79)
GGT (U/L)	199 (10–885)	116 (21–600)

*p < 0.05; **p < 0.01; TLDE — total lifetime dose of ethanol; SBP — systolic blood pressure; MBP — mean blood pressure; DBP — diastolic blood pressure; m — morning; e — evening; PRA — plasma renin activity; ANP — atrial natriuretic peptide; SGOT — serum glutamic oxaloacetic transaminase; SGPT — serum glutamic pyruvic transaminase; GGT — gamma glutamyl transferase

drinks or fewer per day, and weekly intake should not exceed 14 standard drinks for men and nine standard drinks for women [19].

Alcohol and risk of cardiovascular disease

Almost all modern epidemiologic studies have shown reduced risk of myocardial infarction and death due to coronary heart disease in moderate drinkers compared to teetotallers [20, 21]. Patients who have one to two glasses of alcohol per day had fewer myocardial infarctions and an improved survival compared to teetotallers. Moderate alcohol consumption has a wide range of positive effects: 1) it improves insulin sensitivity; 2) increases HDL-cholesterol and reduces atherogenic small size LDL-particles, as well as fasting triglycerides; and 3) it produces beneficial effects on adiponectin, C-reactive protein and adhesion molecules [22–24]. These biological paths of alcohol intake explain more than 85% of the reduced risk of cardiovascular disease observed.

On the other hand, international comparisons [25] suggest less coronary artery disease in wine drinking countries than in liquor drinking countries. There is also data showing apparent coronary artery disease protection similar in beer drinkers to that seen in wine drinkers [26]. In moderate wine and beer drinkers a noticeable safe metabolic, inflammatory, and glycaemic profile might balance higher blood pressure, leading to a net benefit [27]. However, protective effects of alcohol disappear in very heavy drinkers because the beneficial increase in HDL-cholesterol is offset by the increases in BP [28]. This information suggests that low to moderate consumption of alcohol improves cardiovascular risk and this benefit exceeds the risk of hypertension and heart failure. However, it is equally important to recognize the serious adverse effects due to high alcohol ingestion. With chronic high-dose alcohol intake, there is a direct relationship to elevated BP, but also an increase likelihood of developing congestive heart failure, liver disease, and other ethanol-related diseases [17].

Conclusions

Several prospective cross-sectional and epidemiological studies have shown a highly significant association between the consumption of three or more alcoholic drinks per day and hypertension. The mechanisms of ethanol-induced hypertension have been related to genetic factors (sensitivity to the pressor effects of ethanol) and changes in sympathetic modulation, cortisol, the renin–angiotensin system, insulin sensitivity, and endothelial activity. Many patients with ethanol-induced hypertension also show other toxic effects of alcohol on the cardiovascular system such as left ventricular dysfunction and/or dilated cardiomyopathy. The goal in the treatment of ethanol-induced hypertension in chronic alcoholics is to give up alcohol. However, non-dependent patients may limit their ethanol intake to two drinks per day in men and one drink per day in women since several studies have suggested that these doses of ethanol may exert a protective effect on the development of atherosclerosis and prevent cardiovascular morbidity and mortality.

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EXERCISE AND HYPERTENSION

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Physical inactivity and hypertension

The worldwide prevalence of hypertension (HTN) is estimated to be as much as 1 billion, with an estimated 60% increase by the year 2025 [1]. Chronic HTN is considered a risk factor for developing cardiovascular disease and mortality [2] with approximately 7.1 million deaths per year attributed to hypertension [1]. The prevalence of hypertension is perpetuated by lifestyle factors such as consumption of high fat and/or high salt diets, and physical inactivity [1] while positive lifestyle modifications contribute significantly to maintain normal blood pressure [3]. In this regard, a number of reviews and meta analyses concluded that the findings from well-controlled interventional and epidemiologic studies support that physical activity of mild to moderate intensity can prevent or attenuate the development of hypertension or independently lower blood pressure in patients with essential HTN [4, 5]. Furthermore, increased physical activity or exercise capacity is associated with lower mortality in hypertensive individuals, in older men, in patients with type 2 diabetes, in prehypertensives, in those with high normal blood pressure, and even in those with multiple cardiovascular risk factors [6–11]. Consequently, increased physical activity is now strongly recommended as part of the lifestyle modification along or as adjunct to pharmacologic therapy proposed by ESH/ESC Guidelines [12]. Young adults with low fitness were 3-to-6 fold more likely to develop diabetes, hypertension, and the metabolic syndrome than those with high fitness [13].

Exercise definition and exercise components

Exercise is categorized into two types: aerobic and anaerobic. Aerobic exercise consists of repetitive, low resistance movements (walking or cycling) that last for a long period of time (usually more than 10 minutes). Anaerobic exercise consists of high resistance, low repetition movements such as weight lifting, and last only one to three minutes. All of the recommendations focus on aerobic exercise as the primary activity. Aerobic exercise intensity has been characterized by the American College of Sports Medicine as low, moderate, or high [14]. Exercise is defined as low intensity if it elicits < 64% of predicted maximum heart rate (PMHR; 220-subject's age), or < 39% of heart rate reserve (Heart Rate Reserve [HRR] = PMHR-resting HR * [% HR] + resting HR). Moderate intensity is defined as that eliciting 64% to 76% of PMHR, or 40% to 59% HRR. Exercise eliciting a greater response is considered high intensity (Table 1). Moderate intensity activity for most people is comparable to a brisk walking pace of 5 to 6 km per hour, and high intensity activity is comparable to jogging or running.

Exercise interventional studies

Persons who are physically fit maintain a more favourable caloric balance and lower body weight, both of which protect against the development of CVD risk factors. In apparently healthy individuals, systolic blood pressure increases as exercise intensity increases in a dose-response fashion and reaches a plateau at approximately 180–200 mm Hg. Diastolic blood pressure remains very close and even below resting levels. However, in some individuals there is a disproportional increase in both systolic and diastolic blood pressure during exercise. Although a definitive abnormal rise threshold has not yet been established, most studies support that a systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg at or near peak exercise is considered an exaggerated blood pressure response to exercise. Some studies suggest that such a rise in exercise blood pressure is associated with future development of hypertension [15] and predicts cardiovascular mortality [16, 17]. There is also recent evidence to support the theory that fitness levels may play a significant role in the exercise blood pressure response. More specifically, moderate aerobic exercise training may attenuate the excessive elevations of blood pressure during physical activity. We found that higher fitness levels, as indicated by peak exercise time, were inversely associated with blood pressure at six minutes of exercise. We reported significantly lower systolic and diastolic blood pressure levels at sub-maximal and maximal workloads in hypertensive patients following 16 weeks of aerobic training [18]. Some evidence supports the theory that an abnormal rise in systolic blood pressure during sub-maximal levels of exercise is associated with left ventricular hypertrophy (LVH) and may be a better predictor of LVH than peak exercise blood pressure [19]. In a recent study [20] we demonstrated that men and women with normal blood pressure at rest but an abnormal rise in systolic blood pressure during exercise of approximately 5 METs (equivalent to a brisk walk) had a significantly higher left ventricular mass (LVM) and were more likely to have LVH. The exercise systolic blood pressure at five METs and the change in blood pressure from rest to a workload of five METs were the strongest predictors of LVH. Since five METs is equivalent to the metabolic demand of most daily activities, the findings suggest that the impetus for increases in LVM is daily systolic blood pressure. Furthermore, we identified that a systolic blood pressure of 150 mm Hg at the exercise levels of five METs was the threshold for LVH. A meta-analysis that included 54 clinical trials comprising 2,419 participants assessed the effects of aerobic exercise on BP. Aerobic exercise was associated with a significant reduction in mean systolic BP by 3.8 mm Hg and diastolic BP by 2.6 mm Hg [21]. Because the BP reductions related to aerobic exercise did not significantly differ among trials with various types, frequencies, and intensities of exercise intervention, the result from these meta-analyses indicated that all forms of exercise seemed to be effective in reducing BP. A prospective study among Harvard male alumni reported that men who did not participate in vigorous exercise had a 35% higher incidence of hypertension than those who were more active [22]. The ARIC study pointed out that leisure time physical activity reduced the risk of hypertension in middle-aged white men but not in black [23]. Kokkinos P. et al. found that African-American men with severe hypertension and LVH benefit from a combined regimen or regular, moderately intense aerobic exercise and antihypertensive treatment. The antihypertensive effects of exercise substantially reduced the amount of medication required to control blood pressure [24]. Furthermore, Trichopoulou et al. found that the hazard ratio for death in Greeks following the high score of the Mediterranean diet and physical activity > 35 METs-hr/day was 0.83 versus 0.74 for those following low score of the Mediterranean diet and physical activity < 35 MET-hr/day [25]. Only two prospective studies assessed the association of physical activity with the risk of hypertension in men and women separately, and no significant association was found among men. Mechanisms suggested to account for these observations are reduced systemic vascular resistance, decreased cardiac output, and decreased plasma noradrenaline concentrations. Exercise promotes muscle insulin sensitivity, insulin mediated transport of glucose from blood to muscles, improved autonomic nervous system function, and lower heart rates, which each decrease the risk of developing diabetes, independent of body mass [26]. Increased lipoprotein lipase activity in active skeletal muscle (which results in an enhanced clearance rate of plasma triglycerides), increased transport of lipids and lipoproteins from the peripheral circulation and tissue to the liver, and enhanced HDL cholesterol are mechanisms by which lipids may improve with fitness [27]. Physical exercise stimulate NOS3 activity and increases NO release through the augmentation of sheer stress, and thereby is considered generally to lower BP. Kimura T.

Table 1. American College of Sports Medicine Exercise Guidelines for Lowering BP

Exercise type	Primarily endurance physical activity, supplemented by resistance exercise
Frequency	Most days of the week and preferably every day of the week
Duration	30 or more minutes of continuous or accumulated activity per day
Intensity	Moderate intensity activity (40% – < 60% of HRR Brisk walk)

et al. found a significant interaction between the genotype and physical activity level on systolic BP in the Japanese population [28], while Franks PW et al. found that the knowledge of the GPR10 genotype may define those who are least likely to benefit from physical activity [29]. Exercise programs may lead to additional benefits when combined with other lifestyle interventions. The combination of regular physical activity and weight control can reduce the risk of hypertension in both sexes regardless the level of obesity [30]. The Finnish Diabetes Prevention study [31] showed that, in overweight subjects with glucose intolerance who received intensified lifestyle intervention (diet intervention and moderate exercise for at least 30 min per day), the long term reduction in body weight was 3 to 3.5 kg compared with control subjects. This intervention resulted not only in a marked reduction in the risk of developing type 2 diabetes, but also in a significant drop in blood pressure (4 mm Hg for systolic and 2 mm Hg for diastolic BP compared with control subjects).

Fitness and mortality risk in hypertensive individuals

We recently reported an inverse and graded association between exercise capacity and mortality risk in a large cohort of 4,631 hypertensive men [7]. Exercise capacity emerged as a more powerful predictor of risk for all-cause mortality than established risk factors among hypertensive individuals after adjusting for cardiac medications and traditional CV risk factors. The adjusted risk for mortality was 13% lower for every 1-MET increase in exercise capacity. We then considered the mortality risk according to fitness categories. When compared to those who achieved ≤ 5 METs (lowest 25th percentile) the relative risk of those with an exercise capacity of 5.1–7 MET was 34% lower. The mortality risk declines progressively to 59% and 71% lower for those with an exercise capacity of 7.1–10 METs and > 10 METs, respectively. We then explored whether it is better to have low fitness with no risk factors or fit with multiple risk factors. We noted that for individuals with additional risk factors, the mortality risk in the lowest fitness category was 47% higher when compared to those with no risk factors. The risk was further reduced by 44% for those with an exercise capacity of 7.1–10 METs and 63% for those who achieved > 10 MET. Similarly, for individuals with no additional risk factors, the risk was reduced by 34%, 52%, and 67% for the respective fitness categories. Collectively, these findings support that it is better for a hypertensive individual to be fit regardless of risk factors than have no risk factors and be sedentary. Thus, we recommend and encourage physicians and other health care professionals to consider the fitness levels of their hypertensive patients.

ESH/ESC Recommendations

Physical fitness is a rather strong predictor of CV mortality independent of BP and other risk factors. Thus sedentary patients should be advised to take up a modest level of aerobic exercise on a regular basis, such as walking, jogging, or swimming. The American College of Sports Medicine recommends that hypertensive individuals engage in moderate intensity aerobic exercise for 30–60 minutes on most days and preferably every day of the week. This exercise duration can also be fulfilled by a minimum of 10-minute intermittent bouts throughout the day. The expected reduction in BP is approximately 5–10 mm Hg. Although the recommended mode of exercise is aerobic, light resistance exercises are not discouraged [32]. However, heavy weightlifting or isometric exercise can have a pressor effect and should be avoided. If hypertension is poorly controlled, and always in severe hypertension, high-intensity physical exercise should be discouraged or postponed until appropriate drug treatment has been instituted and found to be effective.

Pre-exercise evaluation of the hypertensive patient should be considered. The extent of such evaluation will depend on the extent of the exercise program and on the patient's symptoms, signs, overall cardiovascular risk, and associated clinical conditions.

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HYPERTENSION AND ARRHYTHMIA

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Introduction

Arrhythmia — both atrial and ventricular — is a common comorbidity with hypertension (HT). The underlying mechanisms are many and various, including left ventricular hypertrophy (LVH), myocardial ischaemia, impaired left ventricular function, and left atrial enlargement. Any form of arrhythmia may be associated with LVH, but ventricular arrhythmia is more common as well as being more dangerous.

Atrial arrhythmia

Prevalence

After supraventricular extrasystole, atrial fibrillation (AF) is the next most common form of arrhythmia associated with HT. The relative risk of developing AF in HT is modest compared with other conditions, such as heart failure and valve disease. Nevertheless, HT is the most prevalent, independent, and potentially modifiable risk for AF [1]. AF is most common after the age of 65 and is more common in men than in women [2]. In the recent RecordAF study, analysing the management of paroxysmal/persistent AF in recently diagnosed patients, the prevalence of HT was 68% [3].

Mechanisms

Changes in atrial electrical properties occur early in hypertensive heart disease, preceding the appearance of left ventricular and left atrial enlargement [4]. Cellular mechanisms of focal activity might involve both triggered activity and re-entry [5]. Moreover, AF is perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature [5]. Sympathetic hyperactivity, often present in hypertensives and particularly in apnoeic subjects, represents another mechanism favouring occurrence and chronicisation of AF [6]. **Enlargement of the left atrium:** Enlargement of the left atrium results in stretching of the atrial fibres, which is what leads to the creation of arrhythmogenic foci. In the AFFIRM study, ultrasound measured a left atrium of normal size (diameter < 40 mm) in only 33% of patients [1]. Left atrial enlargement seems to set in before LVH. **Left ventricular hypertrophy:** LVH paves the way for AF by perturbing diastolic function and thereby raising the left atrial pressure [7]. In the Framingham cohort, patients with an electrocardiographic diagnosis of LVH had a 3.0- to 3.8-fold increased risk of developing AF [8]. Verdecchia et al. found that, in hypertensive subjects with sinus rhythm and no major predisposing conditions, the risk of AF increases with age and left ventricular mass whereas increased left atrial size predisposes to chronicisation of AF [9]. **Genetic predisposition:** AF has a familial component, especially AF of early onset [5, 10]. **Abnormal blood potassium levels:** Blood potassium imbalance, especially hypokalaemia (iatrogenic or secondary to hyperaldosteronism) can lead to the development of supraventricular arrhythmia.

Diagnosis and prognosis of atrial arrhythmia

Whenever a hypertensive patient complains of palpitations, the possibility of arrhythmia — supraventricular or ventricular — should be considered. AF-related symptoms can be assessed by the new EHRA score [5]. Definitive diagnosis depends on resting ECG or ambulatory heart rate measurement over a period of 24–48 hours. Identifying causes may require echocardiography (to detect LVH, impairment of left ventricular function, left atrial enlargement, or valve disease) and blood tests (potassium levels and high-sensitivity TSH test).

AF has many consequences. The most dangerous is systemic embolism, with stroke being four to five times more common in patients with AF [11, 12]. Risk stratification for stroke and thromboembolism can be assessed by $CHADS_2$ or CHA_2DS_2-VASc score [5]. AF can lead to cardiomyopathy and may exacerbate pre-existing impairment of left ventricular function [13]. The onset of AF may trigger an episode of congestive heart failure, especially if the ventricular response is rapid or if there is some underlying problem with left ventricular function (either systolic or diastolic) [14]. AF can also cause episodes of dizziness or even syncope. Finally, in the Framingham study, a correlation was observed between AF and mortality in both sexes, and this independently of other variables [15].

Treatment of atrial arrhythmia

Preventing AF in hypertensive subjects depends on controlling blood pressure in order to reduce the risk of hypertensive cardiomyopathy (or at least mitigating the consequences thereof). Antihypertensive therapy has been shown to reverse some of the structural cardiac changes caused by HT, including LVH and atrial enlargement [16, 17]. ACE inhibitors and angiotensin receptor blockers may directly reduce the chance of the recurrence of AF [18] but this is still debated [19].

Any potassium imbalance must be corrected. Moreover, antithrombotic therapy is essential in patients with AF. In contrast, the value of anti-arrhythmic drugs is more controversial. In practice, some physicians prefer to reduce the arrhythmia and then maintain a sinus rhythm, whereas others choose to work with the AF by controlling the heart rate (to between 60 and 90 beats per minute). Beta-blockers, particularly sotalol, seem to be of interest in patients with history of AF [19]. Left atrial catheter ablation should be reserved for patients with AF that remains symptomatic despite optimal medical therapy, including rate and rhythm control [5].

Ventricular arrhythmia

Ventricular arrhythmia is usually triggered by simple or complex ventricular extrasystole whereas the mechanism whereby tachycardia is perpetuated more usually involves a re-entry circuit.

Arrhythmogenic factors

Left ventricular hypertrophy: Ventricular premature complex is more common in hypertensive subjects when there is concomitant LVH [20, 21]. The most dangerous forms of ventricular arrhythmia (tachycardia and ventricular fibrillation) are still rare [22]. Both the incidence and seriousness of these forms correlate with the severity of the LVH, as measured by ECG and ultrasound [23]. Asymmetric septal and eccentric hypertrophy seem to be associated more often with ventricular arrhythmia than concentric LVH [24]. That LVH is involved in the pathogenesis of ventricular arrhythmia is demonstrated by the fact that the incidence of the latter drops once the former has been reversed [25]. **Myocardial ischaemia:** Myocardial ischaemia is the most common arrhythmogenic factor, and this is also true in hypertensive subjects. This comorbidity increases the risk of sudden death. The ischaemia may be secondary to atherosclerosis of the major epicardial coronary arteries, or due to problems in the myocardial capillary system. In the hypertensive subject, there is a link between the frequency and severity of arrhythmia, and myocardial ischaemia (be the episodes symptomatic or subclinical) [26]. **Impaired left ventricular function:** The risk of arrhythmia in hypertensive patients is likewise exacerbated by impaired left ventricular function (systolic or diastolic) as a result of electrical asynchronism. This risk is further increased if the left ventricle is enlarged. As a general rule, at least two of the above-mentioned risk factors (LVH, myocardial ischaemia, or impaired ventricular function) need to be present for onset of the most dangerous forms of ventricular arrhythmia in hypertensive subjects. **Other factors:** Circadian variations and sudden increases in blood pressure can trigger arrhythmia as a result of associated changes in pre- and post-charge [27]. Similarly, the sympathetic irritability which commonly accompanies HT can lead to ventricular arrhythmia [28]. Whether or not variations in blood electrolyte levels (notably of potassium) also constitute an arrhythmogenic factor is more controversial [22, 29].

Diagnosis and prognosis of ventricular arrhythmia

Positive diagnosis depends on resting ECG and ambulatory heart rate measurement over a period of 24–48 hours. Amplified ECG (to detect late ventricular potentials) and programmed ventricular stimulation need not be performed on a systematic basis. Identifying underlying mechanisms will involve carrying out examinations to look for LVH (by ECG or cardiac ultrasound), myocardial ischaemia (ECG or myocardial

ultrasound stress testing, myocardial scintigraphy, Holter monitoring), heart failure, or some underlying metabolic problem.

HT is associated with an increased risk of sudden death, essentially due to ventricular arrhythmia [30]. In patients with LVH, global mortality is increased if there is complex or frequent ventricular extrasystole, even if this is asymptomatic [31].

Treatment of ventricular arrhythmia

If there is no myocardial ischaemia, only the more severe forms of ventricular arrhythmia need positive management. However, if myocardial ischaemia is present, this needs to be corrected as do frequent ventricular extrasystoles, ventricular doublets, and salvoes. Blood potassium abnormalities should always be treated.

Beta-blockers and amiodarone are the drugs of choice in ventricular arrhythmia although calcium-channel blockers and angiotensin converting enzyme inhibitors have been shown to be effective against ventricular arrhythmia by virtue of their action against LVH [25, 29]. Spironolactone may also be prescribed, not only to reverse hypokalaemia but also for its antifibrotic activity in the ventricular myocardium. In patients with either severe ventricular arrhythmia, which has proven refractory to pharmacological treatment, or profoundly impaired ventricular function, an automatic implantable cardioverter defibrillator should be considered [32].

Conclusions

Both ventricular and atrial forms of arrhythmia are common in patients with HT. The underlying mechanisms are many and various, and the most useful diagnostic information comes from ambulatory heart rate monitoring. Arrhythmia needs to be treated on a case-by-case basis with objective criteria in sight.

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HYPERTENSION AND OBSTRUCTIVE SLEEP APNOEA

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Introduction

Many epidemiological and clinical studies are in favour of increased cardiovascular risk in patients with obstructive sleep apnoea (OSA) [1–3]. Several studies have contributed important information to support this theory, particularly concerning the role played by OSA in cardiovascular morbid-mortality, even when the number of nocturnal apnoea episodes is limited. Many pathophysiological mechanisms are suggested to explain morbid associations between OSA and cardiovascular diseases. Cardiovascular responses to apnoeas are acute — following each respiratory episode — and chronic.

Epidemiology and diagnosis of OSA

OSA is a common disease affecting around 5% of the general population, particularly affecting men [4]. The clinical picture includes four main symptoms: diurnal hypersomnia, frequent nocturnal arousals with nycturia, morning asthenia with or without headache, and severe snoring. Factors promoting OSA are not only obesity, age, smoking, and consumption of alcohol, but also, and above all, anomalies of the upper respiratory airways promoting snoring in these patients. Polysomnography is the standard examination for diagnosis of nocturnal respiratory arrest. It simultaneously records sleep, quantified air flow (nasal pressure), thoracic and abdominal respiratory movements, electroencephalogram, and haemoglobin oxygen saturation. Respiratory polygraphy without sleep recording can also be used in establishing a diagnosis of OSA. Apnoea may be obstructive (persistent respiratory effort), central (no respiratory effort), or mixed (starts as central type and ends as obstructive type). The number of apnoeas (airflow stops completely) and hypopneas (reduction of more than 50% in inspiratory flow or 30% linked to more than 3% desaturation and/or microarousals) lasting more than 10 seconds per hour of sleep (apnoea–hypopnea index or AHI) can then be calculated. When the sensitive instruments described above are used, the threshold of 15 events per hour of recording is usually applied for OSA diagnosis.

Pathophysiological aspects of interactions between OSA and the cardiovascular system

Patients suffering from OSA will display permanent oscillations in their haemodynamic parameters during the night. The heart rate, blood pressure (BP), and cardiac output will therefore vary incessantly because of the repeated respiratory events and rapid changes in state of vigilance (cortical microarousals) induced by these respiratory anomalies. BP falls at the start of each episode of apnoea then gradually increases to a peak pressure just at the moment when respiration starts again, with systolic BP possibly increasing by 15 to 80 mm Hg during a cortical microarousal. These variations in BP occur under the influence of four stimuli: O_2 desaturation, increase in P_aCO_2, increased respiratory effort, and microarousal at the end of the apnoea. Respiratory resumption linked to arousal does not last for long with a new episode of apnoea occurring as soon as the patient has gone back to sleep.

Repetition of these stimuli every night leads to chronic changes in the cardiovascular system response and structural modifications. All these stimuli, in particular desaturation-reoxygenation, are a source of sympathetic stimulation [5]. This type of stimulation is well revealed by plasma or urinary catecholamines assay and microneurography data [6, 7]. Moreover, OSA patients exhibit impaired baroreflex sensitivity to a hypotensive stimulus [8, 9]. This baroreflex adaptation may also contribute to the increase in resting autonomic tone observed in OSA patients. The chronic increase in sympathetic tone, alterations in baroreflex sensitivity, and associated deficit in vascular relaxation lead to elevated peripheral vascular resistances in OSA [10]. Other mechanisms explaining OSA-related hypertension include abnormal peripheral chemoreceptor function [11], systemic inflammation [12], oxidative stress [13], endothelial dysfunction [14], increased levels of endothelin [15], metabolic dysfunction [16], and stimulation of the renin–angiotensin system [17, 18].

Prevalence and characteristics of hypertension in OSA

The links between OSA and hypertension are more than a simple association, OSA being accepted by many authors, and acknowledged in the ESH–ESC guidelines for the management of arterial hypertension as a cause of hypertension [19]. There are many predisposing factors for both pathologies, however, particularly overweight and its associated hyperinsulinism [20]. The first major epidemiological study, performed in 1985, showed that the relative risk of hypertension in snorers compared with non-snorers was 1.94 in men and 3.19 in women [21]. At present, the prevalence of hypertension in OSA patients is estimated at nearly 60%. As has been well demonstrated by the Sleep Heart Health Study, this prevalence increases constantly with the AHI [22]. This dose-effect relationship was also detected in another large study involving subjects examined for suspected OSA [23]. In this last study, any increase in an event (apnoea or hypopnea) per hour of sleep was linked independently to a 1% rise in the relative risk of hypertension, and any 10% fall in nocturnal O_2 saturation increases the risk of hypertension by 10%. Another study, the Wisconsin Sleep Cohort Study, with subjects not treated for sleep anomalies, found a relative risk of hypertension after a 4-year follow-up of 1.42 for an AHI < 5 and 2.89 when the AHI was > 15 [24]. In a study performed on apnoeic patients not known to be hypertensive, we found a 42% prevalence of hypertension by clinical measurement but 76% using ambulatory BP monitoring over 24 hours (ABPM) [25]. In OSA patients, daytime systolic BP is generally not different to that of control subjects when matched for age and BMI [26]. On the other hand, using office BP recording and ABPM even more, it has now been well demonstrated that OSA patients have a high prevalence of isolated diastolic hypertension [25, 27, 28]. Taking these data into account, and according to the high prevalence of masked hypertension in apnoeic subjects, ABPM could be proposed for OSA patients whose clinical BP does not display any abnormality [29]. Nearly 30% of hypertensive patients suffer from OSA [30, 31]. This prevalence is even greater in refractory hypertension (about 80%), particularly before the age of 50 [32–34]. The severity of the hypertension also seems to be in proportion to that of the OSA [27].

RR interval variability is decreased and BP variability is markedly increased in patients with OSA [30, 35]. The fall in BP (dipping), which occurs during the night in a normal subject, is often absent in apnoeic patients [25, 36, 37]. If this anomaly is observed during an ABPM analysis in a hypertensive subject, it suggests the possibility of OSA.

Deleterious role of the association of OSA with hypertension

The high prevalence of hypertension in OSA and the close relationships between these two pathologies partly explains the high incidence of cardiovascular events in apnoeic patients. Coronary heart disease, arrhythmias, cardiac conduction disorders, and cerebrovascular events are often encountered during follow-up of apnoeic patients [38–45]. Therefore, it was found that when the AHI was above 20, cardiovascular mortality was around 40% after 8 years in men [46]. Apart from these cardiovascular events, OSA is a major source of social handicap because of the snoring and non-recuperative aspect of the sleep obtained. A diagnosis of OSA, suggested by a specific questionnaire (the Epworth Sleepiness Scale or the Berlin questionnaire) [47, 48], confirmed by polysomnography or respiratory polygraphy, is therefore an essential step because treating this pathology seems to reduce the risk of later cardiovascular complications.

Left ventricular hypertrophy and diastolic function in OSA

Left ventricular hypertrophy (LVH) seems to be more common in cases of OSA, even after taking the BP into account [49, 50]. The frequency of occurrence of LVH rises with severity of OSA [51]. The greater prevalence of LVH in apnoeic patients appears to be related to post-load elevation during apnoea episodes and sympathetic hyperstimulation [51]. However, these data should be viewed with caution because of the difficulty in obtaining reliable measurements of left ventricular mass in OSA patients, who are often overweight. LVH explains some of the functional anomalies of the left ventricle observed in apnoeic patients. Thus, diastolic dysfunction is frequent during OSA and is linked to severity of respiratory events [52].

Effects of OSA treatment on BP

The first treatment for OSA was tracheotomy, which had a beneficial effect on BP values and cardiovascular morbi-mortality [53]. Today, therapeutic strategies for OSA include sleep postural changes, avoiding sleeping on the back, weight loss, avoidance of alcohol and sedative hypnotics, mandibular advancing devices, and upper airway surgical procedures. The most widely used treatment consists of continuous positive airway pressure (CPAP) administered during the night. CPAP treatment prevents airway collapse during inspiratory efforts. Effective long-term treatment of OSA by CPAP has been shown to decrease sympathetic activity, improve baroreflex control of heart rate [54, 55], and improve BP control. Several studies have demonstrated that CPAP can reduce the BP of apnoeic patients, especially diastolic

and nocturnal BP. However, the majority of these studies included less than 50 subjects and many of them were neither randomised nor controlled. Three meta-analyses using 19 randomized controlled trials were published in 2007 [56–58]. The mean BP reduction with active treatment vs. placebo was about 2 mm Hg. Parameters that are positively associated with a BP reduction under CPAP treatment were severe, untreated, or refractory hypertension, severe OSA, and compliance with CPAP > 3 hours per night. The fall in BP with CPAP is parallel to that obtained for plasma and urinary norepinephrine [59]. The mechanism suggested explaining the efficacy of this treatment is the reduction in nocturnal BP peaks and microarousals by CPAP. Concerning medication, hypertension in OSA patients seems to be sensitive to beta-blockers [60]. More recently, we demonstrated than valsartan induced a fourfold higher decrease in mean 24-hour BP than CPAP treatment in untreated hypertensive patients with OSA [61].

In summary, treatment of OSA with nasal CPAP normalizes the nocturnal BP profile by eliminating the large BP swings associated with OSA [55, 62], but has little effect on mean 24-hour or daytime BP [63]. This finding carries three major implications: 1) the decrease in BP associated with OSA treatment, albeit small, can significantly contribute to reduce cardiovascular risk [64]; 2) hypertensive patients with OSA usually need pharmacological treatment in addition to CPAP to normalize BP [61]; and 3) in order to properly assess the effects of OSA on BP, conventional clinic measurements are not enough and should be combined with home [65, 66] and ambulatory BP monitoring. Indeed, ambulatory blood pressure monitoring (ABPM) is the method which appears most useful in the assessment of BP in OSA patients since it allows the detection of masked hypertension and assessment of the BP profile during both wakefulness and sleep [67]. However, ABPM is not routinely performed in many centres. Optimisation of BP measurements in the office or at home is also a very important issue in the diagnosis and treatment of hypertension, as underlined by guidelines issued by the European Society of Hypertension (ESH) [66, 68]. Finally, OSA can be associated with resistant hypertension, i.e. a condition in which normalization of BP is not achieved under treatment with 3 antihypertensive drugs [33]; in these patients, CPAP treatment can help to achieve BP control [69].

Conclusions

OSA is a pathology which is both common and underestimated, and which cannot be summed up as a simple association of snoring and obesity. Its prognosis is closely linked to the occurrence of cardiovascular incidents. The causal link between cardiovascular events and OSA is only formally established for hypertension. There are many pathophysiological mechanisms that may explain the morbid association between OSA and hypertension, with sympathetic hyperactivity in the lead. OSA must be suggested in principle for any hypertensive patient, particularly if the hypertension is refractory to treatment, predominantly diastolic, or linked to a non-dipper profile. The beneficial effect of treating OSA with CPAP with respect to BP seems to be established. BP should be measured not only in the clinic, but also in daily life conditions. Home BP monitoring, and in particular ABPM (which allows BP to be monitored also at night), should be implemented more regularly in OSA patients.

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CONTROL OF HYPERTENSION IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

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Peripheral artery disease has been, up to now, a quite neglected part in the domain of cardiovascular diseases. Even, intermittent claudication of the lower limbs, which is the most common clinical manifestation of peripheral artery disease (PAD), has been considered a minor problem by physicians; still, it often devalues the quality of life of those suffering from it. However, many patients with proven PAD are completely asymptomatic; in such cases, PAD is only detected when complications arise or when non-invasive tests such as measuring ankle brachial blood pressure (ABI) are applied. The most frequent cause of PAD, by far, is atherosclerosis. In line with this particular background, it has been detected in the last decade that PAD, be it symptomatic or not, carries a high risk of cardiovascular morbidity and mortality. Hypertension on the other hand, is also a risk factor for atherosclerosis and vascular disorders, including PAD. Obviously, the total cardiovascular risk is further increased when PAD and hypertension come together. There is no consensus yet on the specific treatment of hypertension in PAD because of the limited number of controlled studies on antihypertensive therapy in such a specific population [1]. The approach to this clinical problem will be outlined in this short review.

Epidemiology

PAD is not an infrequent clinical condition. According to the Rose questionnaire, the prevalence of intermittent claudication in men is approximately 1.5% in those below 50 years of age and reaches 4% to 5% in those above 50. At the age of 70, it can be as high as 10%. In females the prevalence is lower in those below 50, but, contrary to common belief, it is as high as it is among men of over 60 [2]. Also, the clinical presentation in women often is more severe than in men. These figures should be adapted to the fact that the prevalence of asymptomatic PAD is at least twice as high as that of clinical claudication; therefore, the total number of PAD patients becomes surprisingly high, especially at higher age.

The clinical problem

PAD is considered an important marker of systemic atherosclerosis [3]. Therefore, symptoms, if present, can come from peripheral ischaemia as well as from coronary and/or cerebrovascular problems. As a consequence, the clinical syndrome of intermittent claudication has taken on a new dimension because besides the symptoms of aching legs during exercise and the risk to of developing critical limb ischaemia, it is accompanied by symptoms and signs coming from the coronary or cerebral areas and the consequent complications. The Reduction of Atherothrombosis for Continued Health Registry (REACH) study has shown that the risk of cardiovascular death, myocardial infarction, and hospitalization at one and three years is higher in PAD patients than in patients with coronary artery disease [4].

The most potent risk factors for PAD comprise age, smoking, and obesity. There is a striking association between diabetes mellitus and atherosclerotic vascular disease. Additional risk factors are hyperlipidaemia, hypertension, and elevated plasma homocystein [5, 6]. Recently a number of novel subclinical markers have been described [7]. There is a strong and independent association of PAD and increased insulin resistance [8], which could explain, at least partly, the link to diabetes. Also, inflammatory parameters are increased [9].

Hypertension is associated with a twofold to threefold increase in the risk of claudication [4, 5]. Conversely, PAD patients are faced with a significantly increased prevalence of hypertension. Systolic hypertension, in particular, is highly prevalent in PAD patients, most likely due to stiffening of the larger arteries [10].

Diagnosis of PAD

Clinical diagnosis of PAD is made by careful clinical examination with special attention to pulse palpation and auscultation of vascular bruits; even simple palpation of both foot arteries can give a useful indication. Clinical examination can be strengthened by measuring ankle brachial index (ABI). It consists of measuring systolic blood pressure with a simple Doppler ultrasound instrument at both foot arteries; the pressure value obtained is divided by the systolic blood pressure measured at the brachial artery. The technique is simple, quick, non invasive, and cheap. Normal values are between 0.9 and 1.0. Lower figures point toward the presence of a stenotic lesion in the peripheral circulation. Values above 1.3 are indicative of hardening of the arteries in this territory.

There is a remarkable inverse correlation between ABI and cardiovascular event rate at three and five years: the lower the ABI, the higher the event rate [11]. ABI correlates significantly with long-term prognosis, even after adjustment for all regular Framingham risk factors [12]. It is therefore highly recommended that ABI be measured in all patients at risk, not only to make the diagnosis of PAD and its severity, but also to estimate total cardiovascular risk.

Treatment of hypertension and intermittent claudication

Treatment should focus on improving the local symptoms in the legs, controlling blood pressure, and decreasing total CV risk. For local symptoms the general rules concerning lifestyle adaptation remain the same: regular exercise and cessation of smoking. The two most accepted drugs for increasing claudication distance are naftidrofuryl [13], which also improves the quality of life [14], and cilostazol, a phosphodiesterase inhibitor more often used in the USA and Japan [15]. Improved nutrition in the NHANES study was shown to be associated with reduced prevalence of PAD in the US population, also above traditional risk factor control [16].

There is no convincing evidence of any superiority of one hypertensive drug over another in improving claudication distance. Neither is there any convincing proof that better blood pressure control can be obtained with one specific antihypertensive drug compared to another in PAD patients. Slightly better results are obtained by ACE inhibitors; in some studies an increase in muscle blood flow has been shown; ACE inhibition has also been shown to be accompanied by a limited increase in walking distance [1]. Contrary to a common longstanding belief, there is no deleterious effect of beta-blocking agents on walking distance [17, 18]; on the contrary, the newer beta-blocking agents with vasodilator capacities like nebivolol may even improve walking distance; moreover, the protective effect of beta blockade may help in improving prognosis. However, in patients with critical limb ischaemia, it is advisable to choose other antihypertensive drugs. Drugs capable of increasing insulin sensitivity may well be a good choice as many PAD patients have an increased insulin resistance [8].

Blood pressure should be controlled according to the ESC–ESH guidelines [19]. The level to which blood pressure should be decreased in PAD patients with hypertension has not been fully clarified. Guidelines [19] recommend that in patients with diabetes associated with hypertension, values of 130/80 mm Hg or lower should be obtained instead of the regular 140/90 mm Hg. Epidemiological data have shown that in PAD the risk is almost as high as in diabetes; therefore, it seems logical to aim at the same target values for blood pressure in patients with hypertension and PAD as for diabetics. However, this issue should be further clarified as it has not been sufficiently addressed in the literature. In patients with very low ABI it is prudent to monitor ABI during antihypertensive treatment.

In many PAD patients there are abnormalities in other vessels, such as the arm arteries, causing difficulties in blood pressure measurement. Therefore, careful repeated measurement of blood pressure on both arms is essential. The estimation of long-term prognosis can be improved upon in such high-risk patients by 24-hour ambulatory recordings [20].

Control of cardiovascular risk

Because of the clearly increased risk in PAD patients, it is strongly recommended that all efforts be devoted toward decreasing total cardiovascular risk. Antiplatelet drugs such as aspirin or clopidogrel should be administered in all PAD patients [1, 15]; the Antithrombotic Trialists' Collaboration meta-analysis has shown a significant decrease in cardiovascular events with antiplatelet drugs in a large group of PAD patients [21]. Concerning ACE inhibition, information

emerging from the HOPE study has shown that the ACE inhibitor ramipril could significantly decrease cardiovascular morbidity and mortality in high-risk patients [22]. Moreover, the Heart Protection Study (HPS) has convincingly shown that statins are capable of significantly decreasing such risk in this type of patients [23]. This total approach (antiplatelet drugs, statins, ACE inhibitors) obviously requires the use of several drugs besides those necessary for controlling elevated blood pressure; all efforts should therefore be made to improve the compliance of patients to such a treatment regime. Remarkably, in the above-cited REACH registry [4], PAD patients had a worse control of blood pressure and risk profile compared to patients with coronary or cerebral vascular disease [24]. Furthermore, cost calculations should be made to see whether the costs of such an approach would outweigh the benefits of controlling the greatly increased risk in these patients.

Table 1. Treatment of hypertension in PAD patients

PAD, symptomatic or not, carries an elevated risk of CV morbidity and mortality
Hypertension further increases the risk in PAD patients
Effective control of BP is more important than the choice of specific antihypertensive drug
The management of total CV risk by antiplatelet drugs, ACE inhibitors, and statins is essential

Conclusion (Table 1)

In PAD patients with hypertension the total CV risk is substantially increased. All efforts should be made to control blood pressure to at least 140/90 mm Hg or even slightly lower, as in diabetic patients. This can be achieved by all antihypertensive drugs; only ACE inhibitors seem to have, besides their blood pressure lowering properties, a slightly more favourable effect on claudication distance and risk. The most important action in PAD patients will aim at decreasing total CV risk; this can be achieved by adding to the antihypertensive treatment antiplatelet drugs, ACE inhibitors, and statins.

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PREVENTION OF TYPE 2 DIABETES MELLITUS WITH ANTIHYPERTENSIVE DRUGS

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Introduction

Type 2 diabetes is a prevalent and important cardiovascular risk factor [1], and it is well known that patients with established diabetes run a cardiovascular risk between two and four times greater than that run by non-diabetics. It is therefore of importance to prevent the development of type 2 diabetes if possible by an appropriate lifestyle and by a careful selection of antihypertensive drugs in patients at risk, such as those with metabolic syndrome and hypertension. Observational studies have shown that the risk of drug-induced hyperglycaemia is in fact equal to already existing hyperglycaemia and overt type 2 diabetes during follow-up [2]. Data from the Framingham cohort have also shown that approximately 15–18% of hypertensive patients were "glucose intolerant" and that this may contribute to the increased cardiovascular risk in hypertensive patients [3]. It is therefore of interest to investigate the issue of whether different antihypertensive treatment regimens have different effects on glucose metabolism and the development of diabetes mellitus.

Systematic review of drug effects

Padwal et al. [4] reported that the incidence of diabetes is unchanged or increased during treatment with "old/conventional" antihypertensive drugs such as thiazide diuretics and beta-adrenergic blockers, whereas it is unchanged or decreased with "new" drugs including angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and angiotensin receptor blockers (ARBs). New-onset diabetes mellitus during treatment has not influenced the outcome of cardiovascular mortality and morbidity in large clinical trials like ALLHAT [5], INSIGHT [6], and VALUE [7]. However, drug-induced diabetes in hypertensive patients carries the same cardiovascular risk as that seen in patients previously known to have diabetes [2], but it may take 10–15 years for the increased risk to manifest itself and this is not seen in relatively short-term clinical trials. In view of the predicted increase in the number of diabetic patients during the coming decades [8], the choice of treatment strategy of hypertensive subjects may become of increasing importance. As the duration of adverse drug effects on metabolism is important, it is very likely that it is more important to take these effects into consideration for the middle-aged patient with newly discovered hypertension than for the elderly patient for whom the short-term benefits of blood pressure control clearly outweigh the adverse effects on metabolism.

New-onset diabetes in large hypertension trials

The effects of different antihypertensive regimens on new-onset diabetes as demonstrated by some major hypertension trials are shown in Table 1. The difference in risk reduction between conventional and newer therapies ranges from 0% to 34% (87% when including the small ALPINE study [9]). However, different criteria have been used for diagnosing diabetes. Thus the 1985 WHO criteria [10] were used in the CAPPP study [11], the 1999 WHO criteria [12] in the VALUE study [7], and both WHO criteria in the LIFE study [13, 14], whereas new antidiabetic medication, increased glycated haemoglobin (HbA1c), and self-reported diabetes were the criteria in the HOPE study [15]. The study design varies between the trials, and not all the studies were double blind. The CAPPP [11], NORDIL [16], and STOP-2 [17] studies used an open-label design with blinded end-point assessment (PROBE), and this can lead to detection bias; for example, diabetes is more actively sought in thiazide or beta-blocker arms.

There are some randomised placebo-controlled trials, not all of them antihypertensive (CHARM [18], EWPHE [19], HOPE [15], SCOPE [20], SHEP [21], and SOLVD [22]) reporting new-onset diabetes, but it is unclear whether this is due to the antihypertensive effect *per se* or to specific drug effects. It is also difficult to draw conclusions from the results of other trials comparing two or more antihypertensive agents because the observed effects may represent a detrimental effect of one agent in contrast to a beneficial effect of the other. For example, the results from INSIGHT [6] and LIFE [13, 14] might reflect the adverse metabolic effects of thiazide diuretics or beta-blockers rather than the beneficial effects of calcium channel blocker or ARB therapy.

Table 1. Summary of drug effects on the risk of diabetes mellitus.
A. ACEIs or ARBs *vs.* placebo; **B**. ACEIs or ARBs *vs.* conventional therapy; **C**. CCBs *vs.* conventional therapy; **D**. ACEIs or ARBs *vs.* CCB

	Study	Treatment	Duration (years)	Relative risk	p
A.	CHARM [16]	ARB *vs.* placebo	3.1	0.78	0.02
	HOPE [15]	ACEI *vs.* placebo	4.5	0.66	< 0.001
	PEACE [23]	ACEI *vs.* placebo	4.8	0.83	0.01
	SCOPE [20]	ARB *vs.* placebo (conventional)	3.7	0.81	0.09
	SOLVD local centre [22]	ACEI *vs.* placebo	2.9	0.26	< 0.0001
B.	ALLHAT [5]	ACEI *vs.* diuretic	4	0.70	< 0.001
	ALPINE [9]	ARB *vs.* diuretic	1	0.13	0.030
	CAPPP [11]	ACEI *vs.* βB/diuretic	6.1	0.86	0.039
	LIFE [13, 14]	ARB *vs.* βB	4.8	0.75	< 0.001
	STOP-2 [17]	ACEI *vs.* βB/diuretic	4	0.96	0.77
C.	ALLHAT [5]	CCB *vs.* diuretic	4	0.84	0.04
	INSIGHT [6]	CCB *vs.* diuretic	3	0.77	0.02
	INVEST [27]	CCB vs. βB	2.7	0.85	0.004
	NORDIL [16]	CCB *vs.* βB/diuretic	4.5	0.87	0.14
	STOP-2 [17]	CCB *vs.* βB/diuretic	4	0.97	0.83
	ASCOT [28]	CCB *vs.* βB/diuretic	5.5	0.70	0.001
D.	STOP-2 [17]	ACEI *vs.* CCB	4	0.98	0.91
	VALUE [7]	ARB *vs.* CCB	4.2	0.77	< 0.0001

In the HOPE [15] and PEACE trials [23] the results were *post hoc* analysis. This raises the possibility of publication bias, because positive results are more likely to be reported than negative results. Furthermore, there is a possibility of detection bias, because if an end-point is not pre-planned, the studies are not always adequately powered to prove significance. New-onset diabetes was not always a pre-specified primary end point, but the incidence of type 2 diabetes was a predefined secondary end point in nine of the studies: ALPINE [9], CAPPP [11], CHARM [18], INSIGHT [6], LIFE [13, 14], NORDIL [16], SCOPE [20], STOP-2 [17], and VALUE [7].

The effects of different antihypertensive regimens on glucose metabolism

Antihypertensive drug regimens differ in their effects on glucose metabolism. It is at present unclear whether such differences are due to drug-specific effects or to drug class effects. It is also not known whether such effects are permanent or temporary. The detrimental effect of an antihypertensive agent might simply be due to latent diabetes being unmasked by an increase in blood glucose level. Conversely, a glucose-lowering effect might mask a pre-diabetic state.

Angiotensin-converting enzyme inhibitors (ACEIs)

ACEIs have been shown to improve insulin sensitivity and glycaemic control in diabetic patients and have reduced the incidence of new-onset diabetes in the ALLHAT [5], CAPPP [11], HOPE [15], PEACE [23], and STOP-2 [17] trials. The mechanisms by which ACEIs improve insulin sensitivity may include increased glucose uptake in skeletal muscle via

increased GLUT-4 glucose transporter activity [24] and activation of one of the major enzymes of the glucose pathway, hexokinase [25]. Another possible mechanism is an improvement in blood flow and microcirculation to fat and skeletal muscle tissue via bradykinin activation of cell-surface B2-kinin receptors [24]. ACEIs may also improve glucose tolerance in hypertensive individuals by lessening the potassium-lowering effect of insulin and preventing hypokalaemia. This may preserve the insulin secretory response of pancreatic beta cells to glucose, which is decreased during hypokalaemia [26].

Angiotensin receptor blockers (ARBs)

The ARB class has shown a potentially positive effect on insulin action and has a potential role in protecting high-risk hypertensive patients from developing diabetes, as shown in the LIFE [13], SCOPE [20], and VALUE [7] trials, but the mechanisms are still not clear. As expected, some of the hypotheses are the same as with the ACEIs, namely improved skeletal muscle blood flow and microcirculation, enhanced transport of glucose across the skeletal muscle cell membranes, and prevention of hypokalaemia. Alternatively, the effect of the drugs can be related to actions in the pancreas by the enhancement of insulin release by the beta cells.

Calcium channel blockers (CCBs)

Treatment with CCBs has been associated with a reduced incidence of new-onset diabetes in the ALLHAT [5], INSIGHT [6], INVEST [27], and STOP-2 [17] trials. Vasodilatation and improved peripheral blood flow may explain the improvement in insulin sensitivity seen with calcium channel blockade. However, in the VALUE [7] trial new-onset diabetes was reduced with ARBs compared with CCBs from 16.4% in the amlodipine arm to 13.1% in the valsartan arm ($p < 0.001$), a relative risk reduction of 23%. Finally, in the large ASCOT trial [28] new-onset diabetes was less frequent on the amlodipine-based regimen than in the group treated with conventional drugs (567 vs. 799; RR 0.70; 95% confidence interval: 0.63–0.78, $p < 0.0001$).

Diuretics

Thiazide diuretics appear to have an unfavourable dose-dependent effect on glycaemic control, and large doses of thiazides are known to have an adverse metabolic effect [5]. Small doses, however, seem mostly to be neutral to metabolism. There are multiple mechanisms through which thiazide diuretics may worsen glycaemic control. For example, diuretics stimulate renin secretion, which stimulates the production of angiotensin II. Furthermore, the hypokalaemic effect of diuretics may blunt the release of insulin from the pancreas. This was originally proposed by Conn to explain the apparent diabetic state found in primary aldosteronism [29]. Preventing hypokalaemia with potassium supplementation attenuates thiazide-induced glucose intolerance, and the combination of a diuretic and angiotensin-converting enzyme inhibitor may confer a lesser risk of new-onset diabetes [30].

Beta-receptor blockers

In a prospective study of 12,550 adults by Gress et al. [31], beta--blockers increased the risk of subsequent diabetes by 28% among hypertensive patients compared to hypertensive patients not receiving any antihypertensive therapy, with a hazard ratio of 1.28 (95% confidence interval: 1.04–1.57). The mechanism may include weight gain, alterations in insulin clearance and reduced first-phase insulin secretion, and, probably most importantly, reduced peripheral blood flow as a result of increased peripheral vascular resistance [32].

Summary of findings in trials

The majority of hypertensive patients require multiple pharmaceutical preparations for life to prevent cardiovascular risk. Data from cohort and randomised trials suggest that the incidence of type 2 diabetes mellitus is unchanged or increased by thiazides and beta-blockers in a dose-dependent way, while it appears to be unchanged or decreased by ACEIs, CCBs, or ARBs [4, 28, 31]. A meta-analysis of seven studies in 58,010 individuals by Opie et al. [33] showed that the "new" therapies, namely ACEIs, ARBs, and CCBs, provoke less new diabetes than the conventional "old" therapies (diuretics and beta-blockers). ACEIs and ARBs decreased new diabetes by 20% ($p < 0.001$) whereas CCBs decreased new diabetes by 16% ($p < 0.001$).

Conclusions

1) The development of hyperglycaemia in patients with hypertension could either reflect metabolic abnormalities associated with elevated blood pressure per se or the influence of antihypertensive drugs. 2) Hyperglycaemia is a proven risk factor for both macrovascular and microvascular disease and should therefore be taken seriously. 3) Some antihypertensive drugs seem to further increase the risk of hyperglycaemia by impairing insulin sensitivity and/or insulin secretion. Examples of such drugs are beta receptor blockers and high-dose thiazide diuretics, especially when used in combination. Calcium antagonists are mostly neutral. 4) ACE inhibitors or angiotensin receptor blockers (ARB), on the other hand, may improve insulin sensitivity and decrease the risk of new-onset diabetes. 5) The risk associated with hyperglycaemia is likely to increase with the duration of treatment. The choice of antihypertensive drug treatment in this perspective should therefore be a matter of greater relevance for the middle-aged than for the elderly patient with a shorter remaining life expectancy. 6) Blockade of the renin-angiotensin system seems to be an appropriate choice as one of the partner drugs in offering combination therapy to hypertensive patients with an increased risk of developing diabetes.

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TREATMENT OF HYPERTENSIVE URGENCIES AND EMERGENCIES

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Hypertensive emergencies can be defined as severe elevations of blood pressure (BP) in the presence of acute target organ damage. Acute coronary syndromes, dissecting aortic aneurisms, acute pulmonary oedema, hypertensive encephalopathy, acute cerebral infarction, intracerebral haemorrhage, or acute arterial bleeding or eclampsia represent clinical conditions in which an immediate blood pressure reduction is needed to prevent the progression of target-organ damage (TOD) (Table 1). **Hypertensive urgencies** are characterised by severe elevations in BP (> 180/120 mm Hg) without evidence of acute TOD. In hypertensive urgencies BP can usually be reduced in the emergency department (ED) by orally administered drugs without hospital admission and with ambulatory follow-up [1].

Initial evaluation

Appropriate triage of patients is a crucial part of the initial evaluation. After a complete history (with particular attention paid to pre-existing hypertension and TOD) and an accurate physical examination (including fundoscopic examination), selected laboratory studies such as urinalysis, creatinine, urea, electrolytes, and a full blood count should be performed. When a secondary form of hypertension is suspected a sample for plasma renin activity, aldosterone, and catecholamines should also be drawn. It is advisable to obtain in each patient an electrocardiogram and a chest radiogram (Table 2).

Table 1. Hypertensive emergencies

Hypertensive encephalopathy
Severe hypertension associated to acute target organ damage: • acute coronary syndromes • pulmonary oedema • acute aortic dissection • intracerebral haemorrhage, subarachnoid haemorrhage • acute brain infarction • acute or rapidly progressing renal failure
Severe hypertension after thrombolysis for ischaemic stroke
Pheochromocytoma crisis
Guillain-Barré syndrome
Spinal cord injury
Drugs related hypertension (sympathomimetics, cocaine, phencyclidine, phenylpropanolamine, lysergic acid diethylamide, cyclosporine, antihypertensive treatment withdrawal, interaction with MAO inhibitors)
Eclampsia
Postoperative bleeding
Post coronary artery bypass hypertension

Table 2. Diagnostic workup

Repeated blood pressure measurements (first measurements at both arms)
Clinical history and physical examination: • cardiovascular • CNS • *fundus oculi*
Selected laboratory studies: • urinalysis, creatinine, urea, electrolytes, and a full blood count • when a secondary form of hypertension is suspected, a sample for plasma renin activity, aldosterone, and eventually catecholamines should also be drawn
Electrocardiography
Chest X rays
Further investigations (according to the clinical presentation): • echocardiography (TT, TE) • brain CT scan or MRI • abdominal ultrasonography • thoraco-abdominal CT scan or MRI • vascular ultrasound

Blood pressure should be measured according to current Guidelines, both in sitting and standing positions [2]. A significant difference in BP between the two arms should raise the suspicion of aortic dissection. The ED blood pressure should then be strictly monitored.

Treatment of hypertensive emergencies

Patients should be admitted to an intensive care unit for clinical surveillance and continuous BP monitoring. Aggressive treatment with parenteral drugs is the preferred approach; in the majority of cases, however, the initial goal should be a partial reduction (and not normalisation) of BP, with a reduction in BP of no more than 20–25% within the first minutes and up to one or two hours, with possible cautious further decreases in subsequent hours [3, 4]. In most hypertensive emergencies a rapid lowering of BP is beneficial, with the exception of cerebrovascular accidents, in which it is advisable to take a more cautious approach [5–8]. An excessive reduction of BP values is potentially dangerous, possibly leading to ischaemic complications such as acute myocardial infarction and stroke.

Several parenteral agents are available for the treatment of hypertensive emergencies (Table 3); the choice of first-line antihypertensive agents should be tailored to the patient's clinical status. **Nitroprusside** is a highly effective short-acting arteriolar and venous dilator, which can be used in most hypertensive emergencies. In patients with primary intracerebral haemorrhage caution is needed because of the potential antiplatelet effect and intracranial pressure increase. The risk of cyanate toxicity is greater when the

Table 3. Drugs for hypertensive emergencies

Drug	Dose	Onset	Duration	Adverse effects
Sodium nitroprussiate	0.25–10 μg/kg/min	Immediate	1–2 min	Hypotension, vomiting, cyanate toxicity
Labetalol	20–80 mg bolus 1–2 mg/min infusion	5–10 min	2–6 h	Nausea, vomiting, heart block, bronchospasm
Glyceryl trinitrate	5–100 μg/min	1–3 min	5–15 min	Headache, vomiting
Enalaprilat	1.25–5.00 mg bolus	15 min	4–6 h	Hypotension, renal failure, angioedema
Furosemide	40–60 mg	5 min	2 h	Hypotension
Fenoldopam	0.1–0.6 μg/kg/min	5–10 min	10–15 min	Hypotension, headache
Nicardipine	2–10 mg/h	5–10 min	2–4 h	Reflex tachycardia, flushing
Hydralazine	10–20 mg bolus	10 min	2–6 h	Reflex tachycardia
Phentolamine	5–10 mg/min	1–2 min	3–5 min	Reflex tachycardia
Urapidil	25–50 mg bolus	3–4 min	8–12 h	Sedation

drug is used for long periods (days) or in patients with hepatic or renal dysfunction. With nitroprusside, BP should be continuously monitored intra-arterially; hypotension can, however, be managed in most cases by discontinuing the infusion. **Nitroglycerin** is a venous and, to a lesser degree, arteriolar dilator, particularly indicated in acute coronary syndromes and pulmonary oedema. **Labetalol** is an alpha- and beta-adrenergic blocker, which can be given as an intravenous bolus or infusion; it is highly effective and is indicated in most hypertensive emergencies, in particular in aortic dissection and in acute coronary syndromes. It may be given also after cocaine or amphetamine use, which may induce transient but significant hypertension leading to stroke and/or serious cardiac damage. **Urapidil**, an alpha-blocker with additional actions in the central nervous system (it activates 5-HT1A receptors), has also been found effective since it induces vasodilatation without tachycardia. Finally, it must be remembered that **furosemide** can be particularly indicated when volume overload is present, as in left ventricular failure. In the presence of volume depletion, in contrast, diuretics could cause additional reflex vasoconstriction and should therefore be avoided.

Specific hypertensive emergencies

In patients with **acute coronary syndromes** a severe elevation of BP values is not uncommon; on the other hand, myocardial ischaemia may also be induced by acute elevations in BP in patients without haemodynamically relevant coronary artery disease through an increase in left ventricular wall stress and myocardial oxygen consumption. In this setting intravenous vasodilators, such as nitroglycerin and nitroprusside, should be the initial drugs, in combination with a beta-blocker (labetalol, metoprolol, esmolol, or atenolol), which may further decrease BP and reduce heart rate and, consequently, myocardial oxygen consumption. In the presence of **acute left ventricular failure** BP should be rapidly controlled. The preferred drugs are intravenous nitroglycerin or nitroprusside in combination with loops diuretics for volume overload control. In patients with **aortic dissection** and hypertension BP control is crucial. The treatment should be started immediately and systolic BP rapidly reduced to less than 100 mm Hg; the ideal drug should not only allow the reduction of BP but also reduce heart rate and cardiac contractility with the aim of reducing stress on the aortic wall. This can be achieved with a combination of a beta-blocker and a vasodilator, such as nitroprusside or nitroglycerin, administered intravenously. ***Pheochromocytoma crises*** can be managed with an intravenous alpha-blocker such as phentolamine, followed by concomitant infusion of a beta-blocker; nitroprusside may also be added. Beta-blockers should always be associated with alpha-blockers in patients with pheochromocytoma since inhibition of beta-receptor-induced vasodilation may lead to a further increase in BP values in the presence of alpha-adrenergic vasoconstriction. Simultaneous alpha- and beta-blockade may also be achieved with monotherapy with labetalol. In patients with **acute stroke** the use of antihypertensive therapy is still controversial. Autoregulation of blood flow is impaired in ischaemic areas of the brain, and BP reduction may further reduce flow in the ischaemic penumbra and further expand the size of the infarction. It seems reasonable to recommend the institution of antihypertensive treatment only in the presence of BP values above 220/120 mm Hg (or mean BP > 140 mm Hg) in ischaemic stroke and to obtain an initial reduction of BP values of about 10–15%. Treatment may be initiated with intravenous labetalol, and, if needed, with nitroprusside or nitroglycerin. In patients with acute stroke treated with thrombolysis BP should be kept below 185/110 mm Hg. In primary **intracerebral haemorrhage**, treatment should be started if BP values are greater than 180/105 mm Hg [5–8]. For less marked elevations of blood pressure the available data do not support the initiation of antihypertensive treatment in the early phases of stroke. In fact, after the promising results of the ACCESS study (342 patients with acute stroke) [9], more recently, the SCAST study [10] showed no evidence of a beneficial effect of careful blood pressure lowering treatment with an angiotensin-receptor blocker in more than 2000 patients with acute ischaemic (85%) or haemorrhagic (14%) stroke and a mean blood pressure of 171/90 mm Hg. These results are further reinforced by those of a meta-analysis performed by the same authors, including more than 3600 patients, which confirmed the lack of benefit of BP lowering in acute stroke and mild to moderate elevations in BP. For haemorrhagic stroke, in the recently published INTERACT study [11], in which 404 patients with intracerebral haemorrhage and systolic BP between 150 and 220 mm Hg, underwent early intensive BP-lowering treatment, a significant reduction in haematoma growth over 72 hours was observed in actively treated patients. The ongoing main study (INTERACT2) will assess the effect of early intensive BP-lowering on functional outcome on a larger sample of patients (2800). Therefore, while awaiting the results of the ongoing studies, routine BP lowering in the acute phase of stroke in patients with mild to moderate elevations in blood pressure does not appear advisable. **Acute postoperative hypertension** is not uncommon, particularly after cardiothoracic, vascular, head and neck, and neurosurgical procedures. For most non-cardiac types of surgery there is no agreement on BP thresholds for treatment, and the patient's baseline BP, type of surgical procedure, and associated clinical conditions should be taken into account in patient management. It seems reasonable to maintain blood pressure within 20% of preoperative arterial pressure. For cardiothoracic surgery there is more evidence of an increased risk associated with a postoperative increase in BP values, which should be kept below 140/ /90 mm Hg [12, 13]. Labetalol (and other beta-blockers), nitroprusside, nitroglycerin, or fenoldopam should be the preferred intravenous drugs for BP control.

Treatment of hypertensive urgencies

In the majority of patients with severe hypertension no signs of acute TOD are usually observed. In these patients BP should be lowered gradually over a period of 24–48 hours; this can often be achieved by orally administered drugs without hospital admission and with close ambulatory follow-up. Clinical surveillance is advisable during the first few hours after drug administration. Blood pressure lowering should be gradual: there is no proven benefit from a rapid reduction in BP in asymptomatic patients who have no evidence of acute TOD, and a precipitous fall in BP could do more harm than good. In Table 4 recommended oral agents for hypertensive urgencies are reported. An initial approach with a combination of antihypertensive drugs increases the likelihood of effective BP reduction. The degree of BP reduction induced by sublingual nifedipine can neither be predicted nor controlled and this preparation is not recommended [14].

Conclusions

In the presence of severe elevations of BP a prompt and accurate initial work-up is crucial for the identification of acute TOD. Treatment should be started promptly in the ED with parenteral or oral drugs according to the findings of the initial evaluation. Blood pressure should be rapidly reduced but a precipitous fall in BP should be avoided and, in the majority of cases, reduction rather than normalisation of blood pressure should be the initial goal of treatment.

Table 4. Drugs for hypertensive urgencies

Drug	Dose	Time to peak	Half-life	Side effects
Captopril	12.5–25 mg p.o.	15–60 min	1.9 h	Renal failure in patients with renal artery stenosis
Labetalol	200–400 mg p.o.	20–120 min	2.5–8 h	Bronchospasm, depression of myocardial contractility, A-V block, nausea, elevation of liver enzymes
Furosemide	25–50 mg p.o.	1–2 h	0.5–1.1 h	Volume depletion
Amlodipine	5–10 mg p.o.	1–6 h	30–50 h	Headache, tachycardia, flushing, peripheral oedema
Felodipine	5–10 mg p.o.	2–5 h	11–16 h	Headache, tachycardia, flushing, peripheral oedema
Isradipine	5–10 mg p.o.	1–1.5 h	8–16 h	Headache, tachycardia, flushing, peripheral oedema
Prazosin	1–2 mg p.o.	1–2 h	2–4 h	Syncope (first dose), palpitations, tachycardia, orthostatic hypotension

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TREATMENT OF HIGH BLOOD PRESSURE IN THE ELDERLY

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Epidemiology and pathophysiology in elderly and old patients

Hypertension in the elderly (those over the age of 65 years) is an increasing public health concern [1]. Raised blood pressure, especially systolic pressure, confers a significant cardiovascular risk and should be actively treated in elderly patients. Even in the very old (those above the age of 80 years), hypertension is a dominant risk factor; treatment prolongs life and prevents stroke and heart failure. The prevalence of hypertension approaches or even exceeds 50% in people aged 70 and above [2].

Most elderly people with hypertension have isolated systolic hypertension, defined as systolic pressure greater than 140 mm Hg and diastolic pressure less than 90 mm Hg [3, 4]. Systolic hypertension is a more potent risk factor than increases in diastolic pressure.

Sluggish baroreceptor function and reduced cardiovascular sensitivity to catecholamines make the elderly more sensitive to natural or drug-induced falls in blood pressure.

Diagnostic work-up of hypertension in the elderly and target-organ damage

There may be diagnostic problems in the elderly and very old people. 'Pseudohypertension' should be suspected in older patients who, despite high blood pressure measurements, have minimal vascular damage in the retina and who experience inordinate postural dizziness despite cautious therapy. This is a condition in which there is a major discrepancy between intra-arterial and arm-cuff blood pressures, such that cuff pressures are falsely high [5, 6].

Blood pressure readings are far more variable in the elderly, so more readings should be taken initially than for patients in the general population. Blood pressure should be measured in both the sitting and standing positions since there is a high frequency (as much as 30%) of a 20 mm Hg or greater fall in blood pressure in patients with a systolic pressure over 160 mm Hg. In these circumstances standing blood pressure should be used to guide treatment decisions. Side effects like dizziness and light-headedness should alert the investigator of possible over-treatment. Prevalence of clinically significant secondary hypertension is low (probably in the 1–5% range).

Ambulatory and home blood pressure (ABP and HBP)

The last guidelines for the management of hypertension provide detailed suggestions regarding how and when to use ABP monitoring [7]. ABP has been found to be a significant predictor of cardiovascular morbidity, independent of office blood pressure and other risk factors in elderly subjects and those with isolated systolic hypertension [8, 9]. The white coat phenomenon, the difference between office blood pressure and ABP, may be more pronounced in the elderly [10]. The 'reversed white coat phenomenon', when ABP is higher than office blood pressure, has also been revealed in a substantial portion of older hypertensives [11]. However, the reproducibility and therefore the clinical utility of the white coat effect have been questioned [12].

In most people, blood pressure falls at night. The nocturnal dip is less marked with increasing age [12–14] and disappears in centenarians [13].

There is a paucity of data on HBP in elderly subjects. In the Ohasama study, HBP had greater predictive power for mortality and stroke than screening blood pressure [15], suggesting the potential usefulness of HBP measurements. However, physical and intellectual limitations, which are more evident in elderly subjects, may curtail more extensive use of HBP monitoring [7].

Total cardiovascular risk and when to start drug treatment for hypertension in the elderly

The same general rules apply to the whole hypertensive population [16–20]. Calculation of total cardiovascular risk using methods such as those proposed by the 2003 European Society of Hypertension–European Society of Cardiology Guidelines [21] is recommended. The HYVET study showed that reducing systolic BP from approximately 170 to 140 mm Hg in patients above the age of 80 years reduces mortality, stroke, and heart failure [22]. Treatment of hypertension in very old patients should be restricted to those who are otherwise relatively fit and with at least grade II hypertension [22].

Placebo controlled trials

The 2003 European Society of Hypertension-European Society of Cardiology Guidelines [21] for the management of arterial hypertension concluded that randomised controlled trials leave little doubt that elderly patients benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality, irrespective of whether they have systolic–diastolic or isolated systolic hypertension. Benefits in elderly patients [22–25] have been shown with representative agents from several classes such as diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers. Several studies [23, 26–28] have shown major benefits from treating elderly patients with isolated systolic hypertension.

Comparative trials

The first five large comparative trials comprising about 58,000 hypertensive patients showed no difference in the primary cardiovascular endpoint when 'newer' drugs were compared with 'older' drugs. The impression was thus that the most important aspect of management is to lower blood pressure with a combination of well tolerated drugs [29–35].

Several recent comparative trials have included populations with mean ages > 65 years. The LIFE study [35] showed a clear benefit of the angiotensin receptor blocker losartan over the beta-blocker atenolol in patients with left ventricular hypertrophy; thiazide was used similarly as add-on treatment in both arms. The losartan benefits were particularly expressed in two pre-specified subgroups of patients: those with diabetes [36] and those with isolated systolic hypertension [37]. In the SCOPE study [38] the angiotensin receptor blocker candesartan was associated with fewer strokes, but also lower blood pressure [38]. The SHELL Study [39] showed no difference in outcome between calcium antagonists and diuretics in patients with isolated systolic hypertension. In the VALUE trial [40] the angiotensin receptor blocker valsartan and the calcium antagonist amlodipine prevented the primary cardiac endpoint to the same extent, although blood pressure remained higher on valsartan. The VALUE findings [41] strongly suggest that blood pressure should be controlled to a level below 140/90 mm Hg within 3–6 months to prevent new or worsening cardiovascular disease. The ASCOT study [42] showed that treatment with the combination of amlodipine plus the ACE inhibitor perindopril was associated with reduced mortality and fewer cardiovascular endpoints than was treatment with atenolol combined with bendroflumethiazide, but the blood pressure was slightly higher in the latter treatment arm. However, in the ACCOMPLISH trial a fixed amlodipine-ACEI combination was superior to diuretic-ACEI in reduction of endpoints irrespective of age despite little blood pressure difference between the treatment arms [43].

Target blood pressure and the benefits of acetylsalicylic acid and statin as add-on therapy

The Hypertension Optimal Treatment (HOT) study [44] aimed to study the relationship between three levels of target diastolic blood pressure (≤ 90, ≤ 85, and ≤ 80 mm Hg) and cardiovascular morbidity and mortality in hypertensive patients, and to examine the effects on cardiovascular morbidity and mortality of a low dose (75 mg daily) of acetylsalicylic acid. Felodipine was given as baseline therapy with the addition of other agents. The HOT study comprised a large group of elderly patients (> 65 years) [45]. These subjects (n = 5987) averaged 70.6 + 3.9 years of age, 54% were women and their blood pressures were 175 ± 15/105 ± 4 mm Hg at randomisation. Intensive lowering of blood pressure was associated with a low rate of cardiovascular events without differences for the blood pressure target groups. Acetylsalicylic acid significantly reduced major cardiovascular events with the greatest benefit seen in all myocardial infarction. There was no effect on the incidence of stroke or fatal bleeds, but non-fatal major

bleeds were twice as common. Likewise, the effect of atorvastatin was at least as strong in the elderly patients as in the younger patients in the lipid-lowering arm of the ASCOT study [46].

Summary

There is little doubt from randomised controlled trials that elderly patients benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality, whether they have systolic–diastolic or isolated systolic hypertension. The larger randomised controlled trials of antihypertensive treatment versus placebo or no treatment in elderly patients with systolic–diastolic hypertension used a diuretic or a beta-blocker as first line therapy. In trials on isolated systolic hypertension, first-line drugs consisted of a diuretic or a dihydropyridine calcium channel blocker. In all these trials active therapy was superior to placebo or no treatment. Other drug classes have only been used in comparative trials. Benefit has been shown in older patients for at least one representative agent of several drug classes, including diuretics, beta-blockers, calcium channel blockers, converting enzyme inhibitors, and angiotensin receptor antagonists.

Initiation of antihypertensive treatment in elderly patients should follow the general guidelines. Many patients will have other risk factors, target-organ damage, and associated cardiovascular conditions, to which the choice of the first drug should be tailored. Furthermore, many patients will need two or more drugs to control blood pressure, particularly since it is often difficult to lower systolic pressure to below 140 mm Hg.

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HYPERTENSION AND HEART FAILURE

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Epidemiology

At the present time, a persistent increase in morbidity and mortality associated with CHF has been observed and heart failure remains a common cause of premature death [1].

Hypertension is the most important modifiable risk factor for heart failure [2] and it increases the risk for heart failure in all age groups. It has been calculated that in subjects aged 40 years or older with increased blood pressure (≥ 140 and/or 90 mm Hg) the lifetime risk of developing HF is double compared with those subjects with BP lower than 140/90 mm Hg. For CHF occurring in the absence of myocardial infarction it has been calculated that lifetime risk is 1 in 9 for men and 1 in 6 for women, which indicates the risk of CHF that is largely attributable to hypertension. In the Framingham Study update in 2003 only 25% of patients with heart failure suffered a myocardial infarction and about 75% of patients had a history of arterial hypertension; a significant association was observed between systolic and/or pulse pressure and incidence of HF [3]. Night-time blood pressure appears to convey additional risk information about congestive heart failure beyond office blood pressure measurements and other established risk factors, as shown in a cohort of uncomplicated elderly men in Sweden [4].

In patients with an acute myocardial infarction, the diagnosis of hypertension antecedent to the acute coronary event increases the risk of heart failure, interacting with age, neurohormonal activation, and early LV remodelling [5].

Despite the well-recognized beneficial effect of antihypertensive treatment on systolic heart failure, a persistent increase in morbidity and mortality associated with congestive heart failure has been observed in recent years [6, 7]. This phenomenon may also represent the consequence of diastolic dysfunction (i.e. impairment in ventricular relaxation and filling). In fact, approximately half of the patients with overt congestive heart failure may display normal ejection fraction and marked impairment in diastolic function [6] (Table 1).

Mechanisms

Hypertension can lead directly to the development of chronic heart failure by several mechanisms, alone or in combination, such as haemodynamic load, decreased intrinsic myocardial contractility, adverse chamber remodelling and left ventricular hypertrophy, coronary microvascular disease with impaired coronary haemodynamics, and ventricular fibrosis. In fact, in the presence of a chronic pressure overload, a parallel addition of sarcomeres takes place, with an increase in myocite width, which in turn increases wall thickness, and the development of concentric remodelling or hypertrophy [7]. Myocite hypertrophy is also associated with apoptosis, collagen deposition, and ventricular fibrosis. A variety of hormones, including angiotensin II and aldosterone, cytokines, such as TGF-β_1 and cardiotrophin-1, and growth factors, such as insulin like growth factor, have profibrotic effects and favour perivascular and interstitial fibrosis. Myocite degeneration, cell death, and replacement or reparative fibrosis lead to irreversible myocardial damage.

In addition, hypertension is a major risk factor for epicardial coronary artery atherosclerosis, and coronary artery disease, in turn, represents another important risk factor for HF [8].

Table 1. Characteristics of patients with systolic or diastolic heart failure

Characteristic	Diastolic heart failure	Systolic heart failure
Age	Frequently elderly	All ages, typically 50–70 yr
Sex	Frequently female	More often male
Left ventricular ejection fraction	Preserved or normal, approximately 40% or higher	Depressed approximately 40% or lower
Left ventricular cavity size	Usually normal, often with concentric left ventricular hypertrophy	Usually dilated
Left ventricular hypertrophy on electrocardiogram	Usually present	Sometimes present
Chest radiography	Congestion with or without cardiomegaly	Congestion and cardiomegaly
Gallop rhythm present	Fourth heart sound	Third heart sound

Clinical manifestations

As expected, asymptomatic systolic and diastolic dysfunction are more prevalent than symptomatic disease [9]. In many hypertensive patients LV chamber performance is often found to be normal in resting conditions, although an abnormal ejection fraction response to exercise may be observed, particularly in those with concentric hypertrophy, or in those with eccentric hypertrophy and obesity. The use of a more physiological midwall mechanics index (midwall fractional shortening) has shown that LV midwall function is commonly reduced at rest in about 15–20% of hypertensive patients. Asymptomatic chamber LV dysfunction (as evaluated by ejection fraction) may be also identified in about 3–4% of hypertensive patients and is associated with a higher risk of cardiovascular events.

Many patients are diagnosed with the onset of typical symptoms of heart failure, i.e. dyspnoea at rest or with exertion, consequent to elevated pulmonary capillary pressure and pulmonary congestion [10]. Patients with diastolic dysfunction do not tolerate tachycardia and rapid changes in blood pressure. The occurrence of atrial fibrillation may cause a reduction in cardiac output and the development of pulmonary congestion.

In hypertensive patients, regression of LVH is associated with an improvement of midwall systolic function, diastolic relaxation, and filling parameters, and with a reduced incidence of new onset atrial fibrillation. More importantly it has been shown that regression of LVH improves cardiovascular prognosis and in particular it decreases the incidence of heart failure, as shown by the HOPE [11] and LIFE [12, 13] studies.

Diagnosis

The low-cost electrocardiogram is commonly used to evaluate the presence of LVH and/or of arrhythmias. Echocardiography is more sensible for the detection of increased LV mass and can give information on LV geometry and systolic chamber or midwall performance. Doppler echocardiography with the analysis of transmitral flow combined with pulmonary vein flow may be used to define diastolic dysfunction. New other echocardiographic technologies, such as tissue Doppler imaging (TDI) and speckle tracking, are less load dependent and may increase the diagnostic accuracy of systolic and diastolic dysfunction [14].

Another tool for the diagnosis of heart failure is the measurement of plasma brain natriuretic peptide (BNP). The increase in LV stress activates the transcription and release of BNP that can be measured in the plasma of patients with systolic and/or diastolic dysfunction; the elevation in plasma BNP levels cannot, however, discriminate systolic from diastolic dysfunction.

Treatment

Most of the earlier randomised clinical trials evaluating the efficacy of antihypertensive drugs have been associated with a significant prevention of systolic cardiac failure, increasing patients' survival [15]. The efficacy of antihypertensive therapy supports the important contribution of persistently elevated blood pressure to onset and progression of CHF [16]. In the UKPDS study a significant reduction in heart failure rate was associated with the progressive decrease of blood pressure (12% decrease in the incidence of heart failure for 10 mm Hg decrease of systolic blood pressure) [17].

However, the meta-analysis of the results of major interventional randomized trials conducted in hypertensive patients have shown that the reduction in the incidence of CHF is related not only to the degree of blood pressure reduction, but also to the class of drug used [18].

Diuretics and beta-blockers were comparable to ACE inhibitors in preventing the development of heart failure, and diuretics, beta-blockers, and ACE inhibitors were more effective than calcium antagonists [18]. Angiotensin II receptor blockers (ARBs) have been demonstrated to be more effective than diuretics, beta-blockers, and calcium-antagonists in reducing the incidence of heart failure in hypertensive diabetic patients with renal disease (RENAAL, IDNT) or LVH (LIFE) [19] (Table 2).

Table 2. Effects of angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and angiotensin II receptors blockers vs. placebo and BP-lowering regimens based on different drug classes, on the risk of heart failure (modified from ref [18])

Class of drug	Comparison	Relative risk	(95% confidence intervals)
No DM	ACE inhibitors	Placebo	0.78 (0.62–0.98)
DM	ACE inhibitors	Placebo	0.88 (0.67–1.16)
Overall	**ACE inhibitors**	**Placebo**	**0.82 (0.69–0.98)**
No DM	Calcium-antagonists	Placebo	1.07 (0.43–2.62)
DM	Calcium-antagonists	Placebo	1.29 (0.97–1.72)
Overall	**Calcium-antagonists**	**Placebo**	**0.99 (0.53–1.86)**
No DM	ACE inhibitors	Diuretics/β-blockers	1.09 (0.95–1.25)
DM	ACE inhibitors	Diuretics/β-blockers	0.94 (0.55–1.59)
Overall	**ACE inhibitors**	**Diuretics/β-blockers**	**1.07 (0.96–1.20)**
No DM	Calcium-antagonists	Diuretics/β-blockers	1.33 (1.16–1.52)
DM	Calcium-antagonists	Diuretics/β-blockers	1.09 (1.01–1.61)
Overall	**Calcium-antagonists**	**Diuretics/β-blockers**	**1.09 (1.01–1.61)**
No DM	ACE inhibitors	Calcium-antagonists	0.86 (0.73–1.01)
DM	ACE inhibitors	Calcium-antagonists	0.92 (0.67–1.27)
Overall	**ACE inhibitors**	**Calcium-antagonists**	**0.84 (0.75–0.95)**
No DM	ARB	Other	1.13 (0.87–1.46)
DM	ARB	Other	0.70 (0.59–0.83)
Overall	**ARB**	**Other**	**0.79 (0.66–0.95)***

*Indicates that there is a difference in the effectiveness of the treatment regimen between patients with and without diabetes that is fairly unlikely to have occurred by chance alone; DM — diabetes mellitus; ARB — angiotensin II receptor blockers

On the other hand, in the ALLHAT study [20], symptoms of heart failure increased in patients randomized to treatment with the angiotensin-converting enzyme (ACE) inhibitor or with the calcium-antagonist, possibly because previous therapy including a diuretic was withdrawn at inclusion; in addition, despite significant differences in the incidence of heart failure, heart failure mortality did not differ among treatment arms with different antihypertensive drugs.

In the VALUE study [21] heart failure incidence was significantly lower in patients receiving valsartan in respect to those treated with amlodipine only after three years of treatment. In hypertensive patients with coronary artery disease, the control of blood pressure seems to be particularly relevant in the prevention of heart failure. The ACTION study [22] has shown that nifedipine GITS may reduce the number of new-onset heart failure in all patients (–29%) and to a greater extent in the subgroup of hypertensives (–38%). More recently BP reduction with an ACE inhibitor and diuretic combination was associated with a striking reduction in heart failure incidence as compared to placebo in very elderly (> 80 years of age) patients with hypertension [23].

The goal of antihypertensive treatment for the prevention of heart failure should be the control of blood pressure, but also the regression of left ventricular hypertrophy, of coronary epicardial artery atherosclerosis and of small vessel structural alterations, in addition to the decrease of ventricular fibrosis. ACE inhibitors and angiotensin II receptor blockers (ARBs) seem more effective in favouring the regression of LVH and of small vessel structural changes. They may also have a favourable effect in the reversal of myocardial fibrosis [24].

Only a few studies have evaluated the effect of blood pressure reduction in patients with heart failure, because of the lack of systematic recordings of arterial pressure. The SOLVD study [25] has clearly shown a beneficial effect of treatment with ACE inhibitors in comparison to a placebo in hypertensive patients, superimposable to that obtained in normotensive subjects.

Specific treatment of hypertension in heart failure may depend on the type of heart failure, systolic vs. diastolic. In systolic dysfunction, the aim of antihypertensive treatment is the reduction of preload and afterload, improvement of LV function, and control of symptoms and signs of pulmonary and systemic congestion. In diastolic dysfunction, the main task is lowering of blood pressure, and a reduction of heart rate together with control of fluid homeostasis and myocardial ischaemia. The CHARM (Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity) study [26] showed that in patients with diastolic dysfunction (Preserved group) treated with candesartan the hospitalization rate for heart failure was significantly lower in comparison with patients treated with placebo, while differences in cardiovascular mortality did not reach the level of statistical significance. Another study (I-Preserve) evaluated the effect of an ARB (irbesartan) in patients with diastolic dysfunction, and did not show a significant benefit in respect to "standard" treatment [27]; it should be pointed out that 39% of the patients randomized to the ARB were also concurrently treated with an ACE inhibitor. The ongoing TOPCAT study is aimed at evaluating the effect of the treatment with an anti-aldosterone drug in patients with preserved systolic function.

The Joint National Committee VII guidelines [28] state that a decrease in blood pressure is beneficial for all patients with heart failure. Although target blood pressure values are not clearly defined, systolic blood pressure values between 110 and 130 mm Hg are associated with an increased benefit.

The European hypertension guidelines recommend the treatment of hypertension in patients with heart failure, who are frequently complicated with coronary heart disease and atrial fibrillation, and suggest following the heart failure guidelines and introducing blood pressure-lowering drugs that simultaneously deal with the concomitant diseases [29, 30]. Drugs of choice are ACE inhibitors, ARBs, diuretics, beta-blockers, and aldosterone receptor antagonists. Alpha-blockers and calcium antagonists may be needed in combination with other drugs in order to achieve the target blood pressure, which is a stable value close to 130/80 mm Hg.

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HYPERTENSION AND MACROVASCULAR DISEASE

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Arterial stiffness and wave reflection are now well accepted as the most important determinants of increasing systolic and pulse pressures in ageing societies, and thus afford a major contribution to stroke and myocardial infarction. A major reason for measuring arterial stiffness and central blood pressure in hypertensive patients comes from the demonstration that arterial stiffness and central BP have a predictive value for CV events. An expert consensus document has reviewed the methodological agreements for measuring arterial stiffness, central BP, and wave reflections [1]. This newsletter will not address the issue of intima-media thickness (Newsletter No. 15, revised version) and endothelial dysfunction.

Methods of measurement

Large artery damage in hypertension can be non-invasively assessed through the measurement of arterial stiffness, central BP, and central augmentation index (AIx) (Table 1). In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional and local arterial stiffness can be measured directly, and non-invasively, at various sites along the arterial tree.

The measurement of pulse wave velocity (PWV) is generally accepted as the most simple, non-invasive, robust, and reproducible method with which to determine arterial stiffness [1]. Carotid-femoral PWV is a direct measurement of aortic stiffness, and it corresponds to the widely accepted propagative model of the arterial system. Measured along the aortic and aorto-iliac pathway, it is the most clinically relevant since the aorta and its first branches are what the left ventricle 'sees' and are thus responsible for most of the pathophysiological effects of arterial stiffness. PWV is usually measured using the foot-to-foot velocity method [1, 2].

Local arterial stiffness of superficial arteries can be determined using ultrasound devices [3]. Carotid stiffness may be of particular interest since in that artery atherosclerosis is frequent. A major advantage is that local arterial stiffness is directly determined from the change in local pressure driving the change in volume, i.e. without using any model of the circulation. However, because it requires a high degree of technical expertise, and takes longer than measuring PWV, local measurement of arterial stiffness is only really indicated for mechanistic analyses in pathophysiology, pharmacology, and therapeutics, rather than for routine use [1].

Arterial pressure waveform should be analysed at the central level, i.e. the ascending aorta, since it represents the true load imposed on the left ventricle and central large artery walls. Aortic pressure waveform can be estimated either from the radial artery waveform, using a transfer function [4], or from the common carotid waveform, using applanation tonometry [5]. The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. In the case of stiff arteries, PWV rises and the reflected wave arrives back at the central arteries earlier, adding to the forward wave and augmenting the systolic pressure. This phenomenon can be quantified through the augmentation index (AIx) — defined as the difference between the second and first systolic peaks expressed as a percentage of the pulse pressure [4, 5].

Table 1. Methods for measuring arterial stiffness in clinical investigation (adapted from ref [1])

Parameter	Predictive value for CV events	Degree of technical expertise
1. Carotid-femoral PWV Gold standard for arterial stiffness Speed of travel of the pulse along an arterial segment (L/Δt in m/s)	+++	+
2. Central pulse wave analysis Carotid and aortic pressure waves Central pulse pressure (PP) and SBP Central augmentation index (AIx)	++	+
3. Local arterial stiffness Carotid distensibility	+	+++

Pathophysiology of CV events

A generally accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in late systole, increasing central PP, and thus SBP. SBP increases the load on the left ventricle, increasing myocardial oxygen demand [6]. In addition, arterial stiffness is associated with increased sympathetic nerve activity [7] and left ventricular hypertrophy. The increase in central PP and the decrease in diastolic BP may directly cause subendocardial ischaemia [6].

An increased arterial stiffness can increase the risk of stroke through several mechanisms, including an increase in central PP, influencing arterial remodelling both at the site of the extracranial and intracranial arteries, increasing carotid wall thickness, and the development of stenosis and plaques, the likelihood of plaque rupture, and the prevalence and severity of cerebral white matter lesions [8]. Finally, coronary heart disease and heart failure, which are favoured by high PP and arterial stiffness, are also risk factors for stroke.

Predictive value of arterial stiffness and central BP

In the late 1990s, some epidemiological studies [9–11] showed that aortic stiffness had an independent predictive value for all-cause and CV mortality. Currently, as many as 19 studies — some of them included in a recent meta-analysis [12] — consistently showed the independent predictive value of aortic stiffness for fatal and non-fatal CV events in various populations (Table 2). Aortic stiffness can thus be considered as an intermediate end-point for CV events. The independent predictive value of aortic stiffness has been demonstrated after adjustment to classical cardiovascular risk factors, including brachial PP. This indicates that aortic stiffness has a better predictive value than each of the classical risk factors. Although the relationship between aortic stiffness and events is continuous, a threshold > 12 m/s has been suggested as a conservative estimate of significant alterations of aortic function in middle age hypertensives, and was included in the 2007 ESH Guidelines for the management of hypertension [13]. High aortic PWV may thus represent target organ damage, which needs to be detected during estimation of CV risk in hypertensives.

In the early 2000s some epidemiological studies [14, 15] showed that central AIx and PP, directly measured by carotid tonometry [14, 15], were independent predictors of all-cause and CV mortality in ESRD patients. A recent meta-analysis [16] confirmed these findings in several populations. However, central BP has a less independent predictive value than aortic stiffness for CV events, either in ESRD, hypertensives, elderly, or general populations. Also, the additive predictive value of central BP beyond brachial BP was not significant in most studies [17]. Thus, the 2007 ESH Guidelines for the Management of Hypertension [13] and their reappraisal [18] considered that more investigation was necessary before recommending the routine clinical use of central BP. Nevertheless, the measurement of central BP and Aix is of great interest for mechanistic analyses in pathophysiology, pharmacology, and therapeutics.

Clinical application

Non-pharmacological treatments which are able to reduce arterial stiffness and/or central PP and AIx include a number of possible interventions, from exercise training to dietary changes [1]. Antihypertensive treatments are able to reduce arterial stiffness mainly through the lowering of mean BP, thus reducing the load on the arterial wall [1]. Few studies have clearly demonstrated that arterial stiffness can be lowered beyond BP reduction. The reduction in wave reflections, through peripheral vasodilatation, associated with the reduction in aortic stiffness, represents a means to lower central PP and/or AIx. Central PP and/or AIx are best lowered by ACE inhibitors, AT1 blockers, and calcium channel blockers (CCB), and to a lesser degree by diuretics and vasodilating beta-

Table 2. Nineteen longitudinal studies reporting the independent predictive value of aortic stiffness for all-cause and CV mortality and CV events (adapted from ref [1] and [12])

Measurement site, ref	Events	Follow-up (years)	Type of patient (number)	Mean age at entry (years)
Blacher et al, 1999	CV mortality	6.0	ESRD (241)	51
Laurent et al, 2001	CV mortality	9.3	Hypertension (1,980)	50
Meaume et al, 2001	CV mortality	2.5	Elderly (> 70) (141)	87
Shoji et al, 2001	CV mortality	5.2	ESRD (265)	55
Boutouyrie et al, 2002	CHD events	5.7	Hypertension (1,045)	51
Cruickshank et al, 2002	All cause mortality	10.7	IGT (571)	51
Laurent et al, 2003	Fatal strokes	7.9	Hypertension (1,715)	51
Pannier et al, 2005	CV mortality	5.8	ESRD (305)	53
Sutton-Tyrrell et al, 2005	CV mortality and events	4.6	Elderly (2,488)	74
Shokawa et al, 2005	CV mortality	10	General pop. (492)	64
Hansen et al, 2006	CV mortality	9.4	General pop. (1,678)	55
Mattace-Raso et al, 2006	CV mt, CHD	4.1	Elderly (2,835)	72
Choi et al, 2007	CV mortality and events	2.6	Chest pain patients (497)	58
Zoungas et al, 2007	CV mortality and events	3.6	ESRD (207)	55
Terai et al, 2008	CV mortality and events	4.8	Hypertension (676)	62
Anderson et al, 2009	All cause mortality	19.6	General pop. (174)	60
Mitchell et al, 2010	CV events	7.8	General pop. (2,232)	63
Wang et al, 2010	All cause and CV mt	15	General pop. (1,272)	52
Maldonado et al, 2011	CV mortality and events	1.7	General pop. (2,200)	46

CHD — coronary heart disease; ESRD — end-stage renal disease; IGT — impaired glucose tolerance

-blockers. By contrast, non-vasodilating beta-blockers are either ineffective or increase central BP and/or AIx [19]. Three RCTs comparing combination therapies show that central BP and/or AIx are best lowered by a combination of an RAS blocker and a CCB [20–22].

Conclusion

These data highlight the importance of arterial stiffness and central BP for predicting CV outcomes. Arterial stiffening and central BP also provide direct evidence of target organ damage, which is of major importance in determining the overall CV risk of the hypertensive patient. Indeed, measurement of aortic stiffness and central BP may avoid patients being mistakenly classified as at low or moderate risk when they actually have an abnormally high aortic stiffness or central BP placing them within a higher risk group.

Several issues remain to be addressed. Among them, it is crucial to determine whether a reduction in arterial stiffness is a desirable therapeutic goal in terms of hard clinical endpoints such as morbidity and mortality. Although this has been done in patients with ESRD [23], it remains to be shown in a population of hypertensive patients at lower CV risk. In addition, it is important to demonstrate whether a therapeutic strategy aiming at normalizing arterial stiffness and central BP proves to be more effective in preventing CV events than usual care.

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SEXUAL DYSFUNCTION IN HYPERTENSION

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Introduction

Previously encountered as an unspoken reality, sexual dysfunction is now acknowledged as a clinical condition that impairs people's general health and well-being and has a major impact on the quality of life of both patients and their partners [1]. It is thus not surprising that sexual dysfunction represents a real therapeutic challenge to physicians of many specialties. Erectile dysfunction has been defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse [2]. Female sexual dysfunction is described, in a more complex way, as a persistent or recurring decrease in sexual desire or in sexual arousal, the difficulty or the inability to achieve an orgasm, or the feeling of pain during sexual intercourse, which mirrors the multifold aspects of women sexuality [3].

Sexual dysfunction and cardiovascular disease: what is new?

Not long since erectile dysfunction was first projected as an "early diagnostic window" of coronary heart disease, accumulating evidence is now available that sustains and reinforces this argument. Valuable data have been derived from prospective studies; erectile dysfunction was identified as an independent predictor of cardiovascular events over a long-term follow-up (9 years), with a hazard ratio of 1.45 that was found to be equal to or greater than traditional risk factors like hyperlipidaemia, smoking, or positive family history of myocardial infarction [4]. In another study the mean interval between the presence of erectile dysfunction and the onset of evident coronary artery disease was estimated in 39 months [5]. Additional prospective data in type II diabetic patients establish erectile dysfunction as an independent strong predictor of future cardiovascular events, even after adjustment for other known traditional risk factors. This was confirmed in a group of diabetic patients with no clinical evidence of cardiovascular disease, with a hazard ratio of 1.58 [6], as well as in diabetic patients with angiographically documented silent coronary artery disease, who were twice as likely to exhibit major adverse cardiac events under the presence of erectile dysfunction [7]. Similarly, the recently published substudy of the ONTARGET–TRANSCEND trials demonstrated that erectile dysfunction predicted cardiovascular events in high-risk patients as well [8].

It appears, therefore, that our knowledge about the interface between erectile dysfunction and cardiovascular disease has moved one step forward; current data strongly point towards a bilateral direction in the causative link between these two clinical entities. Nonetheless, in patients without subsistent cardiovascular disease, the predictive value of erectile dysfunction for cardiovascular disease beyond traditional risk factors was recently disproven [9]. Further research is required to establish or negate the role of both erectile and female sexual dysfunction as independent and potent predictors of cardiovascular disease.

Sexual activity is a form of exercise that can sometimes be intense. A recent meta-analysis revealed an almost 3-fold increased relative risk for MI during or immediately after sexual intercourse [10]. It should be noticed however that the absolute risk is low (2–3 per 10,000 person-years with one hour of sexual activity per week). Therefore, low-risk patients may safely proceed with sexual intercourse, while sexual activity should be deferred in high-risk patients until appropriate cardiologic evaluation [11].

Sexual dysfunction: defining the extent of the problem

Despite the accumulation of multiple epidemiological studies, the exact prevalence of sexual dysfunction in the general population remains unclarified. The prevalence of erectile dysfunction varies according to different reports and ranges from 7–53%, with 15–20% being the most probable estimation [12]. Data regarding female sexual dysfunction are scarce, but it emerges that, although understudied, it is more commonly encountered than erectile dysfunction (43% vs. 31% in the USA in 1999) [13]. The disparity of available data reflects the differences in the study populations with regard to age, selection criteria, and cultural habits, in combination with the variant and often invalidated assessment methodologies; yet it highlights that sexual dysfunction is commonly encountered in the general population and may even represent a major burden in specific groups of patients.

Sexual dysfunction in hypertensive patients

Currently considered a disease of vascular origin [14], erectile dysfunction has been repeatedly found to be higher among hypertensive compared to normotensive subjects (i.e. 45.8% vs. 18.9% in Spain, 35.2% vs. 14.1% in Greece). Similarly, accumulating evidence shows that hypertensive women exhibit a higher prevalence of sexual dysfunction compared to normotensives (42.1% vs. 19.4% according to one study, odds ratio 3.2) [15]. Duration and severity of hypertension were positively correlated with the degree of sexual dysfunction [16]. Obstructive sleep apnoea that is frequently accompanied by hypertension could be considered as an additional contributing factor, since sexual dysfunction is highly prevalent in such patients [17].

Sexual dysfunction in cardiovascular disease

Remarkably, several traditional cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia, smoking) constitute risk factors for erectile dysfunction as well [18, 19]. Since patients with cardiovascular disease exhibit increased prevalence of these comorbidities, they subsequently present increased frequency of sexual dysfunction. Indeed, prevalence of erectile dysfunction in patients with coronary artery disease is overtly higher than in the general population, with estimations ranging from 49–75% [20, 21].

(Patho)physiological pathways in hypertension leading to sexual dysfunction

Penile erection represents a neurovascular pathway in which psychological and hormonal factors play a pivotal role. In erectile dysfunction, blood flow of the penile vasculature is impaired in correspondence to the systemic structural changes caused by hypertension, with stenotic lesions secondary to atherosclerosis comprising the common background. Elevated blood pressure levels induce endothelial dysfunction, activate the renin–angiotensin system, and impair the neurogenic and smooth-muscle-induced relaxation in response to nitric oxide. The combination of the aforementioned structural and functional abnormalities triggered by increased blood pressure renders hypertension a key promoter of erectile dysfunction. Although data regarding the pathophysiology of female sexual dysfunction are significantly limited, it appears that hypertension exerts similar effects on the sexual functioning of both sexes.

Effects of antihypertensive drug therapy on sexual function

The prevalent perception that antihypertensive treatment is detrimental to sexual functioning may dramatically extenuate patients' adherence, exposing them to the risks of all the short- and long-term negative consequences of hypertension. However, the superiority or inferiority of each class of antihypertensive drugs regarding sexual function is difficult to determine beyond doubt since the incidence of sexual dysfunction must be co-estimated with several factors other than antihypertensive treatment, such as hypertension characteristics, personal characteristics, existing comorbidities and co-administered drugs. So far, outcomes from relevant studies suggest the classification of antihypertensive treatment to: drugs negatively affecting erectile function, including central acting, diuretics, and β-blockers, with the only possible exception being nebivolol [22–27]; drugs that appear to exert a neutral effect on erectile dysfunction, including calcium antagonists and angiotensin-converting enzyme (ACE)-inhibitors [28, 29]; and drugs that seem to improve erectile dysfunction, with angiotensin receptor blockers (ARBs) being recommended as first-line treatment in patients

with pre-existing sexual dysfunction or as substitution therapy in patients with antihypertensive drug-induced erectile dysfunction [30].

Of note, the quantity and quality of available data does not allow the extraction of definite conclusions, particularly in regard to the newer generation antihypertensive agents. Indeed, the beneficial effect of ARBs on erectile dysfunction was recently questioned by the outcomes of the substudy of the ONTARGET–TRANSCEND trials, in which ARB administration neither significantly improved nor impaired erectile dysfunction [8]. However, extrapolation of these results should be circumspect, taking into consideration the fact that ARBs were added on top of previous multidrug therapy in high-risk patients. In addition, there is a lack of solid evidence regarding the newest medication of the renin–angiotensin axis, the renin-inhibitor aliskiren; data regarding combination therapy are inconclusive, and the field is still unclear when it comes to female sexual dysfunction. Since extraction of conclusions is insecure in the absence of sound data, heading towards the direction of large randomized, double-blind, prospective trials examining effects of different antihypertensive drugs on sexual dysfunction emerges as extremely important.

Sexual dysfunction and hypertension: a mutual target for PDE-5 inhibitors?

Despite the initial circumspection regarding administration of phosphodiesterase (PDE)-5 inhibitors in hypertensive subjects, a wealth of clinical data convincingly proclaims that its concomitant use with all classes of antihypertensive drugs is not only safe, but provides additional benefits beyond treatment of erectile dysfunction [31]. Precautions need to be taken with alpha-blockers due to the risk of marked hypotension; therefore, initiation of treatment with half doses of either drug is recommended.

The addition of a PDE-5 inhibitor in hypertensives with erectile dysfunction enhances the possibility of initiation rather than discontinuation, and addition rather than rejection of antihypertensive medication [32]. Indeed, adherence to antihypertensive therapy is significantly improved, with 36% of noncompliant patients becoming adherent after administration of PDE-5 inhibitors in one report [33].

PDE-5 inhibitors exhibit a degree of systemic vasorelaxing activity, which accounts for usually small, clinically insignificant blood pressure reductions both in normotensive and hypertensive individuals [34––36]. Although the initial concept in developing PDE-5 inhibitors was towards the management of cardiovascular disease, this potential was left aside thereafter. However, a new, long-acting PDE-5 inhibitor was recently administered as an antihypertensive agent and achieved a sustained, moderate blood pressure decrease with a good safety and tolerability profile [37]. Interestingly, addition of a PDE-5 inhibitor in resistant hypertensive patients, alone or in combination with a nitrate, provided an additional clinically significant BP reduction without significant adverse effects [38]. The small number of participants, however, and the potential risks of this combination prohibit the extraction of safe conclusions.

Concluding remarks

Sexual dysfunction is frequently encountered in hypertensive patients, either as a result of penile atherosclerotic disease due to high blood pressure levels, or caused by certain antihypertensive drugs, or a combination of both factors. Sexual dysfunction requires special interest by hypertension specialists, cardiologists, internists, and primary care physicians because:

- sexual dysfunction may be used as an 'early diagnostic indicator' for asymptomatic coronary artery disease, providing a unique opportunity for timely recognition of cardiovascular disease;
- sexual dysfunction affects patients' and their sexual partners' quality of life. Management of erectile dysfunction not only improves quality of life but greatly increases adherence to antihypertensive medication.

A Working Group on Sexual Dysfunction has recently been formed by the European Society of Hypertension aiming to improve the detection and management of sexual dysfunction by all clinicians dealing with hypertensive patients. In addition, the Working Group aims to sensitize other specialties (Urologists, Gynaecologists, and Psychiatrists) that sexual dysfunction may be the first sign of cardiovascular disease and requires cardiologic evaluation.

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DISCOVERING THE GENETIC DETERMINANTS OF HYPERTENSION

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Hypertension (HTN) and blood pressure (BP) are examples of complex (polygenic) traits influenced by multiple genetic and environmental factors. The determination of the genetic variants involved in HTN should provide new insight into the disease susceptibility, progression, and severity, leading to novel pharmaceutical targets, with the ultimate goal of improving prevention, diagnosis, and treatment [1, 2]. There are multiple lines of evidence indicating a genetic contribution to the BP phenotype. Family studies have shown BP to be highly heritable with estimates ranging from 31–34% for office systolic blood pressure (SBP) and diastolic blood pressure (DBP), through 56–57% for long-term average SBP and DBP phenotype, to 44–63% for 24-hour SBP and DBP [3–6]. Further evidence for a genetic contribution to BP comes from the discovery of highly penetrant rare genetic variants with large effects in families with Mendelian forms of HTN and hypotension [7, 8]. The genetic dissection of BP and HTN has, however, been one of the most challenging of all the polygenic traits. We outline the successes and limitations of current approaches and the prospects and obstacles to future progress in blood pressure genetics.

Gene mapping studies in hypertension

There are three key characteristics of a genetic variant that determine its impact on the phenotype studied: 1) the frequency of the variant; 2) the effect size of the variant on the phenotype, and 3) the number of genetic variants acting on the phenotype. Monogenic HTN syndromes are due to rare variants with large effect sizes [7, 8], and these account for less than 1% of human HTN. The high prevalence of essential HTN and the continuous nature of the BP phenotype suggest that these traits cannot be explained by rare variants harbouring large effect-sizes. The "common disease, common variant" hypothesis (CD:CV) is the model invoked to explain how genes influence common traits like BP or HTN [9, 10]. This model proposes using an evolutionary framework that common disease is due to allelic variants with a frequency greater than 5% in the general population and a small individual effect size.

Linkage and candidate gene studies

Initial systematic approaches to identifying genes for BP/HTN were linkage and candidate gene studies. Linkage mapping is a method of studying genetic markers of known chromosomal location that are co-inherited with the disease in related individuals. Association mapping, commonly used in candidate gene studies, is based on linkage disequilibrium (LD). LD is the non-random association of alleles at two or more loci on a chromosome and results in the greater co-occurrence of two genetic markers in a population than would be expected for independent markers. In practical terms, LD results in single nucleotide polymorphisms (SNPs) that are in close proximity and travel together in a block when passed from parent to child, allowing one SNP in a block to serve as a surrogate for the other SNPs in the block, thus obviating the need for testing all the SNPs individually. A new mutation that arises within a block travels along with the members of the block for hundreds of generations. In short, linkage measures the cosegregation between a genetic marker and a disease affection status in a pedigree, due to meiotic recombination events in the last 2–3 generations [9]; while LD measures cosegregation in a population (a very large pedigree extending back to the founders) resulting from much earlier ancestral meiotic recombination events [10]. Linkage analysis, while powerful for finding Mendelian disease genes, showed modest to minimal success in the mapping of complex traits [11–14]. The key limitations of linkage studies are relatively low analytical power (especially for detecting common alleles that have low penetrance), a lack of positional resolution, multiple pleiotropic variants of low penetrance, epistasis, poor replication, ethnic diversity of human populations, phenotypic heterogeneity, and the inability to control for environmental factors [14–16].

A number of candidate genes have been tested for association with BP/HTN with inconclusive results. Some of the limitations of the candidate gene approach include: 1) the choice of candidate genes may be inappropriate; 2) the genes that affect blood pressure might be involved in events that take place either upstream of the points of action of the selected candidates or in the downstream signalling events, and 3) candidate gene studies rely on prior hypotheses about disease mechanisms, so that discovery of genetic variants in previously unknown pathways is precluded [17, 18].

Genome-wide association studies

The CD:CV framework requires population-wide genotyping of very large numbers of common SNP variants to determine which variants show significant association with blood pressure or hypertension. Technological advances now allow reliable and high-throughput genotyping of hundreds of thousands of SNPs, permitting Genome-Wide Association Studies (GWAS). These studies employ large scale association mapping using SNPs, making no assumptions of the genomic location or function of the causal variant, and test the hypothesis that allele frequency differs between individuals with differences in phenotype [17]. In GWAS, each SNP is tested for association with a phenotype of interest. This creates a major multiple testing problem requiring the observed P-values to be corrected because highly significant results can occur by chance given the number of tests performed in GWAS. The current popular method to multiple-test correction is the frequentist approach of adjusting for a number of independent tests, as originally proposed by Risch and Merikangas [10]. Based on this, a significance level of 5×10^{-8} in populations of European ancestry for an overall genome-wide significance threshold of 0.05, adjusted for an estimated 1 million independent SNPs in the genome by the Bonferroni method, is commonly used [19]. This threshold will vary in samples of non-European ancestries as the number of independent tests are based on the extent of variation and LD.

Finding an SNP association signal that attains genome-wide significance requires further validation to prove that this is indeed a true signal. This is usually in the form of technical validation and exact replication. A false positive signal can be due to a multitude of potential methodological errors (batch effects, genotyping errors, confounding by ancestry), and ultimate proof of association must come from replication of significantly associated SNPs in independent samples [20]. One simple clue suggesting that the apparent association is not due to genotyping artefacts is the presence of multiple correlated SNPs at a locus with comparable association. Technical validation refers to reanalysis of associated SNPs on a different genotyping platform, and provides evidence that an observed association signal is not due to systematic genotyping errors. A replication study of a putative association tests the same direction of effect for the same polymorphism in the same phenotype and in a sample from the same ancestral origin and similar ascertainment, often termed exact replication. True positive results tend to overestimate the true effect size due to random chance ("winner's curse") [21]. This will hinder replication of a finding in a second sample if the sample is inadequately powered to find a weaker effect; hence replication sample size calculations need to take this into account.

The first GWAS study for HTN was the Wellcome Trust Case Control Consortium (WTCCC) study which showed an absence of any positive signals for hypertension using 2000 cases and 3000 common population controls [22]. This study also did not detect any genes previously implicated by candidate gene association studies. This was followed by more successful GWAS studies in American Amish [23], African Americans [24], Europeans [25, 26], and Asians [27] and large-scale GWAS meta-analysis [28, 29] with robust evidence of replication of all the top signals. Table 1 summarises the replicated signals in BP/HTN GWAS. The main reason why the WTCCC did not identify any signals for HTN is attributed to the dilution of contrast between cases and controls as the WTCCC controls were not screened to exclude individuals with HTN. In general, among all the GWA studies for BP/HTN, there is a paucity of signals for HTN compared to BP as a continuous trait. It is very likely that the reason for this is due to differences in power, as continuous traits have greater power than discrete traits, which translates to a higher chance of obtaining a significant result. One strategy to increase power is meta-analysis GWAS, which increases the sample size by combining samples from a number of medium- to large-scale epidemiological studies, as done in CHARGE and Global BPGen [28, 29]. Another strategy successfully employed to increase power without increasing sample size is sampling from the extremes of the BP distribution [26].

The top signals presented in Table 1 are landmark findings in that these are the first true and unequivocal genetic signals for BP/HTN. However, the majority of these SNPs are not likely to be causal SNPs. This is because the genotyped SNPs are usually proxies for untyped SNPs and other genetic variants. Most of the genes listed in Table 1 for each SNP are selected because of proximity to the SNP. Identification of the causal gene and causal variant will require fine-mapping and ultimately resequencing of the associated locus to identify all the potential variants that could explain an SNPs association. This needs to be followed by molecular biological approaches to determine which one is the causal variant. Among the GWAS hits, only two loci contained known BP genes. The SNP rs17367504 is correlated with an SNP associated with plasma atrial natriuretic peptide in a previous candidate gene study, suggesting that this SNP may mediate its effect through regulation of the natriuretic peptide gene [30]. However, rs17367504 is also strongly associated with hepatic expression of *CLCN6* which encodes a renally expressed chloride channel, suggesting the genotype-phenotype association is not straightforward [31]. The other locus is rs11191548, which is near *CYP17A1* and a few other genes. Missense mutations in *CYP17A1* cause congenital adrenal hyperplasia (CAH) with hypertension and hypokalaemia, making this a more likely causative gene but probably not the causative variant.

All the other genes closest to the variants identified were previously largely unsuspected of involvement in hypertension. The most plausible biological candidate is rs13333226 in the promoter region of the Uromodulin (*UMOD*) gene identified in a GWA study of blood pressure extremes [26]. The minor G allele of this SNP is associated with a lower risk of HTN (OR [95% CI]: 0.87 [0.84; 0.91]), reduced urinary UMOD excretion and increased estimated glomerular filtration rate (eGFR) (3.6 ml/min/minor-allele, p = 0.012), and borderline association with renal sodium balance. Thus only two genes, *UMOD* and *NPPA*, have shown evidence of association between GWAS SNP variation and gene protein product, making them early targets for further molecular and functional dissection [26, 30].

The effect sizes of all the variants listed in Table 1 are modest, with a per allele change in BP of 1 mm Hg SBP and 0.5 mm Hg DBP. These are small BP changes and well below the measurement error, but significant in large cohorts. It is likely that many genes act conjointly, and the individual contribution of each gene to overall BP variation is very small. Attempts have been made to develop a risk score which estimates the conjoint effect of the top hits to be several mm Hg [28]. However, the accuracy of this is limited by the "winner's curse" effect, and more generally the predictive power of the genetic variants identified for BP and HTN, even when taken collectively, is too small to be clinically useful.

The total of all the common variants identified through GWAS explain less than 1% of the overall population variation in BP and a very small fraction of the heritability of BP [28, 32]. This is not unique to BP, and there are a number of potential reasons proposed — the most notable are: 1) the causal variants may be present at lower allele frequencies in the same genes; and 2) the methods used to estimate human heritability in these traits have overestimated genetic factors and underestimated other influences (shared environment, diet, age, exercise, BMI) [33].

There is now evidence that rare variants with strong effects contribute to hypertension and common diseases [34–36]. Lifton et al. [35], after resequencing three candidate genes in which homozygous mutations cause Gitelman's or Bartter's syndromes: *NCCT (SLC12A3)*, *NKCC2 (SLC12A1)*, and *ROMK (KCNJ1)*, identified 30 putative functional mutations. Carriers had 6.3 mm Hg lower SBP and 3.4 mm Hg lower DBP compared with non-carriers, and remarkably 1 of every 64 subjects in the Framingham cohort was found to carry a mutation of potential functional significance in 1 of these 3 genes [35]. Future studies will be directed towards sequencing and identification of rare variants that influence BP/HTN and can explain the remaining missing heritability.

Another type of genetic variation overlooked in all association studies are structural variations, specifically sub-microscopic rearrangements between 500 bp

Table 1. Genome-wide association studies: replicated findings for BP and HTN

Chr	SNP	Position	Ethnicity	N	Phenotype	Risk allele	Risk allele frequency	OR or β	p	Nearest gene	Ref
1	rs17367504	11,785,365	E	34,433	SBP	G	0.14	–0.85	2×10^{-13}	*MTHFR, CLCN6, NPPA, NPPB, AGTRAP*	[28, 32]
2	rs6749447	168,749,632	E	542	SBP	G	0.28	1.90	8×10^{-5}	*STK39*	[23]
3	rs9815354	41,887,655	E	29,136	DBP	A	0.17	0.49	3×10^{-9}	*ULK4*	[28, 32]
4	rs16998073	81,403,365	E	34,433	DBP	T	0.21	0.50	1×10^{-21}	*FGF5, PRDM8, C4orf22*	[28, 32]
4	rs991316	100,541,468	AA	1017	SBP	T	0.45	1.62	5×10^{-6}	*ADH7*	[24]
10	rs11014166	18,748,804	E	29,136	DBP	A	0.66	0.37	1×10^{-8}	*CACNB2*	[28, 32]
10	rs1530440	63,194,597	E	34,433	DBP	T	0.19	–0.39	1×10^{-9}	*C10orf107, TMEM26, RTKN2, RHOBTB1, ARID5B, CYP17A1*	[28, 32]
10	rs1004467	104,584,497	E	29,136	SBP	A	0.90	1.05	1×10^{-10}	*TMEM26, RTKN2, RHOBTB1, ARID5B, CYP17A1*	[28, 32]
10	rs11191548	104,836,168	E	34,433	SBP	T	0.91	1.16	3×10^{-7}	*CYP17A1, AS3MT, CNNM2, NT5C2*	[28, 32]
11	rs381815	16,858,844	E	29,136	SBP	T	0.26	0.65	2×10^{-9}	*PLEKHA7*	[28, 32]
12	rs17249754	88,584	EA	8,842	SBP, DBP	A	0.37	1.06	9×10^{-7}	*ATP2B1*	[27]
12	rs2681472	88,533,090	E	29,136	SBP, DBP, HTN	A	0.83	0.50	2×10^{-9}	*ATP2B1*	[28, 32]
12	rs2681492	88,537,220	E	29,136	SBP, DBP, HTN	T	0.80	0.85	4×10^{-11}	*ATP2B1*	[28, 32]
12	rs3184504	110,368,991	E	29,136	SBP, DBP	T	0.49	0.48	3×10^{-14}	*ATXN2, SH2B3*	[28, 32]
12	rs653178	110,492,139	E	34,433	DBP	T	0.53	–0.46	3×10^{-18}	*ATXN2, SH2B3*	[28, 32]
12	rs2384550	113,837,114	E	29,136	DBP	A	0.35	0.43	4×10^{-8}	*TBX3, TBX5*	[28, 32]
15	rs1550576	56,000,706	AA	1,017	SBP	C	0.86	1.92	3×10^{-6}	*ALDH1A2*	[24]
15	rs1378942	72,865,396	E	34,433	DBP	C	0.36	0.43	1×10^{-23}	*CSK, CYP1A1, CYP1A2, LMAN1L, CPLX3, ARID3B, ULK3*	[28, 32]
15	rs6495122	72,912,698	E	29,136	DBP	A	0.42	0.40	2×10^{-10}	*CSK, CYP1A1, CYP1A2, LMAN1L, CPLX3, ARID3B, ULK3*	[28, 32]
16	rs13333226	20,273,155	E	3,320	HTN	A	0.81	1.15	4×10^{-11}	*UMOD*	[26]
16	rs11646213	81,200,152	E	1,977	HTN	T	0.60	1.28	8×10^{-6}	*CDH13*	[25]
17	rs12946454	40,563,647	E	34,433	SBP	T	0.28	0.57	1×10^{-8}	*PLCD3, ACBD4, HEXIM1, HEXIM2*	[28, 32]
17	rs16948048	44,795,465	E	34,433	DBP	G	0.39	0.31	5×10^{-9}	*ZNF652, PHB*	[28, 32]

E — European; AA — African American; EA — East Asians; SBP — systolic blood pressure; DBP — diastolic blood pressure; HTN — hypertension; *ACBD4* — acyl-CoA binding domain containing 4; *ADH7* — alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide; *AGTRAP* — angiotensin II receptor-associated protein; *ALDH1A2* — aldehyde dehydrogenase 1 family, member A2; *ARID5B* — AT rich interactive domain 5B (MRF1-like); *AS3MT* — arsenic (+3 oxidation state) methyltransferase; *ATP2B1* — ATPase; Ca++ transporting, plasma membrane 1; *ATXN2* — ataxin 2; *C10orf107* — chromosome 10 open reading frame 107; *C4orf22* — chromosome 4 open reading frame 22; *CACNB2* — calcium channel, voltage-dependent, beta 2 subunit; *CDH13* — cadherin 13, H-cadherin (heart); *CLCN6* — chloride channel 6; *CNNM2* — cyclin M2; *CPLX3* — complexin 3; *CSK* — c-src tyrosine kinase; *CYP17A1* — cytochrome P450, family 17, subfamily A, polypeptide 1; *CYP1A1* — cytochrome P450, family 1, subfamily A, polypeptide 1; *CYP1A2* — cytochrome P450, family 1, subfamily A, polypeptide 2; *FGF5* — fibroblast growth factor 5; *HEXIM1* — hexamethylene bis-acetamide inducible 1; *HEXIM2* — hexamthylene bis-acetamide inducible 2; *LMAN1L* — lectin, mannose-binding, 1 like; *MTHFR* — methylenetetrahydrofolate reductase (NAD(P)H); *NPPA* — natriuretic peptide A; *NPPB* — natriuretic peptide B; *NT5C2* — 5′-nucleotidase, cytosolic II; *PHB* — prohibitin; *PLCD3* —phospholipase C, delta 3; *PLEKHA7* — pleckstrin homology domain containing, family A member 7; *PRDM8* — PR domain containing 8; *RHOBTB1* — Rho-related BTB domain containing 1; *RTKN2* — rhotekin 2; *SH2B3* — SH2B adaptor protein 3; *STK39* — serine threonine kinase 39; *TBX3* — T-box 3; *TBX5* — T-box 5; *TMEM26* — transmembrane protein 26; *ULK3* — unc-51-like kinase 3 (*C. elegans*); *ULK* — unc-51-like kinase 4 (*C. elegans*); *UMOD* — uromodulin; *ZNF652* — zinc finger protein 652

and 5Mb in size, commonly called copy number variation (CNV). Early studies looking at the association of CNVs in HTN have not been promising [37].

Future

The next phase in the genetic dissection of blood pressure related traits will include larger meta-analysis of BP as quantitative traits and BP extremes. Next generation sequencing technologies will allow identification of both rare and common DNA sequence variants and enable a complete analysis of all risk variants. While these strategies will uncover additional BP/HTN genetic variants, it is unclear if these would explain the entire heritability of the traits. Other equally important strategies include analysis of intermediate phenotypes such as sodium homeostasis, endothelial function, and the sympathetic nervous system, gene-environment interactions, and gene–gene interactions, which will help to understand the physiological link between gene variants and phenotype.

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THE MICROCIRCULATION AND THE HAEMODYNAMICS OF HYPERTENSION

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The haemodynamic characteristic of essential and most forms of secondary hypertension consists of an elevated blood pressure and peripheral vascular resistance. Blood pressure comprises two components: a pulsatile (pulse pressure) and a steady (mean arterial pressure; MAP) component. Pulse pressure is predominantly influenced by the elastic properties of the larger conduit arteries, whereas MAP is determined by the resistance to flow in smaller arteries and arterioles, ranging in diameter from 10 to 300 μm [1, 2]. The small arteries and arterioles are a continuous segment of the vascular system associated with a gradual drop in pressure. Instead of referring to specific components as resistance vessels, the entire arterial microcirculation vessels of between 10 and 300 μm should be regarded as a site of resistance, and thus MAP, control. The exact location of the pressure drop may differ in relation to tissue. In cardiac tissue, for example, the pressure drop occurs distally in the arterial tree, whereas in the mesentery it is located more proximally [2].

Isolated small arteries

Great progress has been made in the last decade in understanding the pathological changes in the small arteries and arterioles in hypertension. This progress is at least partly due to progress in technologies which study microcirculation in humans. One area of advancement has been the use of isolated small arteries mounted using a steel wire or pressure micromyograph. Biopsies of subcutaneous fat from the gluteal region have been used to investigate the function of small arteries 100–300 μm in diameter. Rizzoni et al. showed that small arteries taken from patients with essential hypertension showed an inward eutrophic remodelling, different from the outward hypertrophic remodelling observed in diabetic patients [3]. In addition, these authors showed that microvascular changes in small arteries taken from subcutaneous fat tissue were related to coronary flow reserve [4] and were predictive of cardiovascular morbidity in a heterogeneous cohort of hypertensive patients at high cardiovascular risk, including those with secondary hypertension and diabetes [5]. Those patients in whom a hypertrophic remodelling was present (patients with diabetes mellitus, obesity, metabolic syndrome, renovascular hypertension, etc.) had an even worse prognosis compared with those with eutrophic remodelling [6].

Increased wall-to-lumen ratios of subcutaneous tissue have also recently been found to predict cardiovascular events and loss of renal function [7] in hypertensive patients at mild cardiovascular risk [8, 9].

Interestingly, there was no prognostic role pertaining to endothelial dysfunction in the subcutaneous small arteries of hypertensive patients [10].

Retinal arterioles

Recent studies have expanded the *in vitro* analyses of subcutaneous small arteries to *in vivo* retinal arterioles ranging from 100 to 250 μm in diameter. Advances in retinal photography and computing technologies have enabled precise measurements to be made of small artery and arteriolar vessel size from digital retinal images. Several large, population-based studies have applied this approach to quantitatively determine retinal vessel diameters, and these have documented a consistent association between elevated blood pressure and narrowed retinal arterioles [11–13]. Similar studies have also indicated that retinal arteriolar narrowing predicts future blood pressure elevation in previously normotensive persons [14–16].

Schmieder et al. [17, 18] have taken retinal microvascular analysis a step further by applying *in vivo* scanning laser Doppler flowmetry. This approach has not only allowed them to determine retinal arteriolar diameters, but also their wall-to-lumen ratio. They found that subjects with essential hypertension had a higher wall-to-lumen ratio of retinal arterioles than normotensive subjects [18]. Multiple regression analysis including a variety of known cardiovascular risk factors revealed that blood pressure is independently associated with an increased wall-to--lumen ratio of retinal arterioles. They showed that the wall-to-lumen ratio was significantly increased in patients with overt cerebrovascular disease as well as in hypertensive patients with poor blood pressure control, when compared to patients with good blood pressure control [17]. Furthermore, increased wall-to-lumen ratio of retinal arterioles is related with increased urinary albumin excretion [19].

Coronary microcirculation

Currently, no technique allows the direct *in vivo* visualisation of coronary microcirculation in humans [20]. Several measurements that rely on the quantification of blood flow through the coronary circulation are commonly used to describe the function of coronary microvasculature. These include intracoronary thermodilution, an intracoronary Doppler wire, and transthoracic Doppler echocardiography [20]. Cardiovascular magnetic resonance imaging and positron-emission tomography are some of the technically more demanding methods to assess coronary microvascular function. A parameter often used to express coronary microvascular function is the coronary flow reserve. Coronary flow reserve is the magnitude of the increase in coronary flow that can be achieved in going from basal coronary perfusion to maximal coronary vasodilatation. Coronary flow reserve is determined by measuring coronary or myocardial blood flow and taking measurements both at rest and with maximal hyperaemia. Abnormal coronary flow reserve has been demonstrated in patients with essential hypertension, despite the presence of angiographically normal coronary arteries and the absence of left ventricular hypertrophy [20, 21]. The cause of the reduced coronary flow reserve in hypertension has been related to remodelling of the coronary small arteries and arterioles as well as the interstitial fibrosis. The remodelling of the arterioles leads to a decreased density of vessels in the coronary microvasculature, whereas the interstitial fibrosis reinforces their effects by compressive forces, increased myocardial wall stress, and impaired relaxation. Abnormalities of coronary flow reserve are regionally heterogeneous in some patients, whereas in others the entire myocardium is affected [22]. Regional abnormal myocardial function may predispose patients to abnormal patterns of electrical activity or to regional myocardial ischaemia during conditions in which a high flow is necessary.

Capillary densities in hypertension

One of the most consistently observed microcirculatory changes in hypertension is rarefaction of the capillaries. In humans capillary rarefaction is usually assessed using *in vivo* capillaroscopy of the nailfold microvasculature. Capillary rarefaction is not only a consequence of hypertension, but can also precede elevation of blood pressure. Evidence for an early role of capillary rarefaction was obtained in borderline hypertensives [23] as well as in offspring from hypertensive parents [24]. Furthermore, modest changes in salt intake affect skin capillary densities in individuals with mild hypertension [25]. In animal models of hypertension both capillary and arteriolar rarefaction were observed in a range of tissues. This raised the question of whether an impaired angiogenic response to tissue ischaemia might be the basis of early microvascular abnormalities in hypertension [1, 26].

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STATINS AND HYPERTENSION

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Cardiovascular disease (CVD) remains the leading cause of death in developed countries [1]. Hypertension and dyslipidaemia are two major CVD risk factors highly prevalent either alone or in combination [2]. Hypertension often clusters with other CVD risk factors associated with a markedly increased risk of CV events. The interaction among CVD risk factors is such that the probability of a CV event is frequently greater in patients with only moderate BP and cholesterol abnormalities in the presence of additional risk factors than in patients with isolated marked elevation of BP or cholesterol levels alone [3]. In addition, the majority of CV events in the population occur among individuals with modest levels of several risk factors rather than among those rare persons with extreme values of just one risk factor. A major aim of treating hypertension is a maximal decrease in long-term total CV risk. This can only be achieved by treatment of all reversible risk factors and associated conditions in addition to treatment of raised BP *per se*.

Lipid abnormalities and hypertension

There is evidence that normotensive subjects with hypercholesterolaemia have an excessive BP response to a mental arithmetic stress test [4]. Furthermore, up to 40% of patients with essential hypertension and many patients with borderline hypertension already have lipid abnormalities. An analysis of the Physicians' Health Study prospectively examined data from 3110 participants who were free of hypertension, CVD, and cancer at baseline [5]. Over an average of 14 years of follow-up, approximately one third of the men developed hypertension. Elevated levels of total cholesterol, non-HDL-cholesterol, and the total cholesterol/HDL-cholesterol ratio were independently associated with an increased risk of hypertension in middle-aged and older men. Furthermore, higher levels of cholesterol were associated with a higher risk of hypertension.

Genetic studies in humans and in animal models suggest that a predisposition to the development of both hypertension and dyslipidaemia may result from the inheritance of shared genetic factors.

Effect of statins on BP in clinical studies

In addition to their beneficial effects on lipids, statins may reduce systolic, diastolic, and mean arterial BP in normotensive, hypercholesterolaemic [6] men and kidney transplant patients [7]. These effects were independent of their lipid actions.

The capacity of statins to lower BP has been reported to be superior to that of other lipid-lowering drugs. In the Brisighela Heart Study [8] a total of 1356 hypercholesterolaemic individuals were randomly treated with a low-fat diet, cholestyramine, gemfibrozil, or simvastatin for five years. Participants were divided at baseline into four quartiles based upon systolic BP. A significant decrease in BP was observed in the two upper quartiles of systolic BP, and was greater in subjects treated with lipid-lowering drugs. In particular, the BP reduction was greater in patients treated with a statin, despite a comparative reduction in LDL-cholesterol (reduction of 13% in both systolic and diastolic BP at the highest quartiles after five years of treatment with a statin as compared with 10% after treatment with non-statin drugs).

The BP-lowering effect of statins is not consistent. Milionis et al. [9] summarized, in an elaborate review of the available data regarding the BP-lowering effect of statins, the effect of statin treatment on BP. This review included studies within a broad spectrum of patients (normotensives, hypertensives, individuals with normal lipids and dyslipidaemia, diabetic patients) published up to 2005. The effect on BP varied from neutral to most favourable (Δ systolic BP 8–13 mm Hg; Δ diastolic BP 5–7.8 mm Hg).

A meta-analysis of all studies published up to 2005 and reporting BP data during treatment with statins included 20 randomised controlled trials (828 patients) [10]. The duration of the studies ranged from 1 to 12 months. Systolic BP was significantly lower in patients on statins than in those on placebo or a comparative lipid-lowering drug (mean difference: –1.9 mm Hg; 95% CI: –3.8 to –0.1). The effect was greater when the analysis was restricted to studies with a baseline systolic BP > 130 mm Hg (D systolic BP –4.0 mm Hg; 95% CI: –5.8 to 2.2). There was a trend toward lower diastolic BP in patients receiving statin therapy compared with controls: –0.9 mm Hg (95% CI: –2.0 to 0.2) overall, and –1.2 mm Hg (95% CI: –2.6 to 0.1) in studies with a baseline diastolic BP > 80 mm Hg.

The California San Diego Statin Study, a randomised, double-blind, placebo-controlled trial with 973 patients allocated equally to simvastatin (20 mg), pravastatin (40 mg), or placebo for six months, showed a modest but significant BP reduction (2.4–2.8 mm Hg for both SBP and DBP) with both statins [11]. Because this effect was seen in patients not receiving antihypertensive treatment (most patients were normotensive), these results are compatible with the above possibility that statins exert a small BP-lowering effect that can be detected only when they are given alone.

By contrast, in the recently published PHYLLIS (randomised, placebo-controlled, double-blind) trial including 508 patients with mild hypertension and hypercholesterolaemia, administration of a statin (pravastatin 40 mg once daily) in hypertensive patients with BP effectively reduced by concomitant antihypertensive treatment did not have an additional BP-lowering effect [12]. The strengths of this study were a 2.6-year follow-up and ambulatory BP monitoring in addition to clinic BP measurement.

Reduction in BP due to statin therapy: pathophysiological mechanisms

Statins induce consistent and predictable reductions in circulating LDL-cholesterol and triglycerides, and have a small effect on HDL-cholesterol. In addition, these agents exhibit ancillary actions which have been attributed to reductions in isoprenoid cholesterol intermediates and reductions in dolichols, geranylgeranoic acid, and farsenylfarsenoic acid. It can be hypothesised that these actions may provide a pleiotropic mechanism by which statins exert actions on BP as well as target organ damage associated with hypertension. Statins improve endothelial function by increasing the bioavailability of NO, promoting re-endothelialisation, reducing oxidative stress, and inhibiting inflammatory responses [13]. Increased angiotensin II sensitivity predisposes to hypertension and plaque instability. It has been reported that the increased sensitivity to angiotensin II in healthy young subjects with isolated hypercholesterolaemia can be partly restored by therapy to reduce the levels of LDL-cholesterol using statins. There is evidence that statins down-regulate AT1-receptor expression [14]. There is also some evidence that statins may reduce the levels of circulating aldosterone [15].

Renal function, hypertension, lipids, and statins

Recent clinical trials have demonstrated that aggressive treatment with statins improves serum creatinine, glomerular filtration rate, and urate levels [16, 17]. This effect is probably another consequence of improved blood flow following treatment with statins. The effect of statin use on the development of renal dysfunction was examined in 197,551 patients (Department of Veterans Affairs, Veterans Integrated Service Network [18]). The odds for developing renal dysfunction were decreased by 13% in statin users. The beneficial effect of statins in preventing the development of renal dysfunction seems to be independent of their lipid-lowering effect.

Statins and BP: implications of large clinical outcome trials

Treatment of hypertension is associated with a reduction in stroke and, to a lesser extent, coronary events. It is also well known that elevated serum total cholesterol significantly increases CHD risk. Therefore, it is logical that co-existing vascular risk factors, including abnormal lipid profiles, should be an integral part of hypertension management.

Statins were prescribed for a long time to various subgroups in large landmark primary and secondary prevention trials. The overall benefit in CVD risk reduction was similar among hypertensive and

normotensive individuals. Although a sizeable number of hypertensive subjects were included among these studies, there are no data as to whether statin treatment produced any significant BP reductions. However, we should keep in mind that: 1) the effect of statin treatment on BP was not included in the study design; and 2) the inclusion of large numbers of normotensive participants could have attenuated any beneficial effect on BP, which could have also been masked by 3) the use of specific antihypertensive therapy. Only statins within the class of lipid-lowering agents have been shown to induce a consistent 20–25% reduction in the risk of stroke or transient ischaemic attacks [19].

The benefit of lowering both BP and cholesterol was evaluated in two large-scale trials: ALLHAT [20] and ASCOT-LLA [21].

A part of ALLHAT was designed to determine whether pravastatin compared with usual care would reduce all-cause mortality in 10,355 patients with hypertension and moderate hypercholesterolaemia, plus at least one additional CHD risk factor [20]. At four years total cholesterol was reduced by 17.2% with pravastatin vs. 7.6% with usual care. All-cause mortality was similar in the two groups, and CHD event rates were not different between the two groups; six-year CHD event rates were 9.3% (pravastatin) and 10.4% (usual care). These results could be attributed to the small difference in total cholesterol (9.6%) and LDL-cholesterol (16.7%) between pravastatin and usual care compared with other statin trials. Adherence to the treatment assigned declined over time. For those assigned to pravastatin, adherence dropped from 87.2% at year 2 to 80% at year 4, and 77% at year 6, although the number of participants was small. On the other hand, in the usual care group, crossovers to statin treatment increased from 8% at year 2 to 17% by year 4. This increase continued at year 6, but the number of participants was small.

In the ASCOT-BPLA trial [22], 19,342 men and women with hypertension and at least three other CV risk factors were randomised to amlodipine (5–10 mg/d) ± perindopril (4–8 mg/d) or to atenolol (50–100 mg/d) ± bendroflumethiazide (1.25–2.5 mg/d). A total of 10,305 of these patients with normal or slightly elevated total cholesterol were randomised to atorvastatin 10 mg/d or placebo [21]. The atorvastatin arm was stopped prematurely at 3.3 years due to a significant reduction in the primary endpoint (–36%; $p = 0.0005$). The benefit of atorvastatin treatment was apparent within the first year of treatment. Fatal/non-fatal stroke and total CV/coronary events were also reduced with atorvastatin. At one year, atorvastatin reduced total cholesterol by 24% and LDL-cholesterol by 35%. However, in the period between 6 weeks and 18 months, a significant 1.1/0.7 mm Hg difference in BP was seen in favour of atorvastatin regardless of titration of doses and numbers of drugs. Overall, amlodipine-perindopril therapy was superior to atenolol-bendroflumethiazide therapy [22], and a further analysis of early monotherapy data comparing amlodipine with atenolol suggested a positive interaction between atorvastatin and amlodipine [23].

The latest meta-analysis so far of large clinical trials, including only those with more than 1000 patients followed for more than 2 years, has been published by Messerli et al. [24]. Besides ASCOT-LLA and ALLHAT-LLT, 12 trials enrolling 69,284 patients met the inclusion criteria. Overall, in these 12 trials, statin therapy decreased cardiac death by 24% (RR 0.76; 95% CI 0.71–0.82). There was no evidence of a difference in RR estimates for hypertensive and normotensive patients. In conclusion, statin therapy effectively decreased CV morbidity and mortality to the same extent in hypertensive and normotensive patients.

Compliance with antihypertensive and lipid-lowering treatment

The critical issue of any long-term medication is adherence, which varies according to diagnosis. The compliance rate for antihypertensive medication, as reported by the US National Council on Patient Information and Education, is 53%. In a retrospective cohort study [25], adherence to medication was analysed in 8406 enrolees in a US managed care plan which initiated treatment with antihypertensive and lipid-lowering drugs within a 90-day period. Adherence to concomitant antihypertensive and lipid-lowering therapy was poor, with only 35.9% of patients adherent to both medications at 6 months. A single pill containing an antihypertensive and lipid-lowering compound may increase patient adherence to these medications and thus improve the simultaneous management of hypertension and dyslipidaemia, which may also improve clinical outcome [26].

Conclusions

The 2007 ESH/ESC guidelines for the management of arterial hypertension [27] recommend considering lipid-lowering agents in all hypertensive patients with established cardiovascular disease or with Type-2 diabetes, aiming at serum total and LDL-cholesterol levels of < 4.5 mmol/l (175 mg/dl) and < 2.5 mmol/l (100 mg/dl), respectively, or lower, if possible.

In view of the results of the ASCOT trial [21], it seems reasonable to consider statin therapy in hypertensive patients aged less than 80 years who have an estimated 10-year risk of cardiovascular disease ≥ 20% or of cardiovascular death (based on the SCORE model) of 5% or more. Target levels should be serum total cholesterol and LDL-cholesterol levels of < 5 mmol/l (190 mg/dl) and < 3 mmol/l (115 mg/dl), respectively.

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MICROALBUMINURIA IN ESSENTIAL HYPERTENSION

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Introduction

The detection of small amounts of urinary albumin excretion (UAE), a condition known as microalbuminuria, by using sensitive immunological methods was initially used in the evaluation and management of renal damage in diabetes. In the last few years, however, it has received increased attention as a prognostic marker for cardiovascular and/or renal risk in non-diabetic subjects [1–11]. Consequently, microalbuminuria assessment is now recommended in a risk stratification strategy for hypertension management [12] since its presence indicates early organ damage and a clustering of cardiovascular risk factors. As the ESH/ESC guidelines indicate, microalbuminuria is a reliable prognostic marker, which is widely available and at low cost [12]. Moreover, recent data indicates that microalbuminuria is potentially an intermediate endpoint during antihypertensive treatment [11, 13].

Definition and prevalence

Microalbuminuria has been defined as a UAE higher than the threshold value obtained from studies assessing the risk for developing nephropathy in diabetes (UAE ≥ 30–300 mg/24 h or ≥ 20–200 μg/min). The albumin/creatinine ratio from spot urine, preferably from the first voided in the morning (30–300 μg/g), is equivalent to the values during a 24-hour urine collection [14]. On the basis of this threshold the prevalence of microalbuminuria in hypertension depends on the characteristics of the patients included, the lowest in Primary Care settings (around 10–12%) and the highest in referral Hypertension Clinics (up to 30%).

At the time of assessing UAE two aspects need to be considered: reproducibility and circadian variability. Since a large intra-individual variability exists, at least two UAE assessments need to be collected. If discrepancies between the UAE values exist, a third sample should be requested. There is frequently a reduction of UAE at night to around 20% of that excreted during daytime activity. Consequently, the first voided urine analysed shows the UAE values at their lowest.

Recently the information collected from prognostic studies (see below) has challenged the concept of using microalbuminuria as a qualitative parameter, and has indicated that quantitative values should be considered [14]. Likewise, the prognostic value has a strong interaction with the estimated glomerular filtration rate (eGFR); therefore, a risk chart with both UAE and eGFR has recently been proposed (Figure 1) [15].

Mechanisms of microalbuminuria

Microalbuminuria in essential hypertensive patients is the consequence of an increased transglomerular passage of albumin rather than the result of a decrease in the proximal tubule reabsorption of albumin. It may result from haemodynamic-mediated mechanisms and/or functional or structural impairment of the glomerular barrier [16]. As regards the haemodynamics, hyperfiltration, with the consequent increment in glomerular pressure, is of particular importance. It is probably mediated by abnormal transmission of systemic hypertension to the glomerulus through a disturbance in glomerular autoregulation and/or from progressive loss of functioning nephrons. Of the non-haemodynamics, functional abnormalities of the glomerular basal membrane have been claimed, although some evidence has been against this in hypertension. More widely accepted, however, is that microalbuminuria reflects the kidney expression of a more generalised state of endothelial dysfunction.

		UAE	A1		A2	A3	A3
		(mg/g)	Optimal < 15	High-normal 15–29	High 30–299	Very high 300–1999	Nefrotic > 2000
GFR stage	Description	(ml/min/1,73 m²)					
G1	High	> 105					
G1	Optimal	90–104					
G2	Mild	60–89					
G3a	Mild to moderate	45–59					
G3b	Moderate to severe	30–44					
G4	Severe	15–29					
G5	Kidney failure	< 15					

Figure 1. Risk categories for kidney and mortality outcomes by GFR and albuminuria or proteinuria stage [15]

Factors related to microalbuminuria

Factors related to the presence of microalbuminuria in essential hypertension have been analysed in cross-sectional as well as in a few prospective studies (reviewed in [17]). From these studies it seems that the significance of microalbuminuria in essential hypertension is much broader than expected, and several factors may influence the presence of microalbuminuria. Both cross-sectional and follow-up studies have indicated that both BP values and hyperinsulinaemia are the main factors associated with the risk. Microalbuminuria may be the consequence of a double product, which is time of hypertension per blood pressure (BP) value. If the patient has insulin-resistance, microalbuminuria can be present even when the double product of time and pressure is small. By contrast, subjects without insulin-resistance need a length of time and/or high blood pressure values to develop microalbuminuria. Over and above these scenarios, the development of nephrosclerosis, less prevalent in non-insulin resistance, adds a new component to the risk of having microalbuminuria.

In **cross-sectional** studies, microalbuminuria has been related to BP values and to hyperinsulinaemia as an expression of insulin resistance. The importance of BP values and alterations in the carbohydrate metabolism has been corroborated by a small number of follow-up studies. Blood pressure values achieved over time and changes in fasting glucose were the most important factors, not only for developing new onset microalbuminuria but also in reducing urinary albumin excretion during antihypertensive treatment.

The influence of glomerular filtration rate (GFR) on the microalbuminuria of hypertension merits a comment. The prevalence of microalbuminuria increases as the GFR decreases, although not always in parallel. Moreover, when GFR is < 60 ml/min/1.73 m^2, the probability of UAE normalisation during antihypertensive treatment is clearly reduced [18].

Other potential factors associated with the presence of microalbuminuria are salt-sensitivity, overactivity of the renin-angiotensin system, inflammation, genetics, obesity, and smoking.

Prognostic value

The potential prognostic value of microalbuminuria to cardiovascular disease has been assessed among diabetics and non-diabetics in the general population, postmenopausal women, and high cardiovascular risk patients. In all of these the highest UAE values observed at the beginning of each study were followed by an increase in morbidity and mortality cardiovascular risk. The UAE threshold value pointing to an increment of risk was largely below the UAE value of 30 mg/24 hours, regardless of the population studied, and the relationship between UAE and risk was continuous at below 30 mg/24 hours.

A key point in considering UAE as an intermediate objective arises from the demonstration that a reduction in urinary proteins is followed by a significant reduction in cardiovascular and/or renal events [19]. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) has amply demonstrated that the rate of the primary composite cardiovascular endpoint of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction increases 4-fold to 5-fold from the lowest to the highest decile of the albumin/creatinine ratio. Schrader et al. [13] observed that normalization of UAE during treatment was associated with a trend towards fewer cardiovascular events as compared with persisting microalbuminuria. Conversely, new-

ly developed proteinuria was associated with a trend towards increasing events. Recently data coming from the ONTARGET study, confirm that a 50% per cent or more increment or reduction in UAE is followed by an increase or decrease of CV and renal events, respectively [20]. In contrast, in normoalbuminuric patients with type 2 diabetes, the reduction in new occurrence of microalbuminuria was not followed for a reduction in CV events although the study was unpowered for CV events [21]. Future studies with appropriate design and analysis are required to give credence to microalbuminuria as an intermediate objective [22].

Recommendation for UAE assessment

Microalbuminuria assessment is now recommended at the initial evaluation of a patient with hypertension. Two first-morning voided urine samples should be tested for the albumin/creatinine ratio. No recommendation exists, however, concerning when UAE measurement should be repeated, if it is considered as an intermediate objective. If so, the proposed algorithm is presented in Figure 2.

Treatment of hypertension with microalbuminuria

Blood pressure reduction is the most important determinant of diminishing UAE during antihypertensive treatment. Renin–angiotensin system blockers are superior to other antihypertensive agents in reducing UAE in subjects, mainly those in the high range of BP. If such treatment reduces BP enough to achieve BP goals, differences in the UAE reduction among antihypertensive classes become smaller, or no differences are observed at all [23, 24].

The role of additional interventions for BP reduction needs to be considered. Statins (agents with ancillary properties beyond their lipid-lowering capabilities) have demonstrated that they ameliorate the course of renal function in type 2 diabetic patients. Furthermore, in hypercholesterolaemic subjects the lowering of LDL-cholesterol with atorvastatin may favourably affect microalbuminuria [25]. It remains to be seen whether this effect can be attributed to lipid lowering alone, improving endothelial function or lowering patterns of LDL oxidation. If in hypertension the UAE reduction with statins is still significant on top of antihypertensive therapy, this needs to be assessed in carefully designed studies. The role of metformin of other glucose lowering agents should be considered in further strategies. A multiple therapeutic approach to hypertensives with microalbuminuria may contribute to a better reduction on UAE due to the frequent clustering of cardiovascular risk factors.

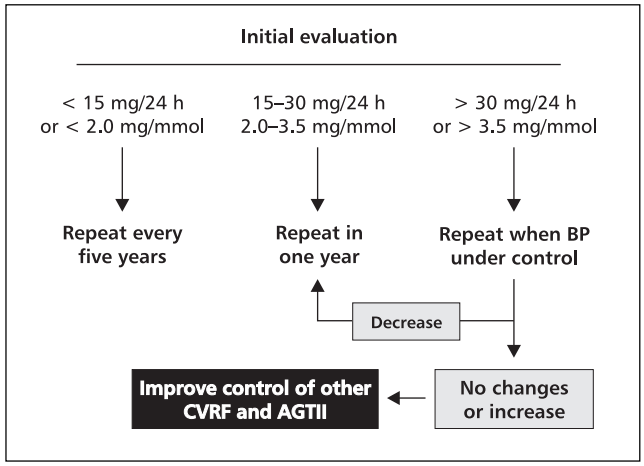

Figure 2. Algorithm for the assessment of urinary albumin excretion (expressed in mg/24 h or albumin/creatinine ratio) in hypertensives according to the initial values; BP — blood pressure; CVRF — cardiovascular risk factors; AGTII — angiotensin II

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HYPERTENSION IN ATHLETES

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Introduction

Blood pressure increases with age. Systolic blood pressure continues to increase throughout adult life, related to progressive arterial stiffening, whereas diastolic blood pressure plateaus in the sixth decade of life and decreases thereafter. The prevalence of hypertension in the population amounts to ~ 25%. When broken down by age and gender, the prevalence is approximately 15%, 30%, and 55% in men aged 18–39 years, 40–59 years, and ≥ 60 years, respectively, and about 5%, 30%, and 65%, respectively, in women in these age groups. These epidemiological data indicate that hypertension may already be present in the young athlete, though rarely, but will occur more frequently in the older sportsman. However, ~ 25% of patients with hypertension by conventional measurements have a normal blood pressure on 24-hour ambulatory monitoring or on home blood pressure measurements, so-called white-coat hypertension [1], and it has been shown that young athletes with clinic hypertension often have normal blood pressure on ambulatory monitoring [2].

Approximately 95% of patients with hypertension have essential or primary hypertension which results from an interaction between genetic factors and lifestyle/ /environmental factors that include being overweight, high salt intake, excessive alcohol consumption, and physical inactivity. However, the role of blood pressure increasing ergogenic aids should be considered in the hypertensive sportsman or athlete. Athletes may be taking large doses of prohibited substances such as anabolic steroids, erythropoietin, stimulants, and so forth. The uncontrolled use of these agents has been associated with numerous side effects including hypertension. Also the use of non-steroidal anti-inflammatory drugs should be specifically considered since these compounds may increase blood pressure and are commonly used in the athletic setting.

Assessment of the severity of hypertension and risk stratification

The severity of hypertension does not only depend on the blood pressure level but also on the presence of other cardiovascular risk factors, target organ damage, and cardiovascular and renal complications, and, accordingly, patients are classified as having low, moderate, high, or very high added risk in comparison with healthy normotensives without risk factors [3]. With regard to left ventricular hypertrophy, it should be noted that sports activity itself may induce hypertrophy; the type of hypertrophy and assessment of diastolic left ventricular function, speckle-tracking echocardiography, tissue Doppler imaging, and strain rate measurements may help to distinguish between hypertensive heart disease and athlete's heart [4–11]. Athlete's heart typically shows maintained diastolic function, and is in general considered a physiological adaptation to training, in contrast to the hypertrophy secondary to hypertension. Hypertensive patients usually have concentric left ventricular hypertrophy, whereas endurance athletes are characterized by predominant eccentric hypertrophy; however, eccentric hypertrophy has also been described in hypertensives [12]. Whether or not hypertension in an athlete will trigger or accentuate the cardiac hypertrophy, or athletic exercise in a person with hypertrophy secondary to hypertension will worsen the hypertrophy, is not known.

Assessment of the risk associated with exercise

Exercise-related sudden death at a younger age is mainly attributed to hypertrophic cardiomyopathy, anomalies of the coronary arteries or arrhythmogenic right ventricular dysplasia [9, 13–15], and is unlikely to be related to hypertension. On the other hand, coronary heart disease has been identified in approximately 75% of victims of exercise--related sudden death above the age of 35 years. Whether or not high blood pressure is a cause of exercise-related sudden death on its own is not known, but hypertension is certainly a major risk factor for the development of coronary artery disease. In addition, hypertension-induced left ventricular hypertrophy may cause life threatening ventricular arrhythmias [16]. It is likely that the risk associated with exercise can be derived from the overall risk stratification. Therefore, the general approach of the hypertensive patient should also apply to the exercising patient.

Diagnostic evaluation

Diagnostic procedures are aimed at 1) establishing blood pressure levels; 2) identifying secondary causes of hypertension; and 3) evaluating the overall cardiovascular risk by searching for other risk factors, target organ damage and concomitant diseases or accompanying clinical conditions [3]. Diagnostic procedures comprise a thorough individual and family history, physical examination, including repeated blood pressure measurements according to established recommendations, and laboratory and instrumental investigations, of which some should be considered part of the routine approach in all subjects with high blood pressure, some are recommended, and some are indicated only when suggested by the core examinations. In addition, echocardiography and exercise testing with ECG and blood pressure monitoring are indicated as routine tests in the competitive athlete with hypertension [17, 18]. In the common hypertensive sportsman, the indication for exercise testing depends on the patient's risk and on the amateur/leisure-time sports characteristics [18, 19] (Table 1). In patients with hypertension about to engage in hard or very hard exercise (intensity ≥ 60% of maximum), a medically supervised peak or symptom-limited exercise test with ECG and blood pressure monitoring is warranted. In asymptomatic men or women with low or moderate added risk, who engage in low-to-moderate physical activity (intensity < 60% of maximum), there is generally no need for further testing beyond the routine evaluation. Asymptomatic individual patients with high or very high added risk may benefit from exercise testing before engaging in moderate-intensity exercise (40–60% of maximum) but not for light or very light activity (< 40% of maximum). Patients with exertional dyspnoea, chest discomfort, or palpitations need further examination, which includes exercise testing, echocardiography, Holtermonitoring, or combinations thereof.

Table 1. Indications for exercise testing for sports participation in patients with hypertension

Demands of exercise Static and/or dynamic	Risk category	
	Low or moderate	High or very high[§]
Light (< 40% of max)	No	No
Moderate (40–59% of max)	No	Yes
High (≥ 60% of max)	Yes	Yes

[§]In case of an associated clinical condition, the recommendations for the specific condition should be observed

A major problem with exercise testing in a population with a low probability of coronary heart disease and in subjects with left ventricular hypertrophy is that the majority of positive tests on electrocardiography are falsely positive. Stress myocardial scintigraphy or echocardiography, and ultimately coronarography, may be indicated in cases of doubt. There is currently insufficient evidence that the blood pressure response to exercise should play a role in the recommendations for exercise in addition to blood pressure at rest [20]. However, subjects with an excessive rise of blood pressure during exercise are more prone to develop hypertension and should be followed-up more closely [19]. Finally, physicians should be aware that high blood pressure may impair exercise tolerance [21].

Effects of exercise on blood pressure

Dynamic exercise

Blood pressure increases during acute dynamic exercise in proportion to the intensity of the effort [21, 22]. During longer-term stable exercise, the blood pressure tends to decrease after an initial increase of short duration. The increase is greater for systolic than for diastolic blood pressure, which only slightly increases or even remains unchanged. For the same oxygen consumption, the rise is more pronounced in older subjects and when exercise is performed with smaller than with larger muscle groups. Acute exercise is usually followed by post-exercise hypotension, which may last for several hours and is generally more pronounced and of longer duration in patients with hypertension than in normotensive subjects [19, 22].

Cross-sectional and longitudinal epidemiological studies indicate that physical inactivity and low fitness levels are associated with 1) higher blood pressure levels and 2) increased incidence of hypertension in the population [23]. Meta-analyses of randomized controlled intervention studies concluded that regular dynamic endurance training at moderate intensity significantly reduces blood pressure [24–26]. A recent meta-analysis involved 72 trials and 105 study groups [26]. After weighting for the number of participants, training induced significant net reductions of resting and daytime ambulatory blood pressure of, respectively, 3.0/2.4 mm Hg ($p < 0.001$) and 3.3/3.5 mm Hg ($p < 0.01$). The reduction of resting blood pressure was more pronounced in the 30 hypertensive study groups (–6.9/–4.9) than in the others (–1.9/–1.6) ($p < 0.001$ for all). There was no convincing evidence that the blood pressure response depended on training intensity between ~ 40% and ~ 80% of maximal aerobic power [24, 26].

Cornelissen et al. [27] compared the effect of training at lower and higher intensity on blood pressure in ≥ 55-year-old sedentary men and women, by use of a randomized cross-over design comprising three 10-week periods. In the first and third period, participants exercised at, respectively, lower or higher intensity (33% or 66% of heart rate reserve) in random order, with a sedentary period in between. Training programmes comprised walking, jogging, cycling, and stepping, were identical except for intensity, and were performed three times for one hour per week. Thirty-nine (18 men) of 48 randomized participants completed the study; age averaged 59 years. The change of aerobic power from baseline to the end of each period was more pronounced ($p < 0.05$) with higher intensity (+3.70 $ml*kg^{-1}*min^{-1}$, $p < 0.001$) than with lower intensity training (+2.31 $ml*kg^{-1}*min^{-1}$, < 0.001). Systolic blood pressure at rest and during submaximal exercise were reduced with both intensities ($p < 0.01$) by about 5 to 6 mm Hg, without significant differences in blood pressure reduction between intensities. In conclusion, endurance training for three times one hour per week at lower intensity increases fitness levels, but to a lesser extent than does higher intensity training, and lower and higher intensity training reduce office and exercise systolic blood pressure to a similar extent.

Static exercise

Blood pressure increases during acute static exercise, and the increase is more pronounced than with dynamic exercise, particularly with heavy static exercise at an intensity of > 40–50% of maximal voluntary contraction. In a meta-analysis of randomized controlled trials, 'resistance' training at moderate intensity was found to decrease blood pressure by 3.5/3.2 mm Hg [28]. The meta-analysis included nine studies designed to increase muscular strength, power and/or endurance, and all but one study involved dynamic rather than purely static exercise. In fact, few sports are characterized by purely static efforts. However, only three trials in the meta-analysis reported on patients with hypertension. In the meantime the number of studies has substantially increased, and the blood pressure lowering effect of resistance training has recently been confirmed in a meta-analysis of 26 randomized controlled trials [29].

Table 2. Recommendation for strenuous leisure time physical activity and competitive sports participation in athletes with systemic hypertension according to the cardiovascular risk profile

Risk category	Evaluation	Criteria for eligibility	Recommendations	Follow-up
Low added risk	History, PE, ECG, ET, echo	Well controlled BP	All sports	Yearly
Moderate added risk	History, PE, ECG, ET, echo	Well controlled BP and risk factors	All sports, with exclusion of high static, high dynamic sports (III C)	Yearly
High added risk	History, PE, ECG, ET, echo	Well controlled BP and risk factors	All sports, with exclusion of high static sports (III A–C)	Yearly
Very high added risk	History, PE, ECG, ET, echo	Well controlled BP and risk factors; no associated clinical conditions	Only low-moderate dynamic, low static sports (I A–B)	6 months

BP — blood pressure; PE — physical examination, including repeated blood pressure measurements according to guidelines; ECG — 12-lead electrocardiography; ET — exercise testing; echo — echocardiography at rest

Recommendations

General recommendations

Athletes with hypertension should be treated according to the general guidelines for the management of hypertension [3, 18, 30]. Appropriate non-pharmacological measures should be considered in all patients. Antihypertensive drug therapy should be started promptly in patients at high or very high added risk for cardiovascular complications. In patients at low or moderate added risk, drug treatment is only initiated when hypertension would persist after several months or weeks, respectively, despite appropriate lifestyle changes. The goal of antihypertensive therapy is to reduce blood pressure to at least below 140/90 mm Hg and to lower values if tolerated in all hypertensive patients, and to below 130/80 mm Hg in diabetics and other high or very high risk conditions, although the latter lower threshold has recently been debated because of lack of hard evidence [31]. Current evidence indicates that patients with white-coat hypertension do not have to be treated with antihypertensive drugs, unless they are at high or very high risk, but regular follow-up and non-pharmacological measures are recommended [3]. Also, subjects with normal blood pressure at rest and exaggerated blood pressure response to exercise should be followed-up more closely.

Choice of drugs

Several drug classes can be considered for the initiation of antihypertensive therapy: diuretics; beta-blockers; calcium channel blockers; angiotensin converting enzyme inhibitors; and angiotensin II receptor blockers [3]. However, diuretics and beta-blockers are not recommended for first-line treatment in patients engaged in competitive or high-intensity endurance exercise [18, 21, 30). Diuretics impair exercise performance and capacity in the first weeks of treatment through a reduction in plasma volume, but exercise tolerance appears to be restored during longer-term treatment; nevertheless, diuretics may cause electrolyte and fluid disturbances, which are not desirable in the endurance athlete. Beta-blockers reduce maximal aerobic power by on average 7% as a result of the reduction in maximal heart rate, which is not fully compensated by increases of maximal stroke volume, peripheral oxygen extraction, or both. Furthermore, the time that submaximal exercise can be sustained is reduced by ~ 20% by cardioselective beta-blockers and by ~ 40% by nonselective beta-blockers, most likely as a result of impaired lipolysis [21, 32, 33]. There are indications that the beta-blocker nebivolol may not impair exercise performance [34]. In addition, diuretics and beta-blockers are on the doping list for some sports, in which weight loss or control of tremor are of paramount importance. Diuretics are also banned because they may be used to conceal the use of other doping agents, such as anabolic steroids, by diluting the urine samples. The hypertensive athlete who has to use a diuretic and/or a beta-blocker for therapeutic purposes should follow the 'International Standard for Therapeutic Use Exceptions' of the World Anti-Doping Agency (WADA).

Calcium channel blockers and blockers of the renin-angiotensin system are currently the drugs of choice for the hypertensive endurance athlete [21, 35] and may be combined in case of insufficient blood pressure control. However, the combination of an angiotensin converting enzyme inhibitor and an angiotensin II receptor blocker is currently not advocated for the treatment of hypertension. If a third drug is required, a low dose thiazide-like diuretic, possibly in combination with a potassium sparing agent, is recommended. There is no unequivocal evidence that antihypertensive agents would impair performance in 'resistance' sports.

Recommendations for sports participation

Recommendations for participation in competitive sports in athletes with hypertension are based on the results of the evaluation and on the risk stratification and with the understanding that the general recommendations for the management of hypertension are observed, as described above, and provided that the clinical condition is stable. Table 2 summarizes the recommendations with regard to competitive sports participation [17, 18]. The same recommendations may apply to patients who aim to engage in hard or very hard leisure-time sports activities in order to substantially enhance performance. However, most recreational physical activities are performed at low-to-moderate intensity. Dynamic sports activities are to be preferred, but also low-to-moderate resistance training is not harmful and may even contribute to blood pressure control [28, 29]. In case of cardiovascular or renal complications, the recommendations are based on the associated clinical conditions.

Finally, all patients should be followed-up at regular intervals, depending on the severity of hypertension and the category of risk. In addition, all exercising patients should be advised on exercise-related warning symptoms, such as chest pain or discomfort, abnormal dyspnoea, dizziness, or malaise, which would necessitate consulting a qualified physician.

Summary

Hypertension is rare in the young but its prevalence increases with age. The overall risk of the hypertension patient does not only depend on blood pressure but also on the presence of other cardiovascular risk factors, target organ damage, and associated clinical conditions. The recommendations for preparticipation screening, sports participation, and follow-up depend on the cardiovascular risk profile of the individual athlete. When antihypertensive treatment is required, calcium channel blockers and blockers of the renin-angiotensin system are currently the drugs of choice in the exercising patient.

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METABOLIC SYNDROME IN HYPERTENSION

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Concept and definition

Arterial hypertension is often part of a constellation of anthropometric and metabolic abnormalities that include abdominal obesity, characteristic dyslipidaemia with low high--density lipoprotein cholesterol and high triglycerides, glucose intolerance, insulin resistance (IR), and hyperuricaemia. These features occur simultaneously to a higher degree than would be expected by chance alone, supporting the existence of a discrete disorder, so-called metabolic syndrome (MS) or cardiometabolic syndrome. MS is currently considered to confer an increased risk of cardiovascular (CV) events attributable, in part, to the individual risk factors which concur in defining it and, in part, to a cluster of other factors such as hyperuricaemia, a proinflammatory state, impaired fibrinolysis, and oxidative stress, which usually go along with it. MS is extremely common worldwide and can be found in approximately one third of patients with essential hypertension, in whom it considerably increases the risk of CV and renal events.

The criteria employed to identify MS have changed over the years [1] (Table 1). After the more mechanistic World Health Organization and European Group for Insulin Resistance definitions, the Adult Treatment Panel III (ATP III), one of the MS definitions presented in 2001, was more clinically oriented. Recently, the International Diabetes Federation definition aimed at considering research needs but also at offering an accessible diagnostic tool suitable for worldwide use. The most important new element, compared to other definitions, is that central obesity and insulin resistance are regarded as the most important causative factors. The last of the definitions was released by the American Heart Association/National Heart Blood and Lung Institute (AHA/NHBLI). It has given support to the ATP III criteria, except for a reduction in the threshold of the impaired fasting glucose component from 6.1 to 5.6 mmol/l (110 to 100 mg/dl) in line with the recent modification proposed by the American Diabetes Association [2].

Although the causes and mechanisms of MS may indeed be diversified, which is what the term "syndrome" implies, there is evidence that the overall CV risk accompanying this condition may be greater than the sum of its identifiable components. Furthermore, these components are often defined by values that are lower than are those meeting the definition of risk factors given by many guidelines, which consequently may fail to detect the presence of a high CV risk in some individuals with MS. Finally, the simple and easy identification of MS favours the use of this approach in clinical practice, which resists use of more complex charts for total CV risk quantification, ultimately helping implementation of CV prevention.

Mechanisms of hypertension in MS

Mechanisms involved in MS are obesity, IR, and a constellation of independent factors which include molecules of hepatic, vascular, and immunologic origin with pro-inflammatory properties [3]. Skeletal muscle and the liver, not adipose tissue, are the two key insulin-response tissues involved in maintaining glucose balance, although abnormal insulin action in the adipocytes also plays a role in development of the syndrome. At each of these key points, IR and obesity/pro-inflammatory molecules, there are interactions of demographics, lifestyle, genetic factors, and environmental foetal programming. Superimposing upon these are infections and//or chronic exposure to certain drugs which can also make their contribution. These all interact to create the final individual phenotype. Likewise, they interact leading to changes in blood pressure regulatory mechanisms.

Hypertension is frequent in MS, and blood pressure abnormality is even more frequent, with values in the high normal range, representing one of the five components that lead to the identification of this condition. In the PAMELA population study, for example, a blood pressure in the high normal or hypertension range was found in more than 80% of the individuals with MS, followed, in a decreasing order of prevalence, by visceral obesity, lipid abnormalities, and impaired fasting glucose [4]. The high prevalence of BP abnormalities in MS explains the very frequent occurrence of subclinical organ damage of the type that is frequently associated with, and is dependent on, blood pressure elevation, such as left ventricular hypertrophy, arterial stiffening, or increased urinary protein excretion. Some of these types of organ damage, however, also show an increased prevalence in individuals who have MS without a blood pressure elevation, suggesting that other components of this condition play a role independently of BP.

In general, the MS components are characterized by a high degree of interaction, one contributing to the establishment of the abnormality of the other and vice versa. It has been recognized for many years, for example, that the two main components of MS, obesity and IR, may play an important role in the increment of blood pressure and the development of hypertension. Factors commonly associated with, and partly dependent on, obesity and IR, such as overactivity of the sympathetic nervous system [5, 6], stimulation of the renin–angiotensin–aldosterone system [7], abnormal renal sodium handling [8], and endothelial dysfunction [9], need to be considered. Recently the role of vitamin D metabolism [10] and a potential genetic contribution has been emphasized [11]. Several cross-sectional and prospective studies have shown an association between low vitamin D status, as indicated by concentrations of serum 25-hydroxyvitamin D and increased prevalence of the MS and individual CVD risk factors. These epidemiological observations are supported by mechanistic studies, but experimental data are limited and no intervention studies exist to confirm the hypothesis, which can be biased by the association of adiposity and ageing with low vitamin D levels [12].

Finally, an association between the allele T of SNP rs17055869 near the alpha--1A-adrenoreceptor gene and metabolic syndrome and the sympathetic overactivity has been described [11].

MS and hypertension-induced organ damage

Metabolic syndrome has been associated with a higher prevalence of early signs of subclinical cardiovascular and renal damage [1]. Several studies have demonstrated that MS is associated with a high prevalence of **left ventricular hypertrophy** (LVH) throughout a wide age spectrum. Moreover, the number of MS components has been directly linked to the risk of having EKG and echocardiographic LVH. The effect of MS on LV structure has been reported to be more pronounced in women than in men, and has been shown to be partly independent of the effect of haemodynamic and non-haemodynamic determinants of LV mass, including blood pressure values over 24 hours. **Atrial enlargement**, a prognostic factor for the development of atrial fibrillation and stroke, has also been associated with overweight, high fasting glucose, and MS, independently of LV mass and geometry.

An increase in the prevalence of abnormal **urinary albumin excretion** has been observed among hypertensives with MS, as compared to those without MS, and indeed microalbuminuria has been considered a diagnostic element for MS in early definitions of this condition. The prevalence of microalbuminuria has been shown to increase with the number of MS components. MS was also associated with a lower **glomerular filtration rate** (GFR), as estimated using the MDRD formula, in a cross-sectional survey of hypertensives seen in primary care. Furthermore, the number of MS components was linearly related to the prevalence of GFR < 60 ml/min/1.73 m^2.

Evidence is available that **aortic pulse wave velocity** (PVW9) is higher in hypertensives with MS, irrespective of age and systolic blood pressure value. Likewise, an

Table 1. Criteria for diagnosing metabolic syndrome according to different scientific organisations: World Health Organization (WHO), European Group of Insulin Resistance (EGIR), Adult Treatment Panel (ATP III), International Diabetes Federation (IDF), American Heart Association (AHA)

Organisation	Principal criteria	Abdominal obesity	Glucose [mg/dl]	HDL [mg/dl]	TG [mg/dl]	BP [mm Hg]
WHO	DM, GI or IR	BMI ≥ 30 kg/m^2 M ≥ 0.90 W ≥ 0.85		M ≤ 35 W ≤ 39 (1.02 mmol/L)	≥ 150 (1.7 mmol/L)	≥ 140/90*
EGIR	IR or FI > P75	BMI ≥ 30 kg/m^2 M ≥ 102 cm W ≥ 88 cm	≥ 110* (6.1 mmol/L)	< 40 (1.03 mmol/L)	≥ 180	≥ 140/90*
ATP III		M ≥ 102 cm W ≥ 88 cm	≥ 110* (6.1 mmol/L)	M ≤ 40 (1.03 mmol/L) W ≤ 50 (1.29 mmol/L)	≥ 150 (1.7 mmol/L)	≥ 135/85*
IDF	Central obesity	M ≥ 94 cm W ≥ 80 cm	≥ 100* (5.6 mmol/L)	M ≤ 40 (1.03 mmol/L) W ≤ 50* (1.29 mmol/L)	≥ 150* (1.7 mmol/L)	≥ 135/85*
AHA		M ≥ 94 cm W ≥ 80 cm	≥ 100* (5.6 mmol/L)	M ≤ 40 (1.03 mmol/L) W ≤ 50* (1.29 mmol/L)	≥ 150* (1.7 mmol/L)	≥ 135/85*

Diagnosis of metabolic syndrome is based on: a) principal criteria plus at least two others; b) in those without principal criteria, at least three. Shaded area denotes the definitions based on carbohydrate metabolism abnormalities. The remaining are based on abdominal obesity; *or in treatment for; BMI — body mass index; DM — diabetes mellitus; GI — glucose intolerance; IR — insulin resistance; FI — fasting insulin; TG — triglycerides; M — men; W — women

association between MS and **carotid intima–media thickness** has been observed in several studies, although to a weaker degree than that observed for markers of organ damage such as LVH and microalbuminuria. The prevalence of carotid atherosclerosis increases progressively with the number of MS components in hypertensives but not in normotensives.

Data on the effects of the components of MS on **small arteries** are lacking, despite the fact that microvascular dysfunction has been claimed as an explanation for the associations among hypertension, obesity, and impaired-mediated glucose disposal.

In the presence of MS, the high prevalence of early organ damage supports the recommendation of a more in-depth assessment of subclinical organ damage [13].

Prognostic value of MS in hypertension

A limited number of studies [4, 14–17] have examined the prognostic importance of MS and its individual components in hypertension in risk to develop subclinical organ damage or cardiovascular events. The presence of MS increased the risk overtime to develop higher pulse pressure, left ventricular hypertrophy, and diabetes in the PAMELA study [4]. Overall, the presence of MS was an independent predictor of CV events [12–14] or CV and all cause mortality [4], even when the other CV risk factor was taken into account. Moreover, the risk increased with the number of MS components [4]. In contrast, in the ELSA study, in a large cohort of well-treated patients, outcomes were not different between MS and non-MS patients, suggesting that effective antihypertensive treatment may largely counteract the obnoxious effects of MS [18].

The impact of MS on intermediate objectives such as PWV [19] or IMT [18] has been evaluated. While progression of PWV was significantly higher in subjects with MS than in subjects with zero, one, or two factors even after adjustments for confounding factors, the progression of IMT was also slightly greater in MS patients, but the significance was lost when adjusted for covariates.

Management of hypertension with MS

In MS, the objective of treatment is both to reduce the high risk of a CV or renal event and to prevent the much greater chance that MS patients have of developing type-2 diabetes or hypertension. The aim is also to delay or prevent the progression (as well as to favour regression) of the types of organ damage that are frequently present and have an adverse prognostic significance.

Targeting metabolic syndrome mechanisms

Lifestyle measures

The underlying factors promoting the development of MS are overweight and obesity, physical inactivity, and an atherogenic diet. Most individuals who develop MS first acquire abdominal obesity without risk factors, but, with time, multiple risk factors tend to appear, initially only with borderline elevations but then with progressive worsening. Thus, a reduction in body weight by means of a proper low-calorie diet and an increase in physical activity can address the very mechanism of MS and is consequently recommended as first-line therapy according to all current guidelines [20, 21]. A modest caloric reduction (500–1000 cal/day), on the other hand, is usually effective and beneficial for long-term weight loss. A realistic goal is to reduce body weight by 7–10% over a period of 6–12 months. Long-term maintenance of weight loss is then best achieved when regular exercise is part of weight reduction management [21]. Current guidelines recommend a daily minimum of 30 minutes of moderate-intensity physical activity. Additional increases in physical activity appear to enhance the beneficial effects.

Nutritional therapy calls for low intake of saturated fats, trans fatty acids, and cholesterol. Reduced consumption of simple carbohydrates and increased intake of fruits, vegetables, and whole grains is recommended. Extremes in intakes of either carbohydrates or fats should be avoided. Smoking cessation is mandatory. Accumulating evidence suggests that the majority of individuals who develop MS do not engage in recommended levels of physical activity and do not follow dietary guidelines, for fat consumption in particular.

Drug treatment

There have been, to date, two types of drugs interfering with the mechanisms of MS: insulin-sensitizers and endogenous cannabinoid receptor blockers (CB_1 receptor blockers). While the former increase peripheral glucose disposal by acting in the peroxisome proliferator-activated receptor-gamma (PPARγ), the latter reduce abdominal obesity leading to favourable modifications in the status of adipose tissue typical of this condition. A promising new type of drug, 11beta-HSD1 enzyme inhibitors, will come in the near future.

Systematic reviews of the literature have found no notable benefits of PPARγ agonists with regard to blood pressure, although some evidence points to some blood pressure-lowering effect, at least in type-2 diabetic individuals and in those with refractory hypertension [22]. The increase in body weight resulting from the shift in fat storage from visceral to subcutaneous fat and fluid retention are the main side effects of the drugs, which limits their use. The fluid retention increases the risk of developing congestive heart failure. The increase in CV risk claimed for rosiglitazone [23], which has not been found for pioglitazone [24], has resulted in its withdrawal from the market. Other therapeutic failure also occured in the **endocannabinoid C1 receptor blockers** (CB1 blocker). Rimonabant, the first drug of the group, led to modest but significant SBP and DBP reductions in overweight/obese patients, although the effect appears to be mediated by weight loss. Increased incidence of depression and a small but significantly greater risk, among depressed people, of suicide caused concern, and the drug was withdrawn from the market [25].

Targeting high blood pressure

The threshold for intervention in BP values is based on the recognition that underlying risk factors raise BP to ranges that increase the risk of CV disease. Consequently, 130/85 mm Hg should be the threshold for intervention in the absence of diabetes. Hypertensive patients with MS should receive hypertensive drugs, according to the 2007 ESH/ESC guidelines on hypertension diagnosis and treatment [13]. In addition to recommendations to undergo intense lifestyle modifications, antihypertensive drugs should be given whenever blood pressure is persistently ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic. In the presence of diabetes, the threshold for drug intervention should be lower, i.e. blood pressure values ≥ 130 mm Hg systolic or 85 mm Hg diastolic, whereas the target blood pressure values should, in both instances, be < 130/80 mm Hg, in line with the goal that is recommended whenever total CV risk is high [3]. Similar goals and an even lower threshold for drug intervention (≥ 130/80 mm Hg) should be considered when MS is present in subjects with a very high CV risk, such as those with manifest CV or advanced renal disease.

The choice of threshold blood pressure for drug intervention to be considered in MS individuals who have no diabetes or history of CV or advanced renal disease is difficult because no trial has tested the benefit of antihypertensive drug interventions in this specific population. When microalbuminuria or other types of organ damage of prognostic significance (LVH, carotid atherosclerosis, arterial stiffening) are present, in addition to intense lifestyle changes, administration of antihypertensive drugs should be at least considered, with the goal of lowering blood pressure at least to < 140/90 mm Hg and below. Treatment should aim at preventing progression or causing regression of the existing organ damage as well as reducing the much greater chance an individual with MS has to develop new-onset diabetes or hypertension. This calls for avoidance of some antihypertensive agents and elective use of some others as outlined in the following section.

Treatments

Ideally, treatment of high BP in MS should be based on lifestyle changes (diet and physical exercise), which allows for weight reduction and improves muscular blood flow. Concerning antihypertensive drugs, whether or not a particular antihypertensive agent is superior to others has not been tested in trials including individuals specifically with MS. However, a large body of information is available from long-term antihypertensive trials with major outcomes as well as from a myriad of shorter studies.

After changes in lifestyle are introduced, the drugs to be preferred should be those which induce reduction of IR and subsequent changes in the lipid profile and in glucose levels. Therefore, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II-AT1 receptor blockers (ARA II), or even calcium channel blockers are preferable to diuretics and β-blockers in monotherapy, if no compelling indications are present for their use. If a combination of drugs is required, low-dose diuretics can be used. A combination of thiazide diuretics and β-blockers should be avoided. These recommendations are based on the impact of particular antihypertensive drugs on other components of MS. Changes in metabolic components, mainly in the lipid profile and IR, during antihypertensive treatment with diuretics and β-blockers have been claimed as the culprit of poorer reductions than expected in coronary heart disease morbidity and mortality. However, reductions in the rates of new-onset diabetes have been observed during treatment with ACEI, angiotensin II-AT1 receptor blockers (ARB), or even calcium channel blockers as compared with diuretics and β-blockers. A novel group of antihypertensive drugs, the direct inhibitors of renin (DIR), can be considered in patients with metabolic syndrome due to the neutral or even beneficial impact in glucose metabolism [26].

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HYPERTENSION AND STROKE

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Introduction

Stroke is the second leading cause of death and the number one cause of disability worldwide [1]. As well as age (non-modifiable risk factor), high blood pressure (BP) is a major risk factor for stroke, and a continuous relationship between BP and the occurrence of stroke has been well established [2]. On the other hand, evidence from hypertension treatment trials has shown that relatively small reductions in BP (5–6 mm Hg in diastolic BP, 10–12 mm Hg in systolic BP over 3–5 years) reduce the risk of stroke by more than one third [3]. The primary prevention of stroke through antihypertensive therapy and BP control is well established. Likewise, higher BP levels after stroke increase the risk of recurrent stroke [4], and there are trials that indicate that BP reduction with antihypertensive therapy is beneficial in reducing stroke recurrence and other vascular events in patients who have had a stroke [5].

Pathophysiology of vascular cerebral damage in essential hypertension

Multiple biological systems are involved in the pathogenesis of stroke [6] (Table 1). The brain represents an early target for organ damage by elevated BP, which is the major modifiable risk factor in men and women for developing ischaemic and haemorrhagic stroke, as well as small vessel disease predisposing to lacunar infarction, white matter lesions (WML), and cerebral microbleeds. Cerebral small vessel disease is an important risk factor for developing stroke and dementia [7, 8]. Hypertension causes vascular brain injury directly (small vessel disease) or by promoting atherosclerosis or cardiac damage. Inflammation plays a central role in the pathogenesis and progression of atherosclerosis and, consequently, stroke. In the same way accumulating evidence implicates oxidative stress as an important underlying cause of cerebral endothelial dysfunction.

In the development and progression of chronic high BP, hypertensive cerebral vasculopathy occurs in the form of reparative changes and adaptive processes at all structural and functional levels of the cerebral vascular system. Chronic intraluminal pressure stimulates the growth of smooth muscle cells and enhanced media thickness in resistance arteries that results in hypertrophic remodelling. Alternatively, inward remodelling may occur, leading to eutrophic remodelling. Hypertension causes marked adaptive changes in the cerebral circulation, including increased brain vascular resistance and loss of the physiological mechanism of autoregulation. Thus, hypertension influences the autoregulation of cerebral blood flow by shifting both the lower and upper limits of autoregulatory capacity towards higher blood pressure, while hypertensive patients may be especially vulnerable to episodes of hypotension, which may play a role in the development of silent cerebrovascular damage such as WML [8]. Increased cerebral vascular resistance could be due to narrowing of small vessels by lipohyalinosis and microatherosclerosis.

Table 1. Mechanisms that increase the risk of cerebrovascular disease

Oxidative stress and endothelial dysfunction
Low-grade inflammation
Increased arterial stiffness (synthesis of collagen and fibronectin)
Upregulation of renin–angiotensin system
Impaired endothelial progenitor cell function
Increased vascular permeability
Remodelling of resistance arteries (reduced lumen, reduced cerebral blood flow, increased vascular resistance)
Contraction of smooth muscle vascular vessels (reduced cerebral blood flow, increased vascular resistance)
Small vessel disease
Cerebral amyloid angiopathy

A family history of cerebrovascular disease and stroke is often perceived as a risk factor for stroke [9]. The Framingham Heart Study found a positive association between a verified paternal or maternal history of stroke and an increased risk of stroke in offspring. The inheritance is complex, multigenic, and heterogeneous. Associations with polymorphisms have been investigated in a variety of candidate genes, including haemostatic genes, genes controlling homocysteine metabolism and lipid metabolism, the angiotensin-converting enzyme (ACE) gene, and the endothelial nitric oxide synthase gene, with conflicting results, which may reflect methodological difficulties since many studies were small and underpowered or required careful case-control matching.

Relationship between high blood pressure and stroke risk

Hypertension represents a relative risk of stroke up to 6 times higher, while stroke is the most frequent complication in hypertensives [10]. In Western countries, ischaemic stroke accounts for approximately 80% of all strokes and haemorrhagic stroke for the remaining 20%. Incidence rates, commonly quoted at 2 per 1000 population, rise steeply from less than 1 per 1000 among people aged under 45, to more than 15 per 1000 among those aged 85 or more, but vary widely. In industrialized countries, approximately 75% of all strokes occur in people aged over 65 years. Around 80% of people survive the first four weeks following stroke and 70% survive for a year or more.

Overviews of large-scale observational studies have demonstrated that usual levels of BP are positively and continuously associated with the risk of stroke in a log-linear fashion [2]. This relationship between BP and stroke holds over a wide BP range, from systolic levels as low as 115 mm Hg and diastolic levels as low as 70 mm Hg [2]. Data from prospective observational studies indicate that usual levels of BP are directly and continuously related to the risk of initial stroke, and a prolonged difference in usual BP levels of just 9/5 mm Hg is associated with an approximately one-third difference in stroke risk, with similar proportional effects in hypertensives and normotensives [2, 3]. Each 5–6 mm Hg reduction in usual diastolic BP is associated with a 38% lower risk of stroke [3]. Elevated BP is positively associated with both ischaemic and haemorrhagic stroke, but the association appears to be steeper for haemorrhagic stroke. The relationship between BP and stroke risk remains virtually unchanged after adjustment for serum cholesterol levels, smoking, alcohol, or a history of previous cardiovascular disease [11]. Similar associations appear to exist between BP and the risk of recurrent stroke although there is less evidence. Data from the United Kingdom Transient Ischaemic Attack (UK TIA) Collaborative Group showed that a 10 mm Hg reduction in usual systolic BP was associated with a 28% reduction in the risk of recurrent stroke [4].

Although a continuous relationship between both systolic and diastolic BP and the occurrence of stroke has been well established, there is epidemiological evidence from the MRFIT study that the systolic component of BP may exert a strong deleterious effect on cerebrovascular disease [11]. It is known that increased arterial stiffness results in increased characteristic impedance of the aorta and increased pulse wave velocity, which increase systolic and pulse pressures. Large-artery stiffness is the main determinant of pulse pressure. Data from the SHEP study show an 11% increase in stroke risk and a 16% increase in the risk of all-cause mortality for each 10 mm Hg increase in pulse pressure [12]. Laurent et al. [13], in a longitudinal study, found that aortic stiffness, assessed by carotid-femoral pulse wave velocity, is an independent predictor of fatal stroke in patients with essential hypertension.

Antihypertensive therapy and primary prevention of stroke

It is generally believed that any of the commonly used antihypertensive drugs are effective in lowering the incidence of stroke, with larger reductions in BP resulting in larger risk reductions.

As mentioned earlier, in a review of 17 randomized trials of antihypertensive treatment, a net BP reduction of 10–12 mm Hg systolic and 5–6 mm Hg diastolic conferred a reduction in stroke incidence of 38% (SD 4), with similar reductions in fatal and non-fatal stroke [14]. Because the proportional effects of treatment were similar in higher and

lower risk patient groups, the absolute effects of treatment on stroke varied in direct proportion to the background risk of stroke. The greatest potential benefits were observed among those with a history of cerebrovascular disease.

In the overviews of randomised trials performed by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) [15] in 2000, the data showed that placebo-controlled trials of calcium antagonists reduced the risk of stroke by 39% (95% CI: 15–56) and that placebo-controlled trials of ACE inhibitors reduced the risk of stroke by 30% (95% CI: 15–43), without significant differences between these groups of regimens. More "intensive therapy" was associated with a 20% stroke risk reduction (95% CI: 2–35) compared with "normal" BP reduction. The differences in BP between the two BP lowering strategies ("normal" versus "intensive") were only 3 mm Hg. In the same line was the last review of the BPLTTC in 2008 (190,606 individuals included from 31 clinical trials) [16]. In this review, reduction of BP produced benefits in younger (< 65 years) and older (≥ 65 years) adults, with no strong evidence that protection against major vascular events afforded by different drug classes varies substantially with age. In the HYVET [17] study, hypertensive patients over 80 years of age on active antihypertensive treatment showed a significant 39% reduction in fatal stroke (secondary endpoint), and a 30% reduction of fatal and non-fatal stroke (CI: 95%: [–1] –51; p = 0.06) compared with placebo. Furthermore, in a meta-regression analysis of 28 major trials in hypertensive or high-risk patients, BP lowering was the major determinant in stroke prevention [18]. A mean BP fall of 10 mm Hg was associated with a decrease of approximately 25% in the incidence of stroke [18].

Although lowering BP is clearly beneficial in preventing stroke, the best drug regimen to achieve this is unclear. Trials comparing different antihypertensive drugs (and their meta-analysis and meta-regressions) have not been able to conclusively demonstrate that for the same reduction in BP different antihypertensive drugs (or drug combinations) reduce stroke. Thus the statement on BP lowering and stroke prevention of the International Society of Hypertension [2] and European Guidelines [19] recommend any of the five classes of antihypertensive drugs: diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers (ARBs), because of the priority in BP reduction *per se*.

Antihypertensive therapy and secondary prevention of stroke

The management of hypertension is important both during the acute phase of ischaemic and haemorrhagic stroke and throughout the long--term course of this condition. Both low BP and high BP, in the setting of acute stroke, are associated with poor outcomes. However, the optimal treatment for patients with hypertension in the first few hours or days after stroke has not been established [20, 21]. In the absence of definitive clinical data, current evidence-based guidelines suggest pursuing a cautious approach to reducing BP in the acute stroke setting. In many cases, the patient's BP will decrease spontaneously during the first few hours after stroke, and no medical intervention will be needed.

Few trials directly address the role of BP treatment in secondary prevention of stroke. A systematic review of the relationship between BP reduction and secondary prevention of stroke and other vascular events [22] included 7 published, randomized controlled trials (Dutch TIA, PATS, HOPE, PROGRESS, and 3 other smaller trials) with a combined sample size of 15,527 participants with ischaemic or haemorrhagic stroke, studied from 3 weeks to 14 months after the event and followed up for 2 to 5 years. Treatment with antihypertensive drugs was associated with significant reductions in all recurrent strokes. The overall reductions in stroke and all vascular events were related to the degree of BP lowering achieved, while data on the relative benefits of specific antihypertensive regimens for secondary stroke prevention were not clear. The impact of BP reduction was similar in the hypertensive group and when all subjects, including those with and without hypertension, were analysed. The small number of studies limited comparisons between antihypertensive drugs in these trials (diuretics, beta-blockers, calcium channel blockers, and ACE inhibitors).

Two additional large trials have been published later with ARBs. The MOSES [23] study evaluated eprosartan vs. nitrendipine in hypertensive patients with stroke or transient ischaemic attack (TIA). There was a reduction in the risk of primary composite events (death, cardiovascular event, or cerebrovascular event) in the eprosartan group. A reduction in TIA accounted for most of the benefit in cerebrovascular events, with no significant difference in ischaemic strokes. The PRoFESS study [24] evaluated telmisartan vs. placebo in patients with stroke or TIA without differences between groups in reducing recurrent strokes or major CV events.

The issue of whether patients with stroke and high normal BP should receive antihypertensive therapy remains unanswered. As focused in the Reappraisal European Guidelines [25], in the PROGRESS [26] study the average SBP achieved on a more intense treatment group was 132 mm Hg, which was better in reducing recurrent strokes than an SBP of 141 mm Hg, which was the average SBP of the placebo patients. However, it does not support the idea to decrease SBP < 130 mm Hg in all these patients. In addition, in the PRoFESS trial, bringing SBP to 136 mm Hg by adding telmisartan, rather than to 140 mm Hg by adding placebo, was not accompanied by any significant reduction in recurrent strokes or major cardiovascular events.

There is still no trial evidence on the benefit of lowering high normal BP or of achieving BP goals below 130/80 mm Hg.

Summary and conclusions

The brain represents an early target for organ damage by elevated BP, which is a major modifiable risk factor in men and women for developing both ischaemic and haemorrhagic stroke, and also small vessel disease predisposing to lacunar infarction, WML, cerebral microbleeds, and cognitive impairment. Primary prevention of stroke by antihypertensive therapy is well established although the best drug regimen to achieve this is unclear.

BP reduction in persons who have had a stroke is recommended for both prevention of recurrent stroke and prevention of other vascular events. Absolute target BP level and reduction are uncertain and should be individualized, but the benefit has been associated with an average reduction of ~ 10/5 mm Hg, and all five classes of antihypertensive drugs are suitable to reach this goal. No trial evidence is available on the benefit of lowering high normal BP or of achieving BP goals below 130/80 mm Hg.

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DIETARY SODIUM INTAKE AND HYPERTENSION

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Introduction

Hypertension is a heterogeneous disease in which both genetic and environmental factors play a role. Among the major environmental determinants of high blood pressure (BP) are high alcohol consumption, physical inactivity, and dietary factors, in particular dietary salt and potassium intakes. In recent years, the benefits of lowering sodium and increasing potassium intakes have been reinforced by the demonstration that these non-pharmacological approaches to hypertension management enable the lowering of blood pressure and the reduction of target organ damage as well as cardiovascular events [1]. However, despite accumulating experimental, epidemiological, and clinical evidence from patients with genetic diseases or from interventional studies, the need and pertinence of promoting a low sodium intake in the management of hypertensive patients remains regularly disputed. When combined with the difficulty to implement such non-pharmacological strategies in clinical practice, unless national initiatives are taken, this scientific dispute has led to a general underuse and lack of promotion of these preventive approaches in favour of therapeutic drug strategies.

Association between dietary salt intake and blood pressure

Experimentally, numerous studies involving various species and genetically modified animals have demonstrated that a prolonged increase in salt intake leads to an increase in blood pressure. Convincing evidence of a link between sodium intake and the level of blood pressure has been obtained in chimpanzees, which are genetically very close to humans [2, 3]. A study conducted on chimpanzees showed that increasing dietary salt intake substantially (> 15 g of salt per day) increased BP during a 20-month period. Blood pressure returned to pre-intervention levels within 3–4 months in the high-salt intake group after salt intake was returned to baseline. Another study was conducted in chimpanzees to analyse BP alterations in response to smaller changes in dietary salt intake [3]. In this study, BP closely followed changes in dietary salt intake. An important piece of information from this study is that BP changes were as large for sodium intakes at or below current guidelines (i.e. 2–6 g/day mmol/24 h) as for higher intakes (6–15 g/day).

In humans, a weak association between salt intake and the level of BP has also been demonstrated. The most frequently cited study is the INTERSALT study [4], which showed that 24-hour urinary sodium excretion, a proxy of sodium intake, was significantly associated with both systolic and diastolic blood pressure in individual subjects. More importantly, the results of this study demonstrated a greater rise in blood pressure with age among subjects with higher salt intake. In the 1990s, an overview of data collected for 47,000 non-African subjects from 24 communities confirmed the positive association between BP and urinary sodium excretion across and within populations, as well as its strengthening with age [5, 6]. Of note, in the INTERSALT study, populations with low dietary salt intakes (i.e. < 50 mmol/24 h for sodium or 3 g/24 h for salt) had little BP increase with age. In the EPIC-Norfolk study involving 23,104 individuals, BP was also higher among subjects with a high sodium intake, the prevalence of an elevated BP (systolic > 160 mm Hg) being 12% when the salt intake was > 12.9 g/day and only 6% in those with a salt intake of 4.7 g/day [7].

Dietary salt intake and target organ damage

A high sodium intake has also been associated with left ventricular hypertrophy (LVH), and the structure and function of large arteries and of the kidney in part, independently of its impact on blood pressure.

Left ventricular hypertrophy is recognized as an independent predictor of cardiovascular complications and mortality [8]. Its prevalence is particularly elevated among hypertensive patients because BP is a major determinant of left ventricular mass. However, there are good experimental data suggesting that a high salt intake can promote left ventricular hypertrophy even in the absence of elevated systemic BP. Experimentally, sodium is a necessary co-factor for the development of LVH and cardiac fibrosis in animals receiving an excess of mineralocorticoids [9]. Moreover, an increase of sodium concentration directly exerts growth stimulating intracellular signals. In humans, several cross-sectional studies have reported a positive association between urinary sodium excretion and left ventricular mass, both in normotensive subjects and hypertensive patients [10, 11]. Careful assessment of dietary salt intake confirmed such a blood pressure-independent relation of sodium intake with left ventricular mass. In these studies, salt intake was found to be a powerful determinant of left ventricular mass. In hypertensive patients, a reduction in salt intake is associated with a reduction of left ventricular mass, concomitant to the reduction in blood pressure.

At the vascular level, increased sodium intake has been reported to induce pronounced structural alterations of arteries, such as cerebral or renal arteries, independently of BP levels [12, 13]. Through changes in shear stress and endothelial function, high sodium intake can induce pressure-independent effects on the vascular wall, affecting the vascular content of collagen and elastin fibres. Clinically, there is also evidence that salt affects arterial stiffness and hence systolic and pulse pressure. In a Chinese study, the age-associated increase in pulse wave velocity was lower in the community with a lower salt intake [13]. Interestingly, salt consumption was double in the urban Chinese population than in the rural population, and the age-related changes in systolic BP and aortic stiffness occurred 30 years of age later in the rural than in the urban community. A reduction in dietary salt intake reduced pulse pressure, suggesting an improvement in arterial distensibility [14].

Experimentally, a low sodium diet prevents renal alterations in several models of hypertension and renal diseases. In rat models of hypertension and reduced renal mass, salt restriction prevents an increase in proteinuria, compensatory kidney growth, and glomerulosclerosis [15]. Similarly, in diabetic animals, long-term salt restriction attenuates the progressive rise in albuminuria and the development of renal hypertrophy. A low sodium intake may also induce renal protection by reducing glomerular hyperfiltration [16]. In humans, the long-term benefits of a low sodium intake on the progression of non-diabetic or diabetic nephropathies are less well documented. However, in a retrospective analysis of chronic kidney disease progression, the rate of decline in creatinine clearance over a 43-month period was two-fold greater in patients on a high sodium intake (> 200 mmol/day) when compared to patients on a low sodium intake (< 100 mmol/day) [17]. Several short-term studies have shown that a high sodium intake increases glomerular filtration and may have a detrimental effect on glomerular haemodynamics, as reflected by an increase in filtration fraction and hence in intraglomerular pressure. The most significant impact of dietary salt intake on renal function is certainly its effect on urinary albumin excretion. In a cross-sectional study including untreated subjects with a wide range of BP levels, the prevalence of microalbuminuria was markedly higher in subjects with a sodium intake higher than 12 g/day [18]. This finding is corroborated by the results of the Groningen population-based study including 7850 subjects, in which an interaction between sodium intake and obesity on the prevalence of microalbuminuria was found [19]. Lowering salt intake in proteinuric patients is associated with a significant reduction in urinary protein excretion, and salt restriction increases the antiproteinuric effect of blockers of the renin–angiotensin system, an effect that can be mimicked by the administration of a thiazide diuretic in combination with an RAS blocker.

Dietary salt intake and the incidence of cardiovascular events

Several prospective observational studies have analysed the association of dietary sodium intake and all-cause mortality. Tuomilehto et al. reported that dietary sodium intake is associated with a 32% increase in all-cause mortality in men, but the association was only observed in overweight men [20]. Other studies [21] found a positive association between dietary sodium intake and cardiovascular mortality, in particular in overweight subjects, whereas other studies found no such association. In the Scottish Heart Health Study, a positive association between dietary sodium intake and coronary death was found in women but not in men [22]. In the NHANES I follow-up study, a negative association was found between dietary salt intake and cardiovascular mortality, but the association was positive when sodium excretion was corrected for calorie intake [23]. In a recent population study involving rather young subjects, Staessen et al. found a higher incidence of cardiovascular mortality among subjects with the lowest sodium excretion. This surprising finding deserves further confirmation in an elderly group of subjects more likely to be salt-sensitive than young normotensive Caucasians with a low incidence of cardiovascular complications [24]. Several prospective studies have examined the association of dietary sodium intake and the risk of stroke. The data gathered so far are inconsistent. However, based on the changes in blood pressure from the meta-analysis of randomized salt-reduction trials and the relationship between BP and stroke and ischaemic heart disease, it has been estimated that a 3 g/day reduction of dietary salt intake would reduce stroke by 13% and ischaemic heart disease by 10% [25].

Interventions to lower dietary salt intake reduce BP and cardiovascular events

Numerous interventional studies have been conducted to investigate the clinical impact of lowering dietary sodium intake on BP. Several of them were limited either by the short duration of the intervention or by the very small or excessive changes in sodium intake obtained during the study. The last meta-analysis of randomized studies, which took into account only studies with a duration of at least one month and modest reductions of sodium intake that can be achieved in daily life practice (mean 4.4–4.6 g of salt/day), demonstrated that a reduction in salt intake is associated with a significant decrease in BP, both in normotensive and hypertensive individuals [26]. A recent study has also demonstrated the benefits of reducing salt intake in patients with resistant hypertension [27].

Several large clinical trials have investigated the impact of lowering salt intake alone or in association with other dietary or non-pharmacological interventions on blood pressure and cardiovascular events. The trial of non-pharmacologic interventions in the elderly (**TONE**) [28] implemented weight loss and/or sodium reduction in obese patients or sodium reduction in non-obese hypertensive subjects aged 60–80 years treated with one antihypertensive drug. The goal was to obtain and maintain a urinary sodium excretion of less than 80 mmol/24 h (< 4.7 g salt/24 h) in addition to a weight loss of at least 4.5 kg. A usual care group was compared to an active intervention group. The combined outcome measures (incident hypertension and/or cardiovascular events) were less frequent among those assigned compared with those not assigned to reduced sodium intake (relative hazard ratio 0.69). Relative to usual care, hazard ratios among the obese participants were 0.60 for reduced sodium intake alone, 0.64 for weight loss alone, and 0.47 for reduced sodium intake and weight loss combined after a median follow-up of 29 months. In the Trial of Hypertension Prevention I (**TOHP I**), multiple lifestyle changes were compared in parallel, including dietary sodium reduction and weight reduction [29]. The target population were healthy men and women aged between 30 and 54 years, with high normal diastolic blood pressure, who were not taking antihypertensive treatment. A significant 55-mmol reduction in urinary sodium excretion was achieved in the sodium reduction group, but not in the control group at 18 months. Systolic and diastolic BPs were significantly reduced in the active group versus the control group for the sodium reduction and weight loss interventions. In the sodium reduction group, there was a non-significant 16% reduction in the incidence of hypertension (RR: 0.84, 95% CI: 0.62–1.13), whereas in the weight loss group, there was a significant 36% reduction in the incidence of hypertension (RR: 0.66, 95% CI: 0.46–0.94). The aim of the Trial of Hypertension Prevention II (**TOHP II**) (2 × 2 factorial randomized, open multicentre trial) was to determine whether weight loss alone, dietary sodium reduction alone, or a combination of both interventions could lower BP and reduce the incidence of hypertension in subjects with high-normal BP [30]. Participants in this trial had high normal diastolic BP (83–89 mm Hg) with systolic BP < 140 mm Hg. Blood pressure was significantly lower in the intervention groups in each time period. The sizeable effects observed at 6 months greatly diminished during follow-up, indicating that long-term interventions for sodium reduction are difficult to maintain. At 48 months of follow-up, the incidence of hypertension was significantly lower in every intervention group as compared to the usual care group. The results of the long-term follow-up (10–15 years) of patients enrolled in the THOP1 and THOP II trials showed a non-significant 20% lower all-cause mortality in the group of subjects assigned to the sodium restriction intervention but a significant 30% lower incidence of cardiovascular disease (defined as myocardial infarction, stroke, coronary artery bypass graft, coronary angioplasty, or death of any cardiovascular cause) as compared to persons in the control groups.

The **DASH** study is a landmark trial which compared a control diet with a diet rich in fruit, vegetables, and low-fat dairy products (i.e. DASH diet). The DASH diet significantly reduced blood pressure at 1 month. In the subsequent DASH-sodium trial, three different dietary sodium intakes were compared, 150, 100, and 50 mmol/24 h, which correspond to approximately 8.8, 5.8, and 2.9 g of salt per day, respectively, with and without DASH diet [31]. Blood pressure was significantly lower when going to a lower group of dietary salt intake in both the control diet and the DASH diet groups. The results of low sodium — DASH diet trial further strengthen the conclusion that reduction of dietary sodium intake through low-salt diet lowers BP effectively and adds to the benefits conferred by the DASH diet. More recently, a large interventional study was conducted to examine the association between metabolic syndrome and salt sensitivity, defined as the BP response to low (50 mmol/day) and high (300 mmol/day) salt intake [32]. The results of this study performed in non-diabetic Chinese subjects revealed that the presence of metabolic syndrome increases the BP response to salt intake. Hence, sodium restriction could be an important component in the strategy to lower BP in subjects with metabolic syndrome.

Conclusions

Non-pharmacological dietary interventions promoting low salt intake should be more systematically considered in the prevention and management of essential hypertension and prevention of hypertensive target organ damage. Although these approaches are considered difficult to implement and sustain over a number of years in most subjects, they provide unique cost-effective opportunities to avoid drug treatment in the early stages of hypertension and to reduce drug therapies in patients with established hypertension. In view of the difficulty in achieving long-term changes in dietary habits at the individual level, nationwide interventions aimed at reducing the sodium content of processed foods may provide substantial health benefits to the general population and also to hypertensive patients.

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HYPERTENSIVE RETINOPATHY

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Introduction

As early as the 19th century retinal abnormalities in hypertensive subjects were described by Liebreich [1] and Gunn [2]. The traditional classification system of hypertensive retinopathy goes back to the pioneering work by Keith, Wagner, and Barker in 1939, in which they demonstrated the prognostic significance of funduscopic abnormalities in hypertensive patients [3]. The impact of funduscopic findings on risk stratification was soon supported by several studies that were conducted in the 1950s and 1960s [4, 5] Nowadays, funduscopy still plays a major role in the management and risk stratification of hypertensive patients: The ESH/ESC 2007 guideline considers hypertensive retinopathy grade 3 and 4 as target-organ damage [6].

Pathophysiology and clinical manifestations

Retinal circulation undergoes a series of pathophysiological changes in hypertension [7]. These changes are mediated either directly by elevated blood pressure or indirectly via vasoactive substances (angiotensin II, endothelin-1, decreased basal nitric oxide activity, among others). Mild changes are reflected by vasoconstriction (generalized and focal arteriolar narrowing), growth of smooth muscle cells, and hyaline degeneration of the wall of retinal arterioles (opacification of arteriolar walls with widening and accentuation of the central light reflex, also described as silver or copper wiring) as well as changes in the arteriolar and venular junctions (arteriovenous nicking). Advanced changes include breakdown of the blood-retina barrier of the retinal arterioles (haemorrhages, hard exudates and cotton-wool spots), micro-and macro-aneurysms, branch vein occlusions, and optic disc swelling (papilloedema).

Classification

In their famous work in 1939 Keith, Wagener, and Barker categorized the signs of hypertensive retinopathy into 4 grades of increasing severity (Table 1) and demonstrated that at that time hypertensive patients with hypertensive retinopathy grade 4 had a 3 year survival rate of 6% versus hypertensive patients with grade 1 signs who had a 3 year survival rate of 70% [3].

The usefulness of the four-grade classification system of Keith, Wagener, and Barker and the five stage classification of Scheie [8] and its importance in current clinical practice has been questioned repeatedly in recent years [9, 10]. Criticism refers especially to hypertensive retinopathy grades 1 and 2. Low retinopathy grades (grade 1 and grade 2 signs) cannot easily been distinguished even by experienced investigators and reveal low inter- and intra-observer variability [11, 12]. Only advanced hypertensive retinopathy grades can be reliably assessed. However, nowadays most hypertensive patients reveal low retinopathy grades (e.g. generalized retinal arteriolar narrowing) whereas very few patients have advanced hypertensive retinopathy.

Table 1. Keith-Wagener-Barker classification [3] of hypertensive retinopathy

	Grade 1	Grade 2	Grade 3	Grade 4
Arteriolar narrowing	+	+ +	+ + +	+ + + +
Arteriovenous nicking		+	+ +	+ + +
Retinal haemorrhages			+	+ +
Micro-aneurysms			+	+ +
Hard exudates			+	+ +
Cotton-wool spots			+	+ +
Optic disc swelling				+
Macular oedema				+

Moreover, retinopathy signs do not necessarily correlate with the severity of hypertension, and the positive and negative predictive values for the association between hypertensive retinopathy and blood pressure are low [6, 12].

Prognostic significance

Recent studies evaluating fundus findings and their relation to systemic disease, such as the Blue Mountains Eye Study, the Atherosclerosis Risk in Communities (ARIC) Study, the Multi-Ethnic Study of Atherosclerosis, and the Beaver Dam Eye Study, have demonstrated the value of fundus findings and their association with the risk of hypertension and associated comorbidities [9, 13]. There is solid evidence that advanced hypertensive retinopathy signs, such as isolated micro-aneurysms, haemorrhages, hard exudates, and cotton-wool spots, are strongly associated with subclinical cerebrovascular disease and predict incident clinical stroke, coronary artery disease, congestive heart failure, and cardiovascular mortality, independently of blood pressure and other traditional risk factors [9, 10]. In contrast, the impact of mild hypertensive retinopathy signs, such as generalized and focal arteriolar narrowing and arteriovenous nicking, on systemic vascular disease and cardiovascular mortality is less stringent [9, 10]. As a consequence, a new classification of hypertensive retinopathy has been posited (Table 2) [9].

Recent approaches in imaging technologies

In parallel to the repeated criticism concerning the traditional classification systems to current management of hypertensive patients, new methodological approaches have been developed focusing on more precisely and reliably assessing early retinal arteriolar abnormalities in hypertensive patients, aiming to improve the diagnostic and prognostic power of mild hypertensive retinopathy [10, 13].

Arteriole-to-venule ratio of retinal vessels

The ability to digitize retinal photographs allowed the assessment of outer arteriolar and outer venule diameter of retinal vessels and subsequent calculation of the arteriole-to-venule ratio [14]. The measurement of the arteriole-to-venule ratio of retinal vessels is based on the concept that a lower arteriole-to-venule ratio of retinal vessels reflects general arteriolar narrowing, which represents an early step of hypertension relating to retinal vascular alterations. Some, but not all, large population-based studies identified the arteriole-to-venule ratio to be predictive of cardiovascular events [9, 15]. However, no study thus far has revealed that the arteriole-to-venule ratio of retinal vessels has a clearly independent value of predicting cardiovascular or total mortality [9, 15]. Recent data indicate that the outer venule diameter also changes in several metabolic conditions that are frequently associated with hypertension [16], which may dilate the prognostic power of the arteriole-venule ratio. Thus, the lack of a prognostic role of the arteriole-to-venule ratio of retinal vessels is probably due to concomitant changes in venule diameters in the majority of hypertensive patients and has also been found to be predict the development of hypertension.

Wall-to-lumen ratio of retinal arterioles

The development of scanning laser Doppler flowmetry (SLDF) with automatic full-field perfusion imaging analysis (AFFPIA) now allows

Table 2. Classification of hypertensive retinopathy [9]

Grade 1	Mild retinopathy	Generalised and focal arteriolar narrowing, arteriolar wall opacification, and arteriovenous nipping
Grade 2	Moderate retinopathy	Flame-shaped or blot-shaped haemorrhages, cotton-wool spots, hard exudates, micro-aneurysms, or a combination of all of these factors
Grade 3	Severe retinopathy	Some or all of these retinopathy signs, as well as swelling of the optic disc

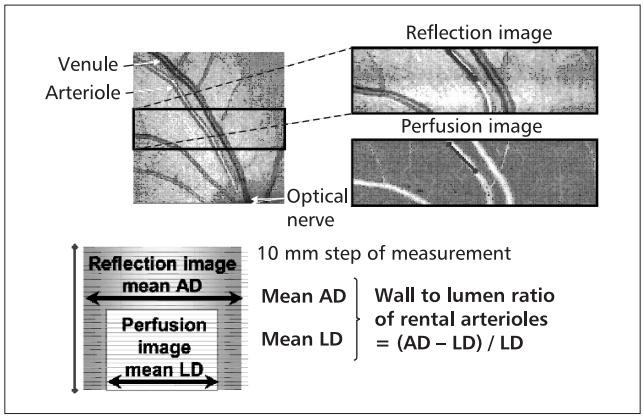

Figure 1. Assessment of the wall-to-lumen ratio of retinal arterioles [19]. A specific length of the arteriole reflecting one heart beat (one systole plus one diastole) is considered for analyses, and diameters at every 10 μm of this specific length are measured. Outer diameters (AD) are measured in reflection image and inner diameters (LD) are measured in perfusion image. The mean of the measured diameters is finally calculated and the average from 3 singular measurements is completed for further analyses

precise assessment of retinal arteriolar structure and remodelling by analysing the outer and inner diameters of retinal arterioles and subsequent assessment of the wall-to-lumen ratio, wall thickness, and wall cross sectional area (volume of vascular wall per unit length) of the retinal arteriole, as previously described in detail [17–19]. In brief, the outer diameter of the retinal arteriole is assessed in reflection images, and the inner diameter is assessed in perfusion images, and the wall-to-lumen ratio is than calculated according to the formula (outer diameter–inner diameter/inner diameter) [17, 18] (Figure 1). The assessment of the wall-to-lumen ratio of retinal arterioles with SLDF with AFFPIA was found to be reliable [18, 19].

Studies analyzing arteriolar structure of vessels obtained through biopsies of subcutaneous tissue from abdominal and gluteal region observed that remodelling of resistance arterioles and small arteries predict cardiovascular complications. Increased wall-to-lumen ratio of arterial vessels indicates an early (probably the earliest) form of hypertension-related atherosclerotic vascular changes and is of prognostic significance in hypertensive patients, with adverse prognosis in those with the greatest wall-to-lumen ratio [20]. An increase in the wall-to-lumen ratio of retinal vessels can be the result of either vasoconstriction, growth of vascular smooth muscle cells, or both [21, 22]. Recent data suggest that retinal arterioles and subcutaneous small arterioles undergo the same type of remodelling in hypertension, and the pattern and quantity of vascular changes are comparable [19]. Thus, it is reasonable to hypothesize that assessment of retinal arteriolar structure and remodelling by assessment of the retinal arteriolar wall-to-lumen ratio may serve as a potential future parameter of target organ damage in hypertension. The prognostic value of remodelling of the small arteries taken from biopsies has already been proven [23, 24]. Until now, only a few studies have examined retinal arteriolar structure in hypertension. In untreated patients with stage 1 and 2 essential hypertension a close relation between systolic and diastolic blood pressure and wall-to-lumen ratio of retinal arterioles was found independently from potential confounding factors, including classical cardiovascular risk factors, urinary albumin excretion, sodium intake, and basal nitric oxide activity [19]. Moreover, the wall-to-lumen ratio of retinal arterioles was found to be greater in patients with essential hypertension compared to normotensive controls [19]. Hypertensive patients with a history of a cerebrovascular event revealed a greater wall-to-lumen ratio of retinal arterioles than hypertensive and normotensive controls [18]. Treated hypertensive subjects with poor blood pressure control were found to have a greater wall-to-lumen ratio of retinal arterioles than those with good blood pressure control [18]. Moreover, the wall-to-lumen ratio of retinal arterioles was found to be associated with other parameters of target organ damage including intima-media-thickness of carotid arteries [25] and urinary albumin excretion. No study thus far has been conducted to evaluate the prognostic value of the wall-to-lumen ratio of retinal arterioles, but its reproducibility has been recently demonstrated [26].

Conclusions and prospects

There is solid evidence that moderate or severe hypertensive retinopathy is of prognostic significance for future cardiovascular events. None of the prospective trials had adequately corrected for concurrent measures of hypertensive target organ damage. New methodologies that determine hypertensive retinal vascular changes earlier and more precisely are on the horizon and may serve as tools for detecting hypertensive retinopathy.

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HYPERTENSION AND ATRIAL FIBRILLATION, WITH AN EMPHASIS ON PREVENTION

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Why discuss atrial fibrillation in hypertension?

Atrial fibrillation (AF) is the most common clinically significant sustained cardiac arrhythmia and it is associated with increased risk of cardiovascular morbidity and mortality. It is a disease of aging, and the prevalence doubles with each decade after 50 years and approaches 10% in those more than 80 years of age [1]. In men and women, respectively, hypertensive patients have a 1.4- and 1.5-fold risk of developing AF [1]. Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling, slowing of atrial conduction velocity, structural changes, and enlargement of the left atria [2]. All these changes in cardiac structure and physiology favour development of AF, and increase the risk of complications. In the following, we will review possible mechanisms for increased risk of AF in hypertensives and look into the effect of different antihypertensive treatment regimens.

Hypertension is a prevalent, independent, and potentially modifiable risk factor for AF development [1]. The relative risk (RR) of developing AF in patients with hypertension has been calculated to be 1.4–2.1, which is modest compared to, for example, heart failure and valvular disease, which have relative risks of AF development of 6.1–17.5 and 2.2–8.3, respectively [2]. However, due to the high prevalence of hypertension in the population, hypertension accounts for more cases of AF than any other risk factor [1]. Increased pulse pressure has recently been recognized as a possible, even more important, risk factor [3]. In the Framingham database, increased systolic pressure was associated with AF, but the association was even stronger when low diastolic pressure with a higher pulse pressure effect was added into the statistical model [3]. Other known risk factors for AF are left ventricular hypertrophy, left atrial size, heart failure, valvular (in particular mitral valve) and ischaemic heart disease, heart rate, gender, diabetes mellitus, hyperthyroidism, severe infection, pulmonary pathology, stroke, obesity, alcohol abuse, and smoking [4]. Recently, new risk factors for AF, such as sleep apnoea, excessive sports practice, inflammation, and genetic influence, have also been recognized [5].

Lone AF is defined as AF in individuals younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension [6]. These patients have a favourable prognosis with respect to thromboembolism and mortality [6]. However, underlying hypertension often may not be recognized in these patients diagnosed with lone AF due to inadequate diagnostic investigations (e.g. no 24-hour ambulatory blood pressure measurement) or treatment with beta-blockers or calcium channel blockers for AF, which also have antihypertensive effects [5].

Atrial fibrillation itself produces electrical and structural remodelling of the heart, and may be important for the recurrence or the maintenance of the AF. Angiotensin II has been suggested as one important mechanism for the atrial remodelling, and blockers of the renin–angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II-receptor blockers (ARBs), have shown promising results in reducing the incidence of AF in heart failure and hypertension trials [7].

New-onset AF in hypertension trials using RAS-blocker

As yet, no prospective hypertension trial has investigated the effect of RAS blockade on the development of AF as a primary endpoint, but there are several secondary analyses of large randomized trials. However, there are limitations in the evaluation of new-onset AF in these trials, which were not designed to investigate this as the primary endpoint, especially as the definitions and evaluations of AF differ between the trials. Annual ECG recordings may underestimate the prevalence of AF (although equal between the treatment groups); therefore, in recently published and ongoing trials, new-onset AF is a pre-specified endpoint, and trans-telephonic ECG monitoring is also included to recognize asymptomatic AF. There have been some hypertension trials with ACEIs reporting the effect on AF, and no significant effects of RAS-blockade have been found [8, 9]. However, these trials were not designed to investigate AF and must be looked upon more as chance findings.

In the LIFE study, more than 9000 hypertensive patients with signs of left ventricular hypertrophy in their electrocardiogram (ECG) were randomized to atenolol (beta-blocker)- or losartan (ARB)-based antihypertensive treatment with similar blood pressure reduction between the two treatment groups [10]. Included in the analyses of AF were 8851 patients with no previous history of AF and in sinus rhythm at baseline. New-onset AF was identified in 371 of these patients from annual in-study ECGs analysed at a single centre, during the mean 4.8 years of follow-up: 221 of the atenolol-treated and 150 in the losartan-treated patients [11]. This indicates that randomization to ARB-treatment was associated with a relative risk reduction of 33% of new-onset AF, independent of other risk factors ($p < 0.001$) [11]. Patients with new-onset AF had an approximately twofold increase in risk of cardiovascular events, a threefold increase in risk of stroke, and fivefold increase in rate of hospitalization for heart failure, even after adjustment for covariates [11].

In the VALUE trial, more than 15,000 high-risk hypertensive patients were treated with amlodipine (calcium channel blocker [CCB]) or valsartan (ARB), and new-onset AF was a secondary pre-specified end-point, and ECGs were obtained every year and centrally analysed [12]. During the average 4.2 years of follow-up of the trial the incidence of at least one ECG-documented episode of new-onset AF was 3.67% in the valsartan-treated and 4.34% in the amlodipine-treated patients, resulting in a hazard ratio of 0.84 (0.713–0.997, $p = 0.0455$) [12]. The incidence of persistent AF was 1.35% with valsartan-treatment and 1.97% with amlodipine-treatment, resulting in an unadjusted hazard ratio of 0.68 (0.525–0.889, $p = 0.0046$). When taking potential confounding covariates into account (age, history of coronary artery disease, left ventricular hypertrophy) the incidence of AF-reduction with ARB-treatment remained significant [12].

In a study comparing various antihypertensive agents on AF recurrence, 369 mild hypertensive patients in sinus rhythm (but with at least two episodes of AF during the last six months) were randomized double-blindly into treatment with ARB (valsartan), ACEI (ramipril), or CCB (amlodipine) for one year [13]. AF recurrence was reduced significantly after treatment with RAS-blockade (ARB and ACEI) compared with treatment with CCB, despite a similar blood pressure lowering effect [13]. Consistently, in the ONTARGET trial, about 69% of the patients were hypertensive and no significant difference was seen between the ACEI ramipril, the ARB telmisartan, or the combination of both ACEI and ARB in cases of new-onset AF [14].

Several smaller studies have analysed the effect of RAS blockade in combination with antiarrhythmic amiodarone after electrical cardioversion in patients with AF. In a study of 154 patients randomized to open-label treatment with the ARB irbesartan, the time until recurrence and the probability of remaining free of AF were greater after treatment with irbesartan and amiodarone than after treatment with amiodarone alone (80% vs. 56%, $p = 0.007$) [15]. In the hypertensive subgroup (< 50%) there was a trend for irbesartan plus amiodarone to be superior to amiodarone alone in reducing AF recurrence, with a relative risk reduction (RR) of 0.49 (0.11–2.06) [15]. Use of ARB was the only significant variable related to the maintenance of sinus rhythm after cardioversion in a multivariate analysis [15]. And in another study the addition of ACEI enalapril to amiodarone facilitated subsequent long-term maintenance of sinus rhythm after cardioversion [16].

In a study of 213 patients with mild hypertension and paroxysmal AF treated with amiodarone, additional treatment with the ARB losartan for one year yielded a significantly lower recurrence rate of AF compared with patients treated with the CCB amlodipine: 13 patients versus 39 patients, respectively ($p < 0.01$) [17]. Treatment with ARB alone, without adjunct antiarrhythmic therapy before electrical cardioversion for AF, was tested in the CAPRAF study [18]. In this study only 25–35% of the patients were hypertensive and no statistically significant difference in AF recurrence was found between the two treatment regimens [18]. In the GISSI-AF trial, secondary prevention with ARB was also not successful in preventing recurrent AF [19]. Therefore, the effect of RAS-blockade on AF recurrence without hypertension and antiarrhythmic treatment is not known for sure.

In a recent meta-analysis, the effects of RAS-blockade for the prevention of AF were investigated, aiming to define when the inhibition is most effective [20]. A total of 23 randomised studies with a total of 87,048 patients were included (6 hypertension trials, 2 post-myocardial infarction trials, 3 heart failure trials (primary prevention), 8 studies after cardio-version, and 4 on medical prevention of paroxysmal AF

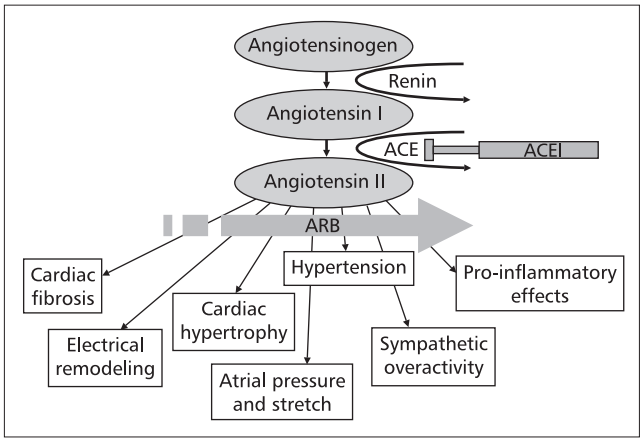

Figure 1. Possible mechanisms of how RAS-blockade may reduce new-onset AF and AF recurrence (reproduced with permission from *Seminars in Cardiology* [21])

(secondary prevention) [20]. Treatment with RAS-blockade reduced the odds ratio for atrial fibrillation by 32% (0.22—0.43, $p < 0.00001$), with similar effects of ACEIs and ARBs [20]. In primary prevention RAS-blockade was most effective in patients with left ventricular hypertrophy and/or heart failure [20]. In secondary prevention, RAS-blockade reduced the odds for AF recurrence after cardio-version by 45% (0.34–0.89, $p = 0.01$) and on medical therapy by 63% (0.27–0.49, $p < 0.00001$) [20]. However, no effect was found in those with the most refractory AF [20].

Possible mechanisms for the AF-reducing effects of RAS blockers are summarized in Figure 1. These mechanisms can give non-haemodynamic or haemodynamic effects, for example, by reducing blood pressure *per se* [21]. Reduction of left ventricular hypertrophy by blockers of RAS may improve left ventricular haemodynamics and the risk of developing AF. Other anti-arrhythmic effects beyond blood pressure lowering have also been suggested, e.g. ion-channel function, reduction of P-wave dispersion, cardiac fibrosis, atrial stretch and left atrial dilatation, and modulation of sympathetic activity [7]. Blockade of RAS may also have potassium-sparing effects that may reduce the risk of tachyarrhythmia, and a direct antiarrhythmic effect of the drugs has also been suggested. ARBs are effective in both non-ACE and ACE-dependent production of angiotensin II by giving a direct blockade at the receptor site, while an ACEI is only a competitive inhibitor of ACE that can also be overcome by a rise in renin during antihypertensive treatment. The above observations provide no definitive indication for the use of RAS blockade to prevent AF, but their use in patients with recurrent AF has been suggested, particularly if there are other indications such as hypertension, heart failure, or diabetes mellitus [22]. It has also been shown that hypertensive patients included in the VALUE trial with new-onset diabetes mellitus had a significantly higher event rate of new-onset AF with a hazard ratio of 1.49 (1.14–1.94, $p = 0.0031$) compared with patients without diabetes mellitus, and this may explain some of these patients' concomitant high risk of hospitalization for heart failure [23]. Preventing the progression from high blood pressure to AF and to heart failure may be of great importance not only for the patients, but also for the health care system.

New-onset AF in trials using other antihypertensive treatment regimens

Lately, the use of beta-blockers as first-line therapy for hypertension has been questioned [22]. However, beta-blockers have known effects in AF rate-control and a possible effect in maintaining sinus rhythm, especially in heart failure and in cardiac postoperative settings [24, 25]. In a meta-analysis including almost 12,000 patients with systolic heart failure (about 90% received RAS-blockade), beta-blockers significantly reduced the incidence of onset of AF with a relative risk reduction of 27% (RR 0.61–0.86, $p < 0.001$) [24]. The non-selective beta-blocker sotalol is effective in maintaining sinus rhythm, but has pro-arrhythmic effects and is not recommended for antihypertensive treatment. Possible mechanisms of action of the plain beta-blockers to reduce risk of AF may be prevention of adverse remodelling and ischaemia, reduced sympathetic drive, or counteraction of the beta-adrenergic shortening of action potential, which could otherwise contribute to perpetuation of AF [24].

Calcium channel blockers are a heterogeneous group of drugs with antihypertensive properties. Non-dihydropyridines, such as diltiazem and verapamil, are used to slow the ventricular response in AF, and verapamil has been investigated for its effectiveness in maintaining sinus rhythm after cardioversion. Calcium lowering drugs could hypothetically attenuate the Ca^{2+} overload in tachycardia-induced electrical remodelling of the atria [26]. However, studies have shown variable results, and in the VALUE trial the ARB valsartan was more effective than the CCB amlodipine in preventing new-onset AF [12].

Diuretics are often included in antihypertensive treatment regimens, but the effect on new-onset AF has seldom been investigated. In the Veteran Affairs Cooperative Study on Single-Drug Therapy in Mild-Moderate Hypertension, comparing different antihypertensive agents, hydrochlorothiazide was associated with a significant reduction in left ventricular mass and a greater overall reduction in left atrial size than the other agents [27, 28]. Left ventricular mass and left atrial size are both known AF risk factors, but the effect on new-onset AF is not known.

Conclusions

AF and hypertension are two prevalent and often coexistent conditions, and both are responsible for considerable morbidity and mortality. Aggressive treatment of hypertension, especially with RAS-blockers, may postpone or prevent development and recurrence of AF and reduce thromboembolic complications. Primary prevention is a new strategy in the treatment of AF as it has previously been more common to focus on prevention of adverse outcome and rate- and rhythm-control of the final condition. However, as our population is aging and an increase in the number of patients with AF is expected, focus on primary prevention with optimal antihypertensive treatment may be important to reduce morbidity, mortality, and health care expenditure in the future.

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MANAGEMENT OF PHEOCHROMOCYTOMA–PARAGANGLIOMA

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The term "paraganglioma" identifies a category of tumour arising from neuroendocrine cells that migrate from the neural crest at the time of embryonic development and cluster in the proximity of parasympathetic and sympathetic ganglia, where they form the so-called paraganglia. The term "pheochromocytoma" should be reserved for those paragangliomas originating from catecholamine-producing chromaffin cells located in the adrenal medulla. On the other hand, paragangliomas of parasympathetic origin are usually located in the head and neck region, rarely synthesize catecholamines, and are chromaffin negative — since these non-functioning paragangliomas are not associated with signs of sympathetic overactivity, they are not seen in the context of arterial hypertension and will be excluded from further consideration in this newsletter.

A rare disease?

A reliable estimate of the incidence of pheochromocytoma has been obtained at the Mayo Clinic in the population of Rochester, resulting in approximately one case per 100,000 subject/years [1]. Lower values (approx. 0.2 cases per 100,000 subject/years) have been found in Japan, Sweden, Denmark, and Spain. On the other hand, different groups report the occurrence of pheochromocytoma in 1–5/1000 hypertensive patients. This apparent inconsistency could be explained by a presumable selection bias in hypertensive patients observed at specialized centres. From another perspective, adrenal incidentalomas were found in 0.4% of individuals from a series of more than 60,000 abdominal CT scans, and another report suggests that approximately 4% of adrenal incidentalomas are pheochromocytomas [2].

Presentation of pheochromocytoma

Signs and symptoms of pheochromocytoma and functional paraganglioma are particularly variable [3]. In some instances, the disease is asymptomatic or its manifestations are easily overlooked by the patient; in fact, in a few cases these tumours are detected at autopsy or as incidentalomas. In other cases, the clinical presentation may be dramatic, with major complications such as myocardial infarction, cerebrovascular accident, fatal arrhythmia, or dissecting aortic aneurysm.

However, the most frequent clinical presentation is hyperadrenergic syndrome, with persistent or paroxysmal hypertension as a leading sign and the classic triad of headache, palpitations, and diaphoresis. More than half of pheochromocytoma patients experience paroxysms or crises. Their frequency varies from sporadic to several times a day and usually increases with disease progression. Sometimes precipitating factors can be observed. They may include ingestion of certain foods containing tyramine or synephrine (parmesan cheese, some red wines, orange juice) and some drugs (opiates, histamine, ACTH, glucagon, methyldopa tricyclic antidepressants, etc). In some patients paroxysms may be precipitated by mechanical compression, as is the case during micturition in patients with a urinary bladder tumour. Usually the duration of a paroxysm varies from a few minutes to one hour. Paroxysmal symptoms are variable, but the clinical picture is quite consistent in the same individual. Most often, the crisis is heralded by a sensation of forceful heartbeat, followed by headache, sweating, anxiety, tremor, nausea, vomiting, abdominal or chest pain, paresthesias, fatigue, and dyspnoea, in variable patterns. In addition, the severity of symptoms may increase with disease progression. Hypertension is present as a true paroxysm (~25%) or as a crisis superimposed to sustained hypertension (~25%). Body temperature may rise slightly during a crisis. Arrhythmias and/or electrocardiographic changes may be detected.

Patients without crises, or in the interictal phase, may experience chronic symptoms similar to those listed above. Chronic hypertension is present in more than half of the patients, often accompanied by significant lability and orthostatic hypotension. Symptoms and signs related to increased metabolic rate (heat intolerance, sweating, weight loss) and to increased glycogenolysis (hyperglycaemia, impaired glucose tolerance) are sometimes present.

The concomitant production of one or more different peptides may be responsible for atypical clinical manifestations (hypercalcaemia, Cushing's syndrome, etc).Other atypical symptomatic presentations are orthostatic hypotension, angina pectoris, idiopathic dilated cardiomyopathy, psychiatric disorders, and many others.

The presence of a pheochromocytoma may also be suggested by the presence of peculiar clinical signs of genetic syndromes, such as neurofibromatosis type I (café-au-lait spots, neurofibromas, Lisch nodules, skin freckling of the axilla or groin), von Hippel Lindau disease (retinal angiomas, cerebellar haemangioblastoma, epididymal cystadenoma, renal and pancreatic cysts, pancreatic neuroendocrine tumours, renal cell carcinoma or cysts), multiple endocrine neoplasia, MEN, type 2A (medullary thyroid carcinoma, hyperparathyroidism), MEN, type 2B (medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, intestinal ganglioneuromatosis, marfanoid body habitus), or by familial recurrence of pheochromocytomas-paragangliomas without other features.

In addition, as mentioned above, over the last two decades the widespread use of imaging techniques has frequently lead to the incidental discovery of adrenal (or in some cases, extra-adrenal) masses, the so-called incidentalomas, that may represent asymptomatic or paucisymptomatic pheochromocytomas.

From clinical suspicion to diagnosis

The diagnosis of pheochromocytoma is relatively straightforward provided the suspicion is raised. Besides patients with suggestive clinical picture, two conditions call for specific diagnostic investigation: subjects with incidentalomas and relatives of patients with a genetic predisposition to pheochromocytoma (see below). International guidelines do not recommend screening for pheochromocytoma in the general hypertensive population unless clinical data suggest the diagnosis [4].

Biochemical tests

The fundamental screening procedure is to obtain biochemical evidence of increased catecholamine production. Test sensitivity is of crucial relevance, since false-positive can be ruled out by further investigation, whereas false-negative may have dramatic clinical consequences. There is now evidence from several independent studies indicating that measurement of plasma levels of free metanephrines (o-methylated metabolites of catecholamines) attains a diagnostic sensitivity of 97–99% [5, 6]. However, measurement of urinary fractionated metanephrines in a twenty-four-hour urine collection is probably equally reliable and has the advantage that it is much more widely available. To improve specificity, it is necessary to withdraw any pharmacological treatment potentially interfering with biochemical assay. In case of intermittent symptoms (and catecholamine secretion) urine sampling during or immediately after a crisis may be of some help.

Provocative tests (e.g. glucagon IV) should be abandoned in clinical practice due to low sensitivity and potentially dangerous blood pressure increase [7]. On the other hand, the clonidine suppression test, aimed at distinguishing between neurogenically mediated catecholamine increase and catecholamine secretion by a pheochromocytoma, has not proven sufficiently reliable in excluding the diagnosis, unless plasma normetanephrine is used instead of plasma noradrenaline [7].

Other tests, such as plasma catecholamines, urinary vanillylmandelic acid, plasma chromogranin A, or neuropeptide Y, have less accuracy than plasma or urinary fractionated metanephrines.

Localization of the tumour(s)

Careful assessment of clinical history and biochemical testing usually provides sufficient information to decide if imaging studies aimed to locate the tumour are justified. Most pheochromocytomas (97–99%) are located in the abdomen, while only 1–3% are found in the thorax (posterior mediastinum) or the neck. Adrenal glands are involved in more than 80% of cases, with both glands involved in 5–25%. Extra-adrenal pheochromocytomas are mainly located near the kidney or in the organ of Zuckerkandl and can be multicentric. Simultaneous adrenal and extra-adrenal involvement can be observed. Of note, multicentric localizations are more frequent in children and in genetically determined syndromes.

First line imaging relies on computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis [8]; these techniques have similar good sensitivity (90–100%) for detecting adrenal pheochromocytomas, whereas MRI is probably better for detecting extra adrenal tumours. The specificity of both CT and MRI is low (50–70%), mainly because of a relatively high frequency of non-catecholamine-producing incidentalomas. CT has the advantage of a slightly better spatial resolution, while MRI may better differentiate pheochromocytomas (appearing hyperintense on T2-weighted images) from other adrenal tumours that are isointense compared with the liver.

If an abdominal mass is detected, ^{123}I-labeled meta-iodo-benzyl-guanidine (MIBG) scanning is still the method of choice to assess whether the tumour is indeed a pheochromocytoma and whether there are metastases [9]. The reported sensitivity is 80–95% and specificity is 95–100%. In cases of scintigraphic confirmation of the CT/MRI localization, the diagnostic procedure is concluded and therapeutic options must be considered. If ^{123}I-MIBG scintigraphy is negative, a "third-line" diagnostic option should be considered, such as positron emission tomography with different radionuclides (^{18}F-fluoro-

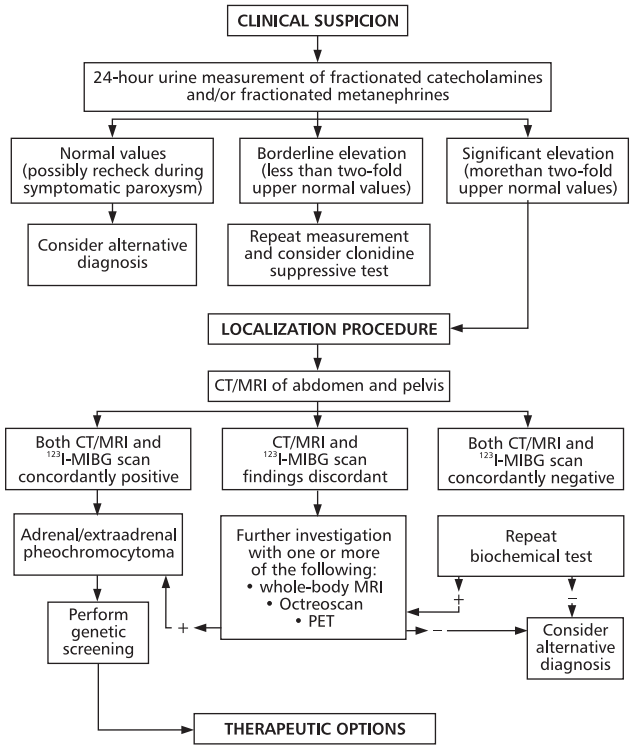

Figure 1. Recommended diagnostic flow-chart

deoxyglucose, ^{18}F-fluorodopamine, and ^{18}F-fluoroDOPA) [10] and ^{111}-In-pentetreotide scintigraphy (Octreoscan).

If CT/MRI of the abdomen/pelvis is negative, the imaging investigation (preferably MRI) should be extended to the whole body and associated with ^{123}I-MIBG scanning.

When both techniques give positive results, a diagnosis of extra-adrenal pheochromocytoma is made and appropriate therapy can be planned. If only ^{123}I-MIBG scanning is positive, the diagnosis of extra-adrenal pheochromocytoma is strongly suspected, but it needs to be confirmed by one of the above "third-line" procedures. If ^{123}I-MIBG is negative, irrespective of the result of CT/MRI, biochemical tests should be repeated, and if excessive catecholamine secretion is confirmed, "third-line" diagnostic investigation is required.

A simplified diagnostic algorithm is illustrated in Figure 1.

Genetic screening

In our view, a systematic screening for genetic predisposition is mandatory in all patients diagnosed with pheochromocytoma. There are many good reasons for such a recommendation. First, many recent studies have consistently shown that a percentage (approx. 15–30%) of pheochromocytoma patients carry pathogenic mutations [11–12]. In addition to the genes involved in syndromic diseases (NF1, VHL, and RET, respectively, for neurofibromatosis type 1, von Hippel-Lindau disease and MEN 2), three different subunits of the succinate dehydrogenase complex (SDHB, SDHC, and SDHD), a succinate dehydrogenase complex assembly factor 2 (SDHAF2) and, most recently, the transmembrane--encoding gene TMEM127 have shown sequence mutations predisposing to pheochromocytoma-paraganglioma. Second, the detection of mutations in genes responsible of syndromic disease may lead to the diagnosis of otherwise unsuspected concomitant pathologic features.

Third, some forms of genetically determined pheochromocytoma, particularly those associated with SDHB mutations, present a higher risk of malignancy, recurrence, and/or multiplicity, all features that should be carefully sought out at the time of diagnosis or at follow-up. Last but not least, the detection of a pathogenic mutation in apparently sporadic, non-syndromic pheochromocytoma patients may disclose the presence of proband's relatives who also carry the mutation and are affected by subclinical disease. Thanks to validated algorithms aimed at minimizing its cost, a complete screening for the "traditional" genes involved in the disease (RET, VHL, SDHB, SDHC, SDHD) can be performed at less than 500 Euros (and much less in the case of relatives' ascertainment).

Treatment

When the diagnosis of pheochromocytoma is made, surgical removal of the mass(es) should be performed, unless particular circumstances (recent myocardial infarction, third trimester pregnancy, concomitant disease, nonresectable malignant tumour) indicate that the surgical procedure should be postponed or is contraindicated.

In any case, medical treatment with an adrenergic antagonist must be started immediately to block the deleterious effects of increased circulating catecholamines and to restore plasma volume (impaired by chronic vasoconstriction). The a-blocker phenoxybenzamine is still considered the drug of choice by many authors, but it is not available in many countries. Alpha1 selective blockers (prazosin, doxazosin, and similar) are also very effective agents. Beta-blockers (preferably β-1 selective) can be associated with control tachycardia or arrhythmias, when present, but must be started after α-blockers to avoid hypertensive crisis due to loss of β-2-mediated vasodilation. If adrenergic antagonists are insufficient to adequately control blood pressure, other antihypertensive agents (calcium antagonists) can be used. A two-week treatment period is usually sufficient to minimize the risk associated to anaesthesia and surgery, but the treatment can be maintained indefinitely, according to clinical needs.

Surgical treatment has traditionally been performed through laparotomy, but the laparoscopic technique should now be considered the procedure of choice for most patients unless multiple, very large or malignant pheochromocytoma/paraganglioma are present [13]. The laparoscopic approach has been associated with reduced perioperative pain, a shorter period of hospitalisation, and reduced incidence of post-operative complications. Management of intraoperative hypertensive crises, arrhythmias, or sudden hypotension after tumour isolation requires an experienced anaesthesiological team. Symptoms disappear after tumour excision; in particular, blood pressure is normalized in the vast majority of patients, whereas persistence of hypertension after surgery may be an expression of underlying "primary" hypertension or incomplete tumour removal. In any case, postoperative control of urinary or plasma metanephrines must be routinely performed to ensure complete tumour removal; in addition, annual biochemical screening (plasma free metanephrines or urinary fractionated metanephrines) is recommended, given the relatively high percentage of recurrence (about 15%) even several years after first presentation. Perioperative mortality should be less than 2–3% (data mostly collected in laparotomic series), and the expected 5-year survival rate is over 95%.

Malignant pheochromocytoma

The incidence of malignant pheochromocytoma ranges between 5 and 10% and in this case the 5-year survival is less than 50%. Malignancy is about four times more frequent in extra-adrenal forms. A malignant pheochromocytoma is characterized by the presence of local invasion of the surrounding tissues or metastases (mostly in bone, liver, lymph nodes, and lung); invasion of tumour capsule and aberrant chromatin can also be observed in benign forms. Debulking surgery is recommended by many experts although data documenting its effect to improve survival and/or reduce symptoms are lacking [14]. Medical treatment of malignant pheochromocytomas includes, besides antiadrenergic agents, the administration of chemotherapeutic agents (a cyclophosphamide––vincristine–dacarbazine scheme) and the use of therapeutic doses of ^{131}I-MIBG (up to 800 mCi and above) when tumour uptake of the radioligand is maintained. It should be noted, however, that the combination of these two approaches has no advantages in view of increased toxicity [14]. The administration of somatostatin analogues may show some benefit in malignant pheochromocytomas expressing somatostatin receptors (positive ^{111}Indium-octreotide scanning) as well as a related radiotherapeutic approach with the radiolabelled somatostatin analogue [DOTA-Tyr(3)]-octreotide (DOTATOC). Targeted therapy with tyrosine kinase inhibitors (sunitinib, sorafenib, imatinib), VEGF inhibitors (thalidomide), mTOR inhibitors (everolimus), and others are under investigation in controlled trials [14]. In any case, the clinician must be aware that all these treatments are palliative at most and their use should be considered whilst bearing in mind the quality of life of such patients.

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PRIMARY ALDOSTERONISM

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Primary aldosteronism (PA) is a common form of endocrine hypertension in which aldosterone production is inappropriate and at least partially autonomous of the renin–angiotensin system. The inappropriate production of aldosterone results in sodium retention and suppression of renin. PA is commonly caused by an adrenal adenoma or bilateral hyperplasia of the adrenocortical zona glomerulosa, and in very rare cases by the inherited condition of glucocorticoid-remediable aldosteronism (GRA) also known as Familial Hyperaldosteronism type 1 (FH1).

Some misconceptions concerning PA must be addressed. PA was held to account for less than 1% of hypertensive patients and, moreover, hypokalaemia was considered a prerequisite for pursuing the diagnostic tests for PA [1] However, recent studies carried out by applying the plasma aldosterone/plasma renin activity (PRA) ratio (ARR) as a screening test in hypertensive patients, regardless of the presence or absence of hypokalaemia, have found a much higher prevalence of this disease, with PA accounting for up to 12% of hypertensive patients. In recent studies, only a minority of patients with PA (9 to 37%) had hypokalaemia [2]. Thus, normokalaemic hypertension constitutes the most common presentation of the disease, with hypokalaemia probably being present only in the more severe cases [3]. An early diagnosis of PA is crucially important not just because PA is common and if overlooked exposes the patient to the need for long-life treatment, but even more so because if undiagnosed and not properly treated these patients have higher cardiovascular morbidity and mortality than age-, sex, blood, and pressure-matched patients with essential hypertension, including a greater incidence of left ventricular hypertrophy, fibrosis, atrial fibrillation, myocardial infarction, and stroke [4]. In fact, aldosterone has been shown to induce endothelial dysfunction, norepinephrine release, cardiovascular fibrosis, and proteinuria, independently from increase of blood pressure. Furthermore, specific treatments are available that ameliorate the impact of this condition on patient-important outcomes (Figure 1).

Diagnosis

The growing recognition of PA as a common and important contributor to hypertension development and cardiovascular disease has led to a "Renaissance" in interest regarding the detection and diagnostic workup of this disorder by clinicians involved in the treatment of hypertensive patients. The Clinical Guidelines Committee of The Endocrine Society [5] has developed clinical practice guidelines for the diagnosis and treatment of patients with PA. Diagnosis of PA is divided into different steps including: case detection, case confirmation, and subtype classification.

Case detection

Case detection of PA is recommended in patient groups with relatively high prevalences of PA. These include patients with: stage 2 (>160–179/100–109 mm Hg), stage 3 (>180/110 mm Hg), or drug-resistant hypertension; hypertension and spontaneous or diuretic-induced hypokalaemia; hypertension with adrenal incidentaloma; or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 yr).

The Aldosterone–Renin Ratio (ARR) is currently the most reliable means available for screening for PA. It is recommended that hypokalaemia be corrected and that those drugs which could cause false-positive or false-negative results be removed for at least 2–3 weeks, before measuring the ARR. Like all biochemical case detection tests, the ARR is not without false positives and false negatives and can be affected by numerous conditions (see Table 1) [3, 6]. The ARR should therefore be regarded as a detection test only and should be repeated if the initial results are inconclusive or difficult to interpret because of suboptimal sampling conditions. It should also be appreciated that the ARR conveys quantitative information: in other words a markedly elevated value should be taken as a strong indication for the presence of PA, which can warrant adrenal vein sampling without any further confirmation, while borderline elevated values should be repeated and perhaps followed by an exclusion test.

In recent years it has become more common to use the direct active renin assay instead of the plasma renin activity (PRA) to evaluate the renin–angiotensin system. A major problem is that there are important and confounding differences across laboratories regarding the methods and units used to report values of renin and aldosterone; this, together with the lack of uniformity in diagnostic protocols, has been associated with substantial variability in cut-off values used by different groups, ranging from 20 to 100 as ng/dl Aldo over ng//dl/hr (or 68 to 338 as pMol/L over mU/L) [7]. Most groups, however, use cut-offs of 20–40 (for Aldo in ng/dl over PRA in ng/ml/h) (68–135) when testing is performed in the morning on a seated ambulatory patient. In the largest available study in which the ARR was used to identify the only PA subtype that could be conclusively diagnosed based on the "four corners" criteria, the optimal cut-off for the ARR (PAC in ng/dl, PRA in ng/ml/h) was 25.86 [3].

Case confirmation

Once a high ARR has been determined confirmatory tests should be performed to definitively confirm or exclude PA [5]. At present, four confirmatory tests to definitively confirm or exclude the diagnosis are used: oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge. These four tests are in common use even though their usefulness is supported at best by a level of evidence C by the AHA criteria, and therefore the level of recommendation for their use is only Iib. Moreover, there is currently insufficient direct evidence to recommend any one of these above the others. These tests may differ in terms of sensitivity, specificity, and reliability, but the choice of a confirmatory test is usually determined by considerations of cost, patient

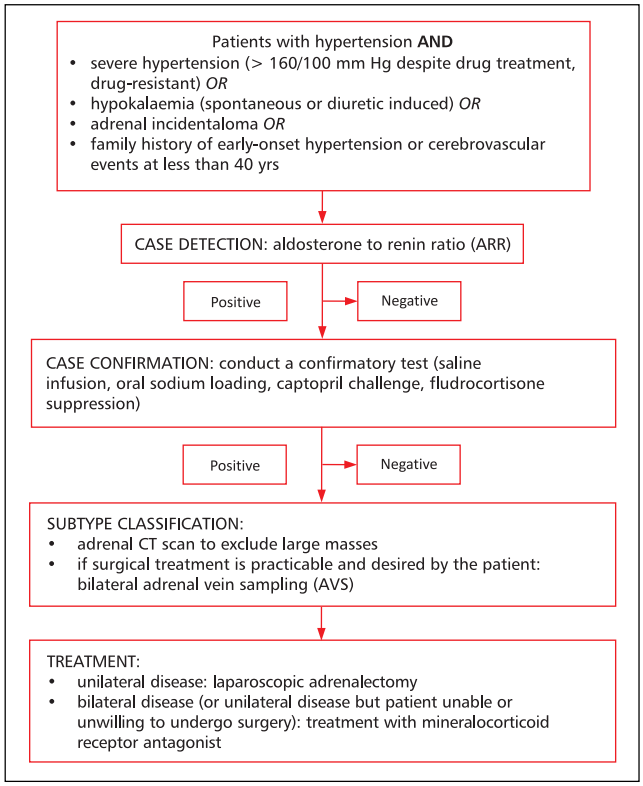

Figure 1. Flowchart outlining the suggested work-up of patients with hypertension and increased risk of hyperaldosteronism [5]

Table 1. Factors that may affect the aldosterone–renin ratio and thus lead to false positive or false negative results [5]

FACTOR	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Medications			
Beta-adrenergic blockers	↓	↓↓	↑(FP)
Central α-2 agonists	↓	↓↓	↑(FP)
NSAIDs	↓	↓↓	↑(FP)
K^+ wasting diuretics	→↑	↑↑	↓(FN)
K^+ sparing diuretics	↑	↑↑	↓(FN)
ACE inhibitors	↓	↑↑	↓(FN)
ARBs	↓	↑↑	↓(FN)
Ca^{2+} blockers (DHPs)	→↑		↓(FN)
Renin inhibitors	↓	↓↑*	↓(FN)* ↑(FP)*
Potassium status			
Hypokalaemia	↓	→↑	↓(FN)
Potassium loading	↑	→↑	↑(FP)
Dietary sodium			
Sodium restricted	↑	↑↑	↓(FN)
Sodium loaded	↓	↓↓	↑(FP)
Advancing age	↓	↓↓	↑(FP)
Other conditions			
Renal impairment	→	↓	↑(FP)
PHA-2	→	↓	↑(FP)
Pregnancy	↑	↑↑	↓(FN)
Renovascular HT	↑	↑↑	↓(FN)
Malignant HT	↑	↑↑	↓(FN)

*Renin inhibitors lower PRA but raise DRC. This would be expected to result in false-positive ARR levels for renin measured as PRA and false negatives for renin measured as DRC; PHA-2 — pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate)

compliance, laboratory facilities, and local expertise. The most commonly used test is the saline infusion test (2 L over 4 hrs) with a temptative cut-off for post infusion plasma aldosterone above 7 ng/dl [8]. It should be noted that confirmatory tests requiring oral or IV sodium loading should be administered with caution in patients with uncontrolled hypertension or congestive heart failure. As all these tests rely on the presumed autonomy of the aldosterone production from angiotensin II, which apparently is not the case in all aldosterone-producing adenoma, these tests are fraught with a large number of false negative and false positive results, and therefore some experts support the view that they should not be used as they can lead to curative adrenalectomy not being given to many patients.

Subtype classification

All patients with primary aldosteronism should undergo **adrenal computed tomography (CT)** as the initial subtype study, to exclude large masses that may represent adrenocortical carcinoma and to ascertain the right adrenal vein anatomy, which is useful for planning and adrenal vein sampling. Of these indications, adrenal CT has no place for differentiation of PA subtypes. In fact, small APAs may be overlooked, and/or non-functioning adenoma ("incidentaloma") on one side can be considered the "culprit" for PA while instead the latter is due to a small CT-undetectable APA or unilateral hyperplasia on the contralateral side. Moreover, apparent adrenal microadenomas may actually represent areas of hyperplasia, and unilateral adrenalectomy would be inappropriate. In addition, non-functioning unilateral adrenal macroadenomas are not uncommon, especially in older patients (> 40 years old) and are indistinguishable from APAs on CT. Unilateral UAH (unilateral adrenal hyperplasia) may be visible, but also invisible on CT. **Magnetic resonance imaging** has no advantage over CT in subtype evaluation of PA, being more expensive and more prone to motion artefacts than CT.

Lateralization of the source of excessive aldosterone secretion is critical to guide the management of PA. Imaging cannot reliably visualize microadenomas or distinguish incidentalomas from APAs with confidence [9], making **Adrenal Vein Sampling (AVS)** the most accurate way of differentiating unilateral from bilateral forms of PA.

It must be understood that AVS should be offered to the patients only if surgical treatment is possible and desired by the patient. The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess are superior to those of adrenal CT (78 and 75%, respectively) [10].

Although AVS can be a difficult procedure, especially on the right adrenal vein (which is smaller than the left and usually empties directly into the IVC rather than the renal vein), the success rate usually improves quickly as the angiographer becomes more experienced [9]. Currently, three protocols for AVS are used: 1) unstimulated sequential or simultaneous bilateral AVS, 2) unstimulated sequential or simultaneous bilateral AVS followed by bolus cosyntropin-stimulated sequential or simultaneous bilateral AVS, and 3) continuous cosyntropin infusion with sequential bilateral AVS. There are actually no clear guidelines which recommend any particular protocol and data are lacking on the impact of AVS on clinical outcomes [11]. Some form of patient stratification is required, possibly firstly identifying which patients should proceed to surgery set against those who can be managed on effective medical therapy with Mineralocorticoid Receptor antagonists. The use of AVS must be justified on a case-by-case basis, asking how it will improve patient care and outcome, and be undertaken in centres of excellence to achieve optimal sensitivity [12].

Other screening tests

- **Posture stimulation test.** In patients with unsuccessful AVS and with a CT scan showing a unilateral adrenal mass, some experts use the posture stimulation test. This test, developed in the 1970s, was based on the finding that the PAC in patients with APA showed diurnal variation and was relatively unaffected by changes in angiotensin II levels, whereas IHA was characterized by enhanced sensitivity to small changes in angiotensin II that occur with standing. Recent reviews showed an accuracy of 85% of this test. The lack of accuracy is explained by the fact that some APAs are sensitive to angiotensin II and some patients with IHA have diurnal variation in aldosterone secretion. Thus, the posture stimulation test may have an ancillary role, for example, in those patients for whom AVS was unsuccessful and CT shows a unilateral adrenal mass [13].
- **Iodocholesterol scintigraphy**. [131I]19-Iodocholesterol scintigraphy was first used in the early 1970s, and an improved agent, [6b-131I]iodomethyl-19-norcholesterol (NP-59), was introduced in 1977. The NP-59 scan, performed with dexamethasone suppression, had the putative advantage of correlating function with anatomical abnormalities. However, the sensitivity of this test depends heavily on the size of the adenoma; consequently, this method is useless in interpreting micronodular findings obtained with high-resolution CT and has no major role in subtype evaluation [14] in most centres. Moreover, the shortage of the radiotracer currently makes this test unfeasible for most centres.
- **18-Hydroxycorticosterone levels**. 18-Hydroxycorticosterone is formed by 18-hydroxylation of corticosterone. Patients with APA generally have recumbent plasma 18-hydroxycorticosterone levels greater than 100 ng/dl at 0800 h, whereas patients with IHA have levels that are usually less than 100 ng/dl. However, this test lacks the accuracy needed to guide the clinician in the subtype evaluation of PA [5].
- **Testing for familiar forms of PA[FH-I (GRA)]**. FH-1 syndrome is responsible for less than 1% of cases of PA and it is inherited in an autosomal dominant fashion. It may be diagnosed in patients with onset of PA earlier than at 20 years of age and in those who have a family history of PA or of strokes at young age. Genetic testing by either Southern blot [15] or long PCR techniques is sensitive and specific for GRA. FH-II syndrome us clinically indistinguishable from non-familiar PA. It is an autosomal dominant disorder. GRA mutation testing is negative. Its prevalence has not been established. An association with chromosomal region 7p22 has been shown [16].
- A further approach that is being tested to identify lateralizedaldosterone excess entails C^{11}methomidate positrone emissiontomography. However, it remains to be demonstrated if it couldidentify the majority of APAs that, as mentioned above, are small.

Treatment

Treatment of choice in documented unilateral PA (APA or UHA) is unilateral laparoscopic adrenalectomy, whereas medical treatment with mineralocorticoid receptor antagonists is indicated in patients with bilateral adrenal disease (idiopathic adrenal hyperplasia, bilateral APA, GRA).

Surgical treatment in patients with unilateral PA shows improvement of serum potassium concentrations in nearly 100% of patients postoperatively [5] when the diagnosis and the indication of adrenalectomy are made based on AVS. Hypertension is cured (defined as blood pressure < 140/90 mm Hg without the aid of antihypertensive drugs) in about 50% (range 35–60%) of patients with APA after unilateral adrenalectomy, with a cure rate as high as 56–77% when the cure threshold is blood pressure less than 160/95 mm Hg [5].

Factors associated with resolution of hypertension in the postoperative period include having no more than one first-degree relative with hypertension, preoperative use of one or two antihypertensive drugs [17], known duration of hypertension, and the presence of vascular remodelling [18]. As compared with open adrenalectomy, laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications [19].

In patients who do not undergo surgery and in those presenting bilateral adrenal disease, medical treatment is indicated as follows:

- **MR antagonists** appear to be effective in the control of blood pressure and providing target organ protection.
- **Spironolactone** has been the agent of choice in the medical treatment of PA for more than four decades. Several observational studies in patients with IHA have reported a mean reduction in systolic blood pressure of 25% and diastolic blood pressure of 22% in response to spironolactone 50–400 mg/d for 1–96 months [5]. The incidence of gynaecomastia with spironolactone therapy is dose related, whereas the exact incidence of menstrual disturbances in premenopausal women with spironolactone therapy is unknown. Where available, canrenone (an active metabolite of spironolactone) or potassium canrenoate, might be considered because they possibly have fewer sex steroid-related side effects. In addition, a small dose of a thiazide diuretic, triamterene, or amiloride can be added to avoid a higher dose of spironolactone which may cause side effects. The starting dose for spironolactone should be 12.5–25 mg daily in a single dose. The lowest effective dose should be found by very gradually titrating upward to a maximum dose of 100 mg/d.
- **Eplerenone** is a newer, selective MR antagonist without antiandrogen and progesterone agonist effects, thus reducing the rate of adverse endocrine side effects. Eplerenone has 60% of the MR antagonist potency of spironolactone; its better tolerability profile needs to be balanced against its higher cost, shorter duration of action requiring multiple daily dosing, and the lack of current clinical trial evidence for its use in PA [20]. The starting dose for eplerenone is 25 mg once or twice daily.

Other agents

Up-regulation of distal tubular sodium epithelial channel activity is a major mechanism whereby aldosterone exerts its actions on sodium and potassium handling. Of the available epithelial sodium channel antagonists, amiloride has been the most studied as a mode of treatment for PA. Although less efficacious than spironolactone, amiloride may be useful. Being a potassium-sparing diuretic, amiloride can ameliorate both hypertension and hypokalaemia in patients with PA and is generally well tolerated, lacking the sex steroid-related side effects of spironolactone, but without the beneficial effects on endothelial function [21]. Calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers have been evaluated in very few patients with PA, and in general they are antihypertensive drugs without a major effect on aldosterone excess. Supportive studies are small and methodologically weak and have not measured patient-important outcomes. Aldosterone synthase inhibitors may play a role in the future.

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SUBCLINICAL BRAIN DAMAGE AND HYPERTENSION

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Hypertension, beyond its well-known effect on the occurrence of clinical stroke, is also associated with the risk of subclinical brain damage noticed on cerebral MRI, in particular in elderly individuals [1, 2]. The most common types of brain lesions are White Matter Hyperintensities (WMH) — which can be seen in almost all elderly individuals with hypertension [1, 2] although with a variable severity (Figure 1) — and silent infarcts, the frequency of which varies between 10% to 30% according to studies (Figure 2) [3].

Both lesions are characterized by high signal on T2-weighted images. Silent infarcts may be singled out by their low signal on T1--weighted images (Figure 2). Another type of lesion, more recently identified, are microbleeds, which are seen in about 5% of individuals and are small, homogeneous, round foci of low signal intensity on MRI Gradient echo (GRE) T2* images. Like WMH and silent infarcts, microbleeds are more frequent in individuals with hypertension.

Hypertension is the main modifiable risk factor for subclinical brain damage. Several studies have suggested that sustained or uncontrolled hypertension is associated with a greater WMH load [2, 4]. The level of blood pressure also seems to play a role — higher blood pressure values being associated with higher grades of WMH [4, 5]. These dose-dependent effects of the duration and level of BP provide strong support for a causal relationship between high BP and WMH, similar to that already reported for stroke.

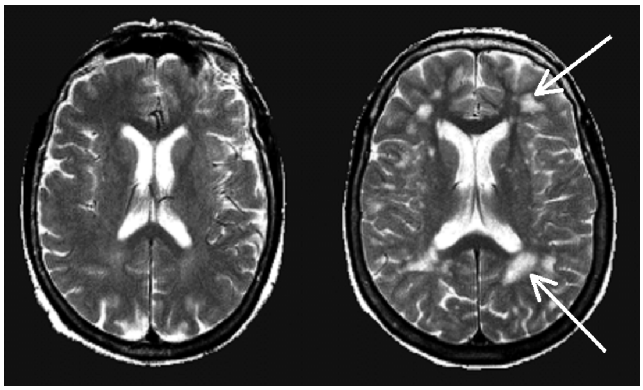

Figure 1. T2-weighted MRI exams of two 65-year-old individuals. The subject on the left has no apparent subclinical brain lesions on this slice whereas the subject on the right has a severe grade of white matter hyperintensities (*arrows*)

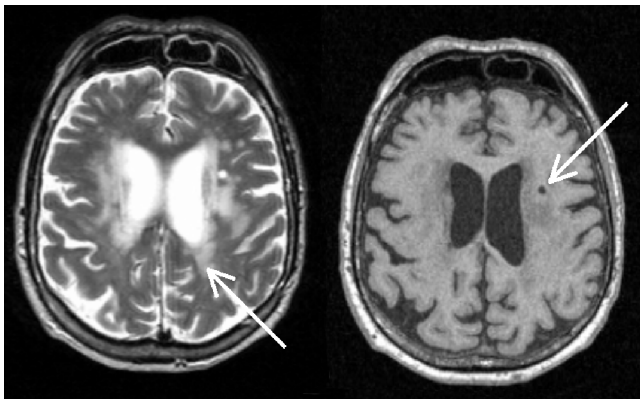

Figure 2. T2-weighted (*on the left*) and T1-weighted (*on the right*) MRI exams of the same subject at 75 years old. This subject has a severe grade of WMH (*arrow*), mainly in the periventricular area, easily seen on the T2 exam (*left*). He also has a silent infarct (*arrow*) in the white matter which appears in hyposignal on the T1-weighted exam (*right*)

Predictive value of subclinical brain damage for cognitive impairment and stroke

At first, these MRI cerebral lesions were considered benign and merely associated with aging. They were even called UBOs — Unidentified Bright Objects! In the past 15 years, several large community-based studies that have included large numbers of individuals with MRI exams have shown that these lesions were not so silent and were associated cross-sectionally with subtle cognitive of motor impairment. It was also recently discovered that they were associated with incident cognitive deterioration or dementia [6], depression [7], and gait disturbances [8].

These associations are probably largely due to the direct consequences of these lesions on the brain circuits and particularly to the disconnection of subcortical-cortical loops. Indeed, small, clinically silent brain infarctions appear to be at least as strong a risk for subsequent dementia [6] as larger, clinically evident strokes. In most cases dementia is not caused by the simple burden of vascular lesions but also by pre-existing neurodegenerative lesions which are very common in the elderly. The occurrence of vascular lesions could simply reveal the ongoing development of Alzheimer's disease in the patient. The interaction between neurodegenerative factors and stroke in the risk of dementia was highlighted in the Nun study [9]. In this study, based on autopsy findings, the presence of a small lacunar infarct was found to multiply the risk of clinical dementia by a factor of 20 in people meeting the neuropathological criteria for Alzheimer's disease.

Several studies have described WMH or the presence of silent infarct as a predictor of incident stroke in the general population [10, 11] and of stroke recurrence among patients with transient ischaemic attack or stroke history. In such instances, WMH could be considered as the harbinger of further clinical events. In the 3C study, a large population-based cohort study in the elderly in which we performed cerebral MRI in 1924 participants 65 years old and over, we found that those in the highest quartile of WMH had a more than five-fold increased risk of stroke during follow-up compared to those with a WMH load below the median [12]. Interestingly, there was no increased risk of other vascular events, suggesting that WMH was a specific predictor of the risk of stroke.

Systemic arterial damage and subclinical brain damage

The precise mechanisms underlying the development of WMH, silent infarcts, and microbleeds remain unclear. In recent years a large number of studies have reported strong relationships between peripheral artery damage and either subclinical brain damage or cognitive impairment. Alterations of carotid wall thickening, aortic stiffening, and small artery remodelling in patients with cognitive decline have allowed a link to be made between vascular aging and vascular cognitive impairment (VCI), underlining the aggravating role of hypertension.

The relationship between carotid intima–media thickness (IMT) and cognitive function has been analyzed cross-sectionally [13] and longitudinally [14–16] in few studies. Studies differed as far as the study population, the definition of carotid IMT, and the neuropsychological test adopted to evaluate cognition were concerned. Despite this heterogeneity, a significant inverse relationship between carotid IMT and cognitive function was observed in all studies. In other words, the thicker the artery the lower the cognitive performance. This relationship was significant after controlling for age and education; some studies further adjusted for the presence of depressive symptoms [15, 16] and/or level of CV risk factors [15].

Carotid-femoral pulse wave velocity (PWV), the "gold standard" for evaluating arterial stiffness [17], was higher in any group of cognitively impaired subjects — with or without dementia [18]. An inverse relationship between PWV and cognitive performance was reported cross-sectionally [13, 19]. Carotid-femoral PWV was also associated prospectively with cognitive decline before dementia, in studies using a cognitive screening test [20, 21] and more specifically tests of verbal learning and delayed recall, nonverbal memory [21]. These relationships remained significant after controlling for age, gender, education, and blood pressure levels. Other studies reported a significant positive relationship between arterial stiffness and volume or localization of WMH — a known factor predisposing to vascular dementia [22] — on neuroimaging [23, 24].

To our knowledge, no study has investigated the relationship between cognitive decline or WMH, and the remodelling of small arteries harvested from human subcutaneous and omental fat tissue. Retinal arterial narrowing, assessed non invasively from fundoscopic methodology or scanning laser flowmetry [25, 26], correlates with increased arterial stiffness [25] and cerebral small-vessel disease [26].

Mechanisms relating systemic arterial damage to subclinical brain damage in hypertension

Hypertension is associated with abnormalities of large arteries: mainly increased wall thickness and stiffness, and small arteries: mainly internal remodelling. The pathophysiological association between systemic arterial damage and VCI can be analysed for each type of arterial damage, although the causal link is difficult to determine. Carotid wall thickening, which reflects both atherosclerosis and a higher strain due to hypertension, has been associated with several CV risk factors, including metabolic, inflammatory, and dietary factors, which have also been associated with cognitive decline [14, 27]. An increased aortic stiffness, in response to high blood pressure levels loading the stiff components of the arterial wall, may be related to microvascular brain damage through several mechanisms: (a) endothelial dysfunction and oxidative stress [28], (b) a mutually reinforcing remodelling of large and small vessels (i.e. large/small artery cross talk) [29], and (c) exposure of small vessels to the high-pressure fluctuations of the cerebral circulation [30], which is passively perfused at high-volume flow throughout systole and diastole, with very low vascular resistance. Internal remodelling of small arteries, which is accelerated by hypertension, ultimately leads to occlusion of end arterioles. Finally, WMH and silent infarcts are considered to be markers of chronic cerebral ischaemia resulting from damage to small cerebral vessels.

Prevention of subclinical brain damage by antihypertensive drugs

WMH and other subclinical brain lesions are involved in the occurrence of major neurological disorders and appear to cause accelerated aging of the brain. Trying to control their aggravation is therefore an important goal. As hypertension is their major modifiable risk factor it seems logical to test first the hypothesis that a blood pressure lowering treatment may modify their evolution.

This question was addressed in a clinical trial, the PROGRESS MRI study [22], a sub-study of the PROGRESS trial. In this sub-study, 192 patients were enrolled (mean age of 60 years), 89 of whom were in the active treatment arm of the study, the other 103 patients being assigned to the placebo arm. Each participant underwent an initial brain MRI at the start of the study and a second MRI examination after a mean follow-up period of 36 months. The variability between the two examinations due to technical aspects (position of the head in the scanner, sections of different sizes taken in different positions) was limited by using image analysis techniques to realign the images and for automatic segmentation after the recording of scans in an object--oriented database. These techniques rendered the images as comparable as possible, and an independent observer blind to the clinical data and order of examinations was then able to compare the scans in detail, detecting and measuring each new lesion. A neurologist analyzed the initial scan results and identified 13% of the patients as having moderate WMH and 19% as having severe WMH. At the time of the second MRI scan, SBP had decreased by a mean of 11.2 mm Hg and DBP by 4.3 mm Hg. The overall risk of a new WMH lesion was 43% lower in the treatment arm than in the placebo arm of the study, although this difference was not statistically significant ($p = 0.10$) [22]. The volume of new WMH lesions in the treatment arm was only one-fifth of that in the placebo arm of the study (0.4 cm^3 versus 2 cm^3; $p = 0.047$). The greatest difference was observed in the group of patients with severe WMH on the first MRI scan. In this group, no new lesions were observed in the treatment arm of the study, whereas the volume of WMH increased by 7.6 cm^3 in the placebo arm of the study ($p = 0.001$) [22]. This group also displayed the most marked progression of WMH over the four-year follow-up period, thus confirming the results of several observation studies. Finally, it was recently shown in the PROGRESS trial that patients with a high load of WMH lesions had a 7.7-times higher risk of severe cognitive deterioration or dementia (95% CI = 2.1–28.6).

These preliminary results are encouraging because they show, for the first time, that it is possible to decrease the development of WMH by lowering arterial blood pressure. However, given the relatively small number of patients studied, these results cannot be considered as conclusive. They require confirmation (or negation) in larger groups of patients. Furthermore, all the patients in the PROGRESS study had a history of stroke, limiting the extent to which these results can be generalized.

Ideally, the next step would be a trial in patients with moderate to severe WMH grades. There is now strong evidence that this group is exposed to a rapid increase in WMH volume but also to an immediate risk of severe cognitive deterioration and dementia. As WMH has been shown to play a role in the occurrence or aggravation of cognitive decline and dementia, limiting their progression may be the cornerstone in a wider strategy to prevent dementia by controlling vascular factors.

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HYPERTENSION AND SLEEP

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Introduction

Cardiovascular control is markedly affected by normal sleep with a differential autonomic regulation of the cardiovascular system with the different sleep stages [1]. Blood pressure (BP) and heart rate (HR) decrease throughout non-rapid eye movement (NREM) sleep, particularly during slow-wave sleep (dipping pattern), whereas in REM sleep BP is highly variable and approximates wakefulness levels. During the night, normal individuals did not exhibit significant change in cardiac output, and the nocturnal fall in arterial pressure is actually the result of a decrease in total peripheral vascular resistance. Any disturbance in sleep quantity or quality, explained either by sleep habits or sleep disorders, may participate in hypertension development or severity.

In this article, we will successively review the different sleep disorders or sleep habits associated with hypertension and summarize the common pathophysiological intermediary mechanisms explaining the relationship.

Obstructive sleep apnea syndrome and hypertension

Obstructive sleep apnea (OSA) is associated with changes in intra thoracic pressures during sleep reflecting variations in respiratory effort, frequent transient arousals, modifications in sleep structure, and intermittent hypoxia. All these factors have an impact on sympathetic activity and may result in long term sympathetic activation contributing to cardiovascular morbidity. During abnormal respiratory events there is a progressive increase in sympathetic activity and an acute rise in blood pressure, which correlates with the severity of oxygen desaturation. Acute respiratory events during sleep are superimposed on chronic adaptations of the cardiovascular system in response to long-term sleep apnea exposure, leading to daytime sustained elevation of sympathetic activity [2]. Obstructive sleep apnea syndrome (OSA) and hypertension are linked in a dose–response fashion. This is true even when taking into account usual confounding factors such as age, alcohol, tobacco consumption, and body mass index (BMI) [3]. Respiratory event-related intermittent hypoxia is the main stimulus leading to adrenergic and renin–angiotensin system (RAS) over-activity and thus to the development of the sustained increase in blood pressure (BP) seen in OSA patients. The endothelial dysfunction evidenced in OSAS also partly explains hypertension, owing to decreased vasodilation and enhanced vasoconstriction, resulting from NO availability reduction. Similarly, the hyperinsulinism often present in apneic subjects, especially when overweight, contributes to OSA-induced HT by favouring peripheral vasodilation impairment, endothelial dysfunction, sympathetic hyperactivity, and an increase in renal sodium reabsorption [4].

Hypertension associated with OSAS has several characteristics: diastolic and nocturnal predominance and commonly encountered masked hypertension with frequent non-dipper status. Furthermore, as OSAS is found in the vast majority of subjects with refractory hypertension, it should be systematically investigated in this situation.

Three meta-analyses derived from 19 randomized controlled trials have demonstrated that continuous positive airway pressure (CPAP), the first-line therapy for moderate to severe OSAS, reduces the 24-h mean BP by approximately –2 mm Hg (pooled estimated effect). Haentjens et al. [5] looked at 12 studies assessing CPAP versus placebo (sham CPAP or pills), including a total of 512 patients. Some of the analyzed studies excluded hypertensive patients whilst others only included hypertensive patients. Furthermore, the presence of an antihypertensive treatment was not constant. This meta-analysis mainly showed that the reduction in mean BP over 24 hours with CPAP was low (–1.69 mm Hg) but significant ($p < 0.001$). This BP reduction is more marked if patients have severe OSAS and if they comply with CPAP treatment. Bazzano LA et al. [6] have taken into account 16 placebo-controlled studies comparing the effect of CPAP on BP over at least two weeks. Out of the 818 OSAS suffering patients included, the mean BP reduction with active treatment vs. placebo was –2.46 mm Hg (95% CI: –4.31 to –0.62) for SBP and –1.83 mm Hg (95% CI: –3.05 to –0.61) for DBP. The SBP and DBP falls were identical for day and night. The studies differed regarding to the BP parameters used (SBP, DBP, or mean BP), the type of control treatment used (8 used sham CPAP, 4 provided a pill, and 4 provided usual care alone), and the outcome measure (ABPM or clinical BP). Again, a significant BP reduction was associated with higher baseline BP levels, and higher BMI and severity of OSA. Mandibular advancement devices (MADs) are the only alternative treatment to CPAP. Even if available data are limited, using MADs has been reported to be associated with a significant reduction in 24-h diastolic blood pressure compared to an inactive oral appliance. The range of blood pressure decrease was similar to that achieved with CPAP [7].

Sleep duration and hypertension

Sleep duration has decreased in the general population over the last 30 years [8]. In the US, the National Sleep Foundation reported an increase from 12% to 16% of subjects sleeping less than 6 hours on workdays between 1998 and 2005, reflecting voluntary sleep restriction. On the other hand, the prevalence of insomnia complaints was 23% in The Atherosclerosis Risk in Communities Study (ARIC), a prospective observational cohort involving 13,563 participants aged 45 to 69 years [9]. Two major community-based cohort studies, the Sleep Heart Health Study (SHHS) [10] and the National Health and Nutrition Examination Survey (NHNES) [11] have reported a relationship between self-reported short sleep duration and prevalence and incidence of hypertension. Gottlieb et al. [10] have demonstrated from SHHS that short and long habitual sleep duration are both associated with higher prevalence of hypertension when compared with subjects sleeping between 7 and 8 hours per night, after adjustment for possible confounders such as age, sex, race, obesity, apnea–hypopnea index, or lifestyle habits. Short sleep duration was associated with higher prevalence of hypertension in the Korean National Health and Nutrition survey 2001 [12]. Subjects participating in NHNES who had self-reported less than 5 hours of sleep by night demonstrated a higher incidence of hypertension after 8 to 10 years follow-up [11]. This association persisted, even though attenuated, when analyses were adjusted for confounders, body weight in particular.

The relationship between sleep duration and hypertension is age and gender dependent. Adolescents with shorter sleep duration assessed by actigraphy demonstrated higher prevalence of prehypertension [13]. Conversely, an association between sleep restriction and incident hypertension was not found in subjects between 60 and 86 years of age in the NHNES study [11]. Hypertension was not associated with sleep duration assessed by either self-report or actigraphy in a cross-sectional study of 5058 participants, aged 58 to 98 years of age in the Rotterdam Study [14]. Finally, considering short sleep duration, hypertension was both more prevalent and more incident in women only, in the Whitehall II Study [15].

Short sleep duration and insomnia, although classically related, are different entities. Insomnia entails dissatisfaction with the quality of sleep that can be explained or not by a true reduction in sleep duration. Individuals with short sleep duration do not necessarily suffer from insomnia since they can voluntarily restrict their sleep time. Insomnia is clearly related to psychiatric and psychosomatic disorders, and some insomniac patients have a misperception of their sleep quality. Whether insomnia is associated with increased somatic disorders, cardiovascular in particular, was controversial in the literature. Recently, Vgontzas et al. [16] have demonstrated in a population based study that only insomnia associated with sleep duration < 5 hours (proven by polysomnography) is associated with a five-fold increased risk of hypertension after adjustment for other sleep disorders. Accordingly, in middle-aged subjects of the NHNES, depression was associated with increased incidence of hypertension, but the strength of this link was weakened by 33% after adjustment for both sleep duration and insomnia, suggesting that these conditions may mediate the relationship between depression and hypertension [17].

Pathophysiological mechanisms underlying short sleep duration and hypertension association

Sleep deprivation studies in normotensive subjects have demonstrated that BP was increased after nights of sleep restriction [18, 19]. This could mainly be activation of the hypothalamic-pituitary-adrenal axis and elevated sympathetic nervous system activity [19, 20]. Sleep deprivation has also been re-

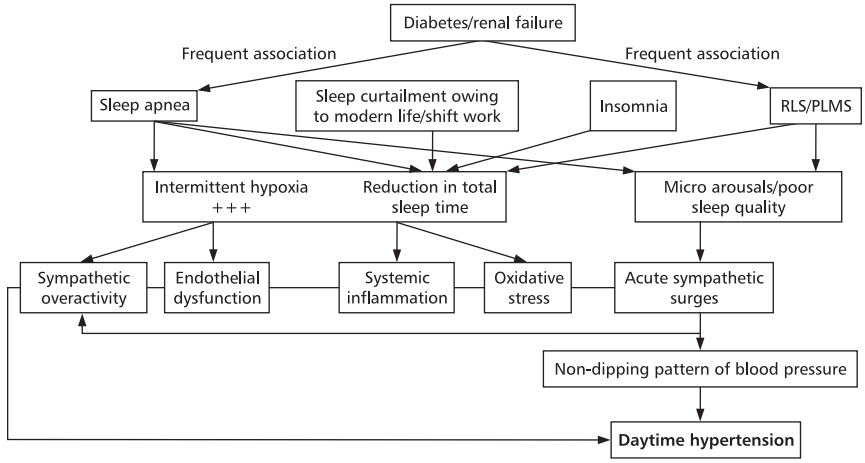

Figure 1. The common intermediary mechanisms for the link between sleep, sleep disorders, and hypertension. Alterations in sleep quality and sleep disorders are associated with intermediary mechanisms that favour the development of hypertension. Any combination of a pre-existing hypertension, whatever the cause, and sleep disturbances may increase hypertension severity and limit treatment efficacy

ported to be associated with systemic inflammation [21], oxidative stress, and endothelial dysfunction — all conditions favouring the appearance of hypertension.

Restless legs syndrome (RLS), periodic limb movement disorder and hypertension

RLS is characterized by dysaesthesia and leg restlessness occurring predominantly at night during periods of immobility [22]. Unpleasant sensations and the irresistible need to move impair the ability to fall asleep and impair sleep quality. RLS is associated in 90% of cases with periodic limb movements in sleep (PLMS), which are repetitive flexions of the hips, knees, and ankles during sleep possibly ended by micro arousals. These micro arousals are associated with abrupt increases in blood pressure and sympathetic hyperactivity. PLMS also occur in patients without RLS and are found in 25% of patients undergoing routine polysomnography. Both RLS and PLMS are possibly associated with changes in sleep quantity and/or quality and have been incriminated as causes of hypertension [23].

Among 4000 men aged 18 to 64 years assessed by mail questionnaires, RLS sufferers were more likely to report hypertension after adjustments for age, witnessed apnea, smoking, and alcohol consumption [24]. In a study by Ohayon et al. [25] including 18,980 individuals from 5 European countries, 732 met criteria for RLS and presented with a 2-fold higher risk for elevated blood pressure (21.8 versus 11.1%, respectively, with an OR for the association between hypertension and RLS of 1.36 after adjustment for confounders). Winkelman et al. [22] studying 2821 participants in the Wisconsin Sleep Cohort found a non significant trend for the association between RLS and hypertension. The relationship seemed to be more robust only in those with severe, as opposed to moderate, RLS. This makes sense as only RLS and PLMS leading to significant impairment in sleep duration and quality are supposed to be linked with hypertension. In summary, the results of epidemiologic studies suggest a possible relationship between self-reported RLS symptoms and daytime hypertension and are more consistent when considering severe cases of RLS with daily symptoms [23].

The common intermediary mechanisms for the link between sleep, sleep disorders, and hypertension (Figure 1)

Among the pathophysiological mechanisms associated with sleep restriction and present in different sleep disturbances such as OSAS, insomnia, and RLS/PLMS, nocturnal sympathetic activation is probably the key mechanism (Figure 1). This nocturnal sympathetic over activity limits the nocturnal BP fall and in turn leads to a diurnal permanent increase in sympathetic tone. Hypertensive subjects in whom the nocturnal BP fall is blunted (non-dipping pattern) are known to develop a higher degree of target organ damage and cardiovascular morbi-mortality. Systemic inflammation, oxidative stress, and endothelial dysfunction are also linked with sleep quantity and sleep disorders and may also influence the development and progression of hypertension. Hypertension is a frequent co morbidity of diabetes and renal failure, which are also frequently associated with OSAS and RLS/PLMS. In these situations both the primary disease and the associated sleep disorder act synergistically to elevate BP. Thus, we recently demonstrated that in type 1 diabetic subjects shorter sleep duration was associated with non-dipping pattern of BP [26]. The same detrimental situation occurs in drug-resistant hypertension. OSA is highly prevalent and present in more than 80% of the drug resistant hypertension patients. OSA suffering patients with additive shorter sleep duration exhibited higher BP values [27]. In summary, both alterations in sleep quality and sleep disorders are associated with intermediary mechanisms that favour the development of hypertension. Any combination of a pre-existing hypertension, whatever the cause, and sleep disturbances may increase hypertension severity and limit treatment efficacy.

Conclusion and perspectives

In hypertension, sleep must be taken into account as a relevant life period [1]. Sleep restriction and sleep disorders are both and synergistically associated with increased prevalence and incidence of hypertension. Intervention studies are now needed to assess whether acting to promote voluntary longer sleep duration and/or efficiently to treat sleep disorders could prevent or reverse hypertension.

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PERIOPERATIVE SCREENING AND MANAGEMENT OF HYPERTENSIVE PATIENTS

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Hypertension (HTN) affects one billion individuals worldwide, particularly the elderly, and represents a major risk factor for coronary artery disease, heart failure, and renal and cerebrovascular disease. Elevated blood pressure is the most frequent preoperative health problem in non-cardiac surgery patients, with an overall prevalence of 20–25%. Numerous studies have shown that stage 1 or stage 2 HTN (< 180/110 mm Hg) is not an independent risk factor for perioperative cardiovascular complications [1]. Unfortunately, despite the high prevalence of HTN and the availability of numerous effective antihypertensive agents, many patients have uncontrolled high blood pressure. Accordingly, the perioperative evaluation is a unique opportunity to identify patients with HTN and initiate appropriate therapy. Although pre-existing HTN is the most common medical reason for postponing a needed surgery, it is unclear whether postponing surgery in order to achieve optimal blood pressure control will lead to reduced cardiac risk [2].

In everyday clinical practice, very often we have to give answers to the following questions: Should I go ahead with a patient with uncontrolled HTN, or should I postpone the surgery? Are patients with uncontrolled HTN at an increased perioperative risk for cardiovascular complications? What is the risk of cardiac complications during and after surgery? How can that risk be reduced or eliminated? Are there any data on which I can base my decision? In this field, we do not have strong data according to 'evidence based medicine', and much of the evidence for the perioperative risks associated with HTN comes from uncontrolled studies performed before current (more effective) management was available.

Pathophysiology

Blood pressure elevation is sustained by an increase of systemic vascular resistance, increased preload, activation of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS), baroreceptor denervation, rapid intravascular volume shifts, serotonergic overproduction, and altered cardiac reflexes. Decreased sympathetic tone during anaesthesia results in a relative decrease in cardiac preload and afterload. During the induction of anaesthesia, sympathetic activation can cause an increase in blood pressure of 20–30 mm Hg and heart rate increase of 15–20 bpm in normotensive individuals [3]. This response may be more pronounced in untreated HTN. As the period of anaesthesia progresses, patients with pre-existing HTN are more likely to experience intraoperative blood pressure lability, which may lead to myocardial ischaemia. During the immediate postoperative period, as the patient recovers from the effect of anaesthesia, blood pressure and heart rate slowly increase [4].

Perioperative evaluation

In this process we have to balance between two points: the safety of the patient during and after the operation and unjustified deferments and cancellations of surgery. It is important to know whether the patient carried the diagnosis of HTN before surgery and was receiving antihypertensive treatment, because many patients are anxious during the preoperative evaluation and may have a transient increase in blood pressure. It is important for physicians to follow the ESH/ESC recommendations for blood pressure measurement and diagnostic approach [5]. The next and most important step is risk stratification because high-risk patients may need further evaluation whereas intermediate- and low-risk patients can undergo surgery without further delay.

Cardiovascular complications following non-cardiac surgery constitute an enormous burden of perioperative morbidity and mortality [6]. Preoperative noninvasive cardiac stress testing is associated with improved one-year survival and reduced hospitalization in high risk patients; however, the benefits were minor in patients with intermediate risk, and delay for cardiac work-up was associated with increased mortality in low-risk patients [7]. Previous or current cardiac disease, diabetes mellitus, functional status, body mass index, nutritional status, and renal insufficiency all confer higher risk for perioperative cardiac complications. Active cardiac conditions for which the patient should undergo detailed evaluation and treatment before surgery include acute coronary syndrome, decompensated heart failure, significant arrhythmia, and severe valvular disease. The revised cardiac risk index discriminated moderately well between patients at low versus high risk for cardiac events after non-cardiac surgery [8]. In addition, we have to pay attention to the identification of symptoms and signs indicative for secondary HTN from the history and physical examination. In a meta-analysis of 30 observational studies the likelihood of experiencing an adverse perioperative cardiac event was found to be, on average, 1.31-fold higher in hypertensives than normotensives [9]. An abnormally low ankle-to-arm index is an independent risk factor for postoperative cardiac complications [10]. Although there seems to be a tendency for increased incidence of perioperative haemodynamic instability in patients with myocardial ischaemia and cardiac arrhythmias in severe hypertension, existing data do not unequivocally support the notion that postponing surgery to optimize blood pressure control will improve perioperative cardiac outcomes. This is in accordance with ACC/AHA guidelines, in which uncontrolled systemic HTN per se is considered only a minor risk factor that does not affect overall perioperative management [11]. However, we lack large-scale trials that include a sufficient number of patients with severe HTN to allow valid statistical analysis and hence to draw conclusions from these patient populations.

Electrocardiogram should be part of all routine assessments of subjects with high blood pressure in order to detect left ventricular hypertrophy, patterns of strain, ischaemia, and arrhythmias. The presence of Q waves or significant ST segment elevation or depression have been associated with increased incidence of perioperative cardiac complications. Therefore, it may be helpful in some cases to contact the referring physician in order to obtain more accurate arterial pressure values than the ones measured at hospital admission (white coat HTN). In these lines, the doctor can follow a clinical algorithm based on 5 questions: 1) Is the operation urgent? 2) Does the patient have any active cardiac condition? 3) Which is the specific risk associated with the particular surgery? 4) What is the functional capacity of the patient? 5) Does the patient have any other clinical risk factors? Figure 1 shows an algorithm with the diagnostic evaluation and approach of a patient undergoing non-cardiac surgery.

Perioperative management

As mentioned previously, careful evaluation prior to surgery to identify the underlying causes of HTN is important in selecting the best treatment option. However, not only HTN but also hypotension is a risk during the perioperative period. While hypertensive peaks need to be avoided, profound hypotension, especially when associated with baroreflex-mediated tachycardia, can be equally detrimental. Severe decrease in intraoperative arterial pressure (decrease to < 50% of preoperative levels or by > 33% for 10 min) was an independent predictor of perioperative adverse events [12]. Maintaining arterial pressure perioperatively at 70–100% of baseline and avoiding tachycardia are key factors in the optimal management of hypertensive surgical patients. Particular care should be taken to avoid withdrawal of β-blockers and clonidine because of potential heart rate or blood pressure rebound. In patients unable to take oral medications, parenteral β-blockers and transdermal clonidine may be used. For stage 3 HTN the potential benefits of delaying surgery to optimize the effects of antihypertensive medications should be weighed against the risk of delaying the surgical procedure. For those patients unable to take oral medication but requiring treatment, parenteral alternatives must be used. Intravenous β-blockers, including propranolol, atenolol, and metoprolol, are attractive because of their anti-is-

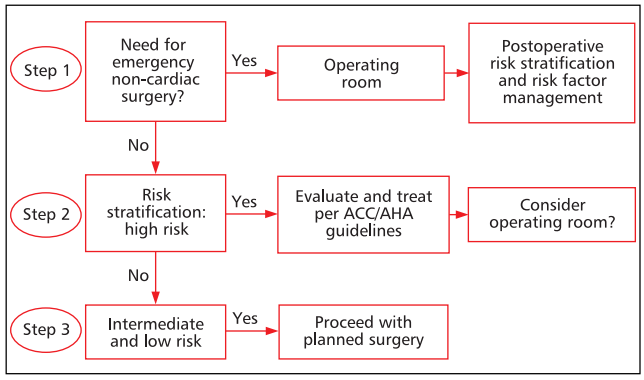

Figure 1. Cardiac algorithm for non-cardiac surgery

Table 1. Perioperative use of antihypertensive drugs

Drug	Perioperative use	Comments
Diuretics	Not on day of surgery	Potential hypokalaemia, volume depletion
Beta-blockers	Avoid starting previous day in high risk patients	With caution in intermediate and low risk
ACE-I/ARB's	Last dose day before operation	Restart ACE-I/ARB's with caution if the patient is euvolemic
Calcium channel blockers		Diltiazem effective in CHD and verapamil in supra-ventricular tachycardia
Clonidine	Continue dose	Withdrawal may cause blood pressure rebound
Esmolol		May cause bradycardia and pulmonary oedema
Labetalol		May cause bradycardia, heart block, and delayed hypotension

Table 2. Initial dosing of antihypertensive agents

Agent	Comment
Enalaprilat	Intravenous intermittent: 0.625–1.25 mg (lower dose if hyponatremia, possible volume depletion, concomitant diuretic therapy, or renal failure) over 5 min, then double at 4- to 6-h intervals until desired response, a single maximal dose of 1.25–5 mg, toxicity, or a cumulative dose of 20 mg within a 24-h period
Esmolol	Intravenous infusion: 250–500 μg/kg/min for 1 min, followed by a 50–100 μg/kg/min infusion for 4 min, then titrate using the same sequence until desired response, a maximal dose of 300 μg/kg/min, or toxicity
Hydralazine	Intravenous intermittent: 3–20 mg slow IV push every 20–60 min
Labetalol	Intravenous intermittent: 20 mg over 2 min, then double at 10 min intervals until desired response, a single maximal dose of 80 mg, toxicity, or a cumulative dose of 300 mg/d
Nitroglycerin	Intravenous infusion: 5 μg/min initially, then titrate in 5μg/min increments every 3–5 min until desired response or toxicity
Nitroprusside	Intravenous infusion: 0.25–0.5 μg/kg/min initially, then titrate dose every 12 min until desired response, a maximal dose of 10 μg/kg/min, or toxicity

chaemic benefits in the perioperative period. Other alternatives are intravenous enalapril verapamil, or diltiazem and a transdermal clonidine patch. For more serious hypertension, labetalol, nitroglycerin, and sodium nitroprusside are appropriate. Parenteral hydralazine should be avoided in patients with ischaemic heart disease (unless the patient is already under β-blockade) because the reflex tachycardia produced may lead to ischaemia. Use of sublingual nifedipine is absolutely contraindicated because it has been associated with strokes, MI, and death. During the intraoperative period, control of blood pressure may be achieved by deep sedation, the use of vasodilators such as nitroglycerin or nitroprusside, or a combination of the two (Tables 1, 2).

As the patient emerges from surgery, anticholinesterase or anticholinergic agents are frequently given to reverse the neuromuscular blockade used during anaesthesia. Post-anaesthesia blood pressure elevation is frequently caused by sympathetic activation due to patient anxiety and pain upon awakening, along with withdrawal from continuous infusion of narcotics. Intravenous agents of any class can be used during the immediate postoperative period; however, agents with slightly longer duration of action may be preferable. Because of the large volume shifts that occur during surgery, administration of blood, saline, or loop diuretics may be necessary depending on the individual needs of the patient [13]. Postoperative blood pressure treatment also includes the control of pain, anxiety, hypoxia, and hypothermia.

Diuretics. Special attention must be paid to the potassium levels of patients on diuretics. Diuretics should not be administered on the day of surgery because of the potential adverse interaction of diuretic-induced volume depletion and hypokalaemia and the use of anaesthetic agents. Hypokalaemia may cause arrhythmias and potentiate the effects of depolarizing and non-depolarizing muscle relaxants.

Beta-blockers. Recent studies have called into question the benefit of newly administered perioperative β-blockade, especially in patients at low to moderate risk of cardiac events. The specific issue of whether to initiate use of β-blockers perioperatively in such patients has been extremely controversial in the past few years, mostly due to conflicting data from two large clinical trials, POISE and DECREASE-IV. According to recently published 2009 ACC/AHA guidelines [14–15], in patients undergoing surgery who are already receiving β-blockers for treatment, β-blockers should be continued perioperatively (class I, recommendation C). For patients undergoing vascular surgery who are at high cardiac risk, β-blockers titrated to heart rate and blood pressure are probably recommended (IIa, B). For patients undergoing either intermediate-risk procedure or vascular surgery, the usefulness of initiating β-blockade is uncertain. The usefulness of β-blockers is also uncertain in patients undergoing lower-risk surgery. Findings from the POISE trial suggest that starting higher doses of β-blockers acutely on the day of surgery is associated with risk. When β-blockade is started preoperatively, it should be started well in advance of surgery at a low dose which can be titrated up as blood pressure and heart rate allow. The guidelines recommend careful patient selection, dose adjustment, and monitoring throughout the perioperative period.

Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB's). There is much debate in the literature over the use of ACE-Is or ARBs in the perioperative period due to their potential central vagotonic effects. These agents alone or in combination have been associated with moderate hypotension and bradycardia, particularly when discontinued less than 10 hours before surgery. In some patients this may be related to a decrease in intravascular volume. The continuation of ACE-I therapy in the morning is not associated with a better control of blood pressure and heart rate but causes a more pronounced hypotension which requires therapeutic intervention. Patients chronically treated with ACE-Is and ARBs should receive them last on the day prior to the operation and without premedication in the morning [16–17]. There is mixed evidence that prophylaxis with glycopyrrolate can attenuate this effect. Consideration should be given to restarting ACE-I in the postoperative period only after the patient is euvolemic, in order to decrease the risk of perioperative renal dysfunction.

Calcium channel blockers. In a meta-analysis of 11 studies involving 1007 patients, calcium channel blockers significantly reduced ischaemia and supraventricular tachycardia [18]. The majority of these benefits were attributable to diltiazem. Dihydropyridines and verapamil did not decrease the incidence of myocardial ischaemia although verapamil did decrease the incidence of supraventricular tachycardia.

Clonidine. Clonidine has a favourable sympathetic-mediated effect with a biphasic response (at lower doses central sympathetic suppression with a vasodilatory effect, at higher doses peripheral activation with a vasoconstrictor effect). It significantly reduces the rate of perioperative cardiovascular complications in patients with coronary artery disease. It is only partially effective for rapid blood pressure control in the perioperative period and contributes to analgesia and sedation.

Esmolol. Esmolol is a β1-selective adrenergic blocker that causes a reduction in heart rate and cardiac output but may increase systemic vascular resistance. It has a rapid onset and short duration of action, and may cause bradycardia, bronchospasm, seizures, and pulmonary oedema.

Labetalol. Labetalol is a non-selective combined α- and β-adrenergic blocker with little effect on heart rate and cardiac output. It has a moderate hypotensive action of long duration and is commonly used in emergency situations. It may cause bronchospasm, bradycardia, heart block, and delayed hypotension.

Nitroglycerin. Nitroglycerin is the most widely used drug. At lower doses it decreases the preload while in higher doses it decreases the afterload, and may increase the heart rate. It is the drug of choice in patients with coronary artery disease, as well as in pulmonary oedema and heart failure.

The key points of the perioperative management include: a) accurate documentation of preoperative medication, b) decision on stopping medications prior to surgery, c) monitoring of appropriate chemistry study results to determine dosages and the occurrence of adverse effects, d) appropriate management of pain, e) administration of adjunctive medications, and f) use of appropriate formulations [19–20].

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CARDIOVASCULAR RISK PROFILE AND ANTIHYPERTENSIVE TREATMENT

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The incidence of cardiovascular disease (CVD) is still increasing globally, but prevention and treatment have improved considerably during the last 20 years. As treatment is not curative, prevention is preferable although it calls for intervention in many more subjects. In order not to treat many subjects unnecessarily, it is important to identify those at highest risk of developing CVD in the future. For this purpose, several tools for cardiovascular risk estimation have been developed. In Europe, the most widely used scoring systems are SCORE [1] in subjects without known CVD or diabetes, and the cardiovascular risk stratification chart of the European Society of Hypertension (ESH) [2] in subjects with hypertension. However, many of these risk scores will, in general, overestimate the cardiovascular risk [3] because improved primary and secondary cardiovascular prevention has reduced both the incidence of myocardial infarctions and case fatalities [4] in many Western countries.

The SCORE system as a basis for strategies of prevention

Like the ESH, the European Society of Cardiology (ESC) has focused on CVD prevention, as reflected in their guidelines for clinical practice [5]. In subjects without known CVD, type 2 diabetes, type 1 diabetes with microalbuminuria, or very high levels of individual risk factors, the risk of developing fatal atherosclerotic events is calculated using the SCORE system, available in chart form (Figure 1) or as an interactive tool (HeartScore) on the ESC website (on-line version or PC-based program) (http://www.escardio.org/Policy/prevention/tools/health-toolkit/Pages/HeartScore.aspx). HeartScore is based on data from European population surveys, and national versions are available in several countries. Absolute risk of cardiovascular death within 10 years < 1% is defined as low risk; 1–4% risk is defined as moderate; 5–9% as increased, and ≥ 10% as high. Generally, there are two SCORE chart versions: for populations with low (Belgium, France, Italy, Luxemburg, Portugal, Spain, and Switzerland) or high CVD risk. In addition, each of the SCORE charts is based either on total cholesterol or the total cholesterol/HDL-cholesterol ratio. The treatment goals for blood pressure as well as other cardiovascular risk factors depend on this risk stratification, but there are no universal thresholds for initiation of drug treatment. For subjects with a 10-year risk of cardiovascular death < 5%, in addition to not smoking, BMI < 25 kg/m^2, and 30 minutes of moderate exercise daily, the following goals are recommended: Blood pressure < 140/90 mm Hg; total cholesterol < 5 mmol/l; low-density lipoprotein (LDL)-cholesterol < 3 mmol/l; and blood glucose < 6 mmol/l. These thresholds are arbitrary for blood pressure as well as for cholesterol as the association between blood pressure [6] as well as cholesterol [7] and the risk of developing CVD are also present at lower values. In general, drug treatment is not recommended in this low-moderate risk group if treatment goals are not met. Subjects at high risk (ł 10%) have the same treatment goals as patients with known CVD or diabetes: Blood pressure < 130/80 mm Hg; total cholesterol < 4.5 (4.0) mmol/l; and LDL-cholesterol < 2.5 (2.0) mmol/l. In this high-risk group, drug treatment is recommended if treatment goals are not met. In subjects with increased risk (5––9%), a less aggressive approach is allowed.

The impact of age on risk calculation

Age is the most important risk factor in the SCORE and may therefore lead to undertreatment in younger subjects and overtreatment in older subjects. To avoid undertreatment in younger subjects, it is recommended to use a relative risk chart or to calculate the absolute risk as if the subject were 60 years old. To avoid overtreatment in the elderly, caution is recommended with drug treatment if age is the major/sole reason for the increased cardiovascular risk. The actual cardiovascular risk may be higher than indicated in the SCORE chart (Figure 1) if some cardiovascular risk factors not included in the SCORE model are present (family history of premature CVD, physical inactivity, abdominal obesity, and others).

Lifestyle modification

In all subjects, intervention should include recommendations of lifestyle changes. Although lifestyle interventions have been demonstrated to reduce blood pressure, they have not yet been demonstrated to prevent cardiovascular complications in patients with hypertension and should therefore not delay initiation of drug treatment in subjects at high risk for developing CVD. As the risk of developing CVD is multifactorial, the management of patients with hypertension should not be restricted to factors affecting blood pressure, but should also include a recommendation of smoking cessation. However, several lifestyle changes have been shown to reduce blood pressure: Weight loss [8], increased physical activity [9], salt restriction, daily fish oil [10], dietary approaches introduced by DASH diet [11], and reduced alcohol intake. These lifestyle changes will be sufficient in many subjects to reduce the cardiovascular risk and may prove to have an enormous impact on CVD prevention on a population scale.

The risk chart of the European Society of Hypertension

The ESH risk chart (Figure 2) [2] uses the terms "low", "moderate", "high", and "very high" to indicate an approximate risk of cardiovascular morbidity and mortality in the following 10 years, which is somewhat analogous to the increasing level of total cardiovascular risk estimated by the Framingham or SCORE models. However, the additional use of cardiovascular morbidity is especially relevant for patients with hypertension who have increased risk of detrimental non-fatal stroke. Similar to the ESC recommendations, the key messages in the ESH risk chart [12] are: 1) All definitions of hypertension are arbitrary because the risk of CVD decreases continuously with decreasing blood pressure down to an optimal blood pressure below 120/70 mm Hg (Figure 2); 2) As hypertension is only one of

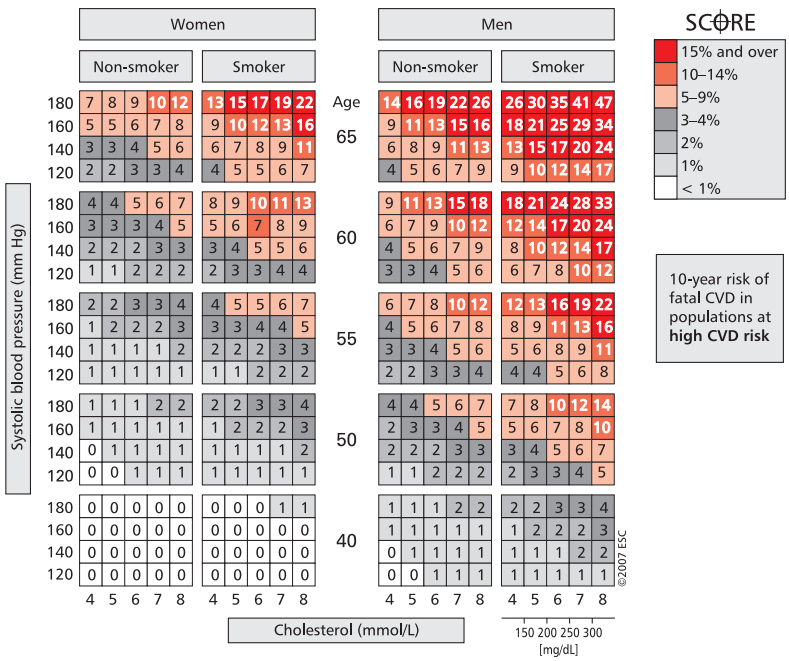

Figure 1. The absolute 10-year risk of fatal cardiovascular events as predicted by age, gender, smoking habits and serum cholesterol in subjects without diabetes or cardiovascular disease (CVD)

Blood pressure (mm Hg)					
Other risk factors, OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 risk factors, MS, OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Figure 2. The added absolute 10-year risk of fatal or non-fatal cardiovascular (CV) events as predicted by blood pressure, traditional CV risk factors, the metabolic syndrome (MS), subclinical CV organ damage (OD), diabetes and CV or renal disease; HT — hypertension; SBP — systolic blood pressure; DBP — diastolic blood pressure

several interacting cardiovascular risk factors, the absolute cardiovascular risk is dependent on all the risk factors; and 3) Treatment indications and goals are determined by the absolute cardiovascular risk and are thereby dependent on cardiovascular risk factors, subclinical cardiovascular damage, and CVD.

As illustrated by the SCORE (Figure 1), a large proportion of patients with hypertension will not be at high absolute risk of cardiovascular death. However, some of these patients may be at high risk of non-fatal cardiovascular events, non-fatal stroke in particular. The ESC guidelines for antihypertensive treatment follow, to a large extent, the ESH guidelines, but they are somewhat more restrictive regarding initiation of antihypertensive drug treatment.

Special considerations

The following three groups of patients are often debated: Hypertensive patients at low added risk, subjects with high normal blood pressure and several additional cardiovascular risk factors or subclinical cardiovascular damage, and normotensive patients with CVD.

Hypertensive patients at low added risk (20% of the middle-aged, healthy population [12])

In patients with grade 1 hypertension without other cardiovascular risk factors, the ESH primarily recommends lifestyle changes, but, if hypertension persists after six months, antihypertensive drug treatment is recommended not based on clear scientific evidence but based on the fact that the patients will eventually develop additional risk factors, and on the assumption that early prevention is better than late [13]. However, the ESC guidelines do not recommend antihypertensive drug treatment in patients with grade 1 hypertension and SCORE < 1%, due to their low cardiovascular risk. As the SCORE often underestimates the risk for non-fatal stroke in women, the risk associated with not treating middle-aged women with hypertension and SCORE < 1% should be carefully considered. Before making this decision, it is crucial to assess all cardiovascular risk factors and to follow these patients because, over time, the 10-year absolute risk of cardiovascular death will increase above 1% thus requiring drug treatment. This risk of undertreatment in middle-aged women may explain the relatively high number of cardiovascular deaths in 40-year-old women in the Västerbotten Intervention Program of northern Sweden [3].

Subjects with high normal blood pressure (15% of the middle-aged, healthy population [12])

Healthy subjects with high normal blood pressure have only slightly elevated cardiovascular risk compared to healthy subjects with optimal blood pressure (< 120/80 mm Hg) [14]. However, a large proportion of cardiovascular events occur in this rather large group, and, since risk assessment is often perceived as complicated, they deserve special attention. In subjects with high normal blood pressure and SCORE < 5%, no diabetes and no sign of subclinical cardiovascular damage, lifestyle advice is recommended by the ESC [5] and ESH [2]. In subjects with high normal blood pressure and diabetes, these societies recommend lifestyle changes as well as antihypertensive drug treatment. In the intermediate group of subjects with high normal blood pressure and SCORE ≥ 5% or with high normal blood pressure and high added cardiovascular risk due to the presence of any three other cardiovascular risk factors, metabolic syndrome or subclinical cardiovascular damage, they recommend lifestyle changes and the consideration of antihypertensive drug treatment. However, antihypertensive treatment in subjects with high normal blood pressure and diabetes or in subjects at high added risk has never been demonstrated to reduce major cardiovascular events [13], but is likely to reduce subclinical cardiovascular damage [2] and is thereby assumed to reduce cardiovascular risk [13]. By measuring subclinical cardiovascular damage, it is also possible to target and monitor treatment on a more individual basis [15]. As blockage of the renin-angiotensin-aldosterone system is associated with regression of subclinical cardiovascular damage without metabolic side effects, typical treatment will include an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II-receptor blocker (ARB) [16].

Normotensive patients with CVD

Despite little evidence, the ESH recommended in their 2007 guidelines [2] antihypertensive drug treatment, especially ACE-inhibitors or ARBs, in patients with CVD or renal insufficiency independently of blood pressure. However, the clear scientific evidence for more aggressive treatment in patients with CVD is lacking [13], and post-hoc analyses from the OnTarget-study [17] have demonstrated a worse prognosis in patients reaching a very low blood pressure, indicating a threshold for how far blood pressure may be reduced in patients with CVD. Therefore, the ESH have modified their rather aggressive recommendation for a treatment goal just below 130/80 mm Hg [13] which is also used by the ESC [5]. The first line of antihypertensive drug treatment is dependent on the type of CVD. In diabetes with microalbuminuria or renal insufficiency, ACE inhibitors or ARBs should be included in the treatment.

Practical use of risk stratification

In general, the SCORE should be used in healthy, normotensive subjects, and the ESH risk chart in hypertensive patients. However, physicians are still reluctant to use risk stratification tools, and the differences between the ESH risk chart and the SCORE, if used as recommended by the ESC, are only small [18]. Therefore, it is more important that doctors use the risk stratification tool with which they are familiar and less important which tool they use. General assessment of subclinical cardiovascular damage in normotensive subjects with SCORE < 5% is an overwhelming task without a substantial clinical impact [19]. However, assessment of subclinical cardiovascular damage in normotensive subjects with 1% < SCORE < 5% may have some clinical impact. In subjects with high normal blood pressure, assessment of subclinical cardiovascular damage may increase the sensitivity for identifying subjects experiencing later cardiovascular events [12]. However, as approximately 80% of healthy subjects with high normal blood pressure and SCORE ≥ 5% have subclinical cardiovascular damage [19], calculation of the SCORE could be considered instead of measuring subclinical cardiovascular damage in this group.

Summary

Estimation of absolute cardiovascular risk is important for the choice of primary as well as secondary cardiovascular prevention. In general, physicians are advised to use the SCORE in apparently healthy subjects with optimal or normal blood pressure, the ESH risk stratification chart in patients with hypertension, and either one or, better still, a combination of the two instruments in apparently healthy subjects with high normal blood pressure.

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THE ROLE OF URIC ACID IN HYPERTENSION, CARDIOVASCULAR EVENTS, AND CHRONIC KIDNEY DISEASE - UPDATE

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Introduction

Following the discovery by Mahomed and Garrod in the early 1800s that hyperuricaemia was the cause of gout, it was proposed that it also had a causal role in a variety of cardiovascular and renal conditions, including hypertension, arteriolosclerosis (the histological lesion of hypertension), kidney disease, and heart disease [1]. By the 1990s, however, prospective studies could not establish uric acid as a causal factor in these conditions [2].

In the early 2000s, a substantial body of clinical, epidemiological, and animal studies convincingly defined a positive association of serum uric acid with cardiovascular events (CVD) in the general population and, particularly, among hypertensive patients.

Definition of serum urate levels

Serum uric acid levels are similar in boys and girls during childhood. However, a gender difference appears at adolescence. In normal healthy adult males, serum urate values exceed those in females of reproductive age due to enhanced renal urate clearance by oestrogenic compounds [3]. After menopause, serum urate values in healthy females increase and approximate those in healthy males of corresponding age. In postmenopausal women, treatment with hormone replacement therapy causes a lesser rise in serum urate values [4].

Serum urate values may vary significantly as a result of factors that modify its generation or urinary excretion. High purine or protein diets, alcohol consumption, high cell turnover, or enzymatic defects of purine metabolism enhance generation, while reduction in glomerular filtration rate (GFR) or administration of diuretics (such as thiazides) decrease urinary excretion of uric acid. As a result, serum uric acid levels are increased. On the other hand, drugs that interfere with purine metabolism or enhance increased urinary excretion are associated with a reduction in serum uric acid levels.

Hyperuricaemia is usually defined as serum levels > 6.5–7 mg/dl and > 6 mg/dl in men and women, respectively [3].

Homeostasis of uric acid

Uric acid (7,9 dihydro-1H-purine-2,6,8(3H)-trione) is a major metabolite of purine nucleotides. In most mammals, purine nucleotides are degraded to xanthine or hypoxanthine through the action of an enzyme complex. In turn, xanthine and hypoxanthine are metabolized to uric acid by xanthine dehydrogenase or urate synthetase and, through urate oxidase, a hepatic derived enzyme, to allantoin, which is highly soluble in urine [5].

During the Miocene Period (about 20 to 5 million years ago), two parallel but distinct mutations occurred during the primate evolution rendering the uricase gene non functional, preventing the further oxidation of uric acid to allantoin in humans [5]. This resulted in serum uric acid levels being higher in humans and great apes than in other mammals.

Uric acid is a weak, odourless organic acid. Its solubility is poor at acid pH but is greatly enhanced at high pH dissociating into urate and a hydrogen ion: **uric acid ⇔ urate + H^+**

At the normal pH of 7.4, this reaction is shifted to the right. As a result, most uric acid circulates as urate anions. Normal humans have serum urate concentrations approaching the theoretical limit of solubility of urate in plasma (about 6.8 mg/dl) and excrete urine that is supersaturated with respect to uric acid.

Uric acid is not typically ingested. It is produced in the liver from the degradation of dietary and endogenously synthesized purine compounds. Dietary intake appears to provide a significant source of urate precursors [6].

The normal adult male has a total body urate of about 1200 mg, twice that of the female. Serum urate levels reflect the net balance between its constant production and excretion. Urate is not metabolized by human tissues. To maintain homeostasis, urate is eliminated by the kidney and the gastrointestinal tract [5].

Renal urate excretion accounts for about 2/3 of the uric acid turnover. Four distinct processes are involved in the renal handling of urate: 1) glomerular filtration; 2) presecretory tubular reabsorption; 3) tubular secretion; and 4) post secretory reabsorption. Tubular reabsorption and secretion mechanisms are mediated by a urate/anion exchanger and a voltage sensitive urate channel [5].

Under normal conditions, urate is freely filtered at the glomerulus as only 5% is bound to plasma proteins. Glomerular filtration accounts for only 7–12% of the excreted filtered urate load. After glomerular filtration, uric acid undergoes both pre- and postsecretory reabsorption and secretion in the proximal convoluted tubule. Incomplete postsecretory reabsorption is a major contributor of urinary excretion of uric acid [5].

The remaining 1/3 of urate load is excreted through the gastrointestinal tract. Urate enters the gut by passive diffusion where it is completely degraded by colonic bacteria with little being excreted in the stools [5].

Persistent hyperuricaemia can result either from diminished renal excretion or excessive overproduction of uric acid. In 85–90% of individuals reduced uric acid excretion by the kidneys accounts for the elevated serum uric acid levels [7].

Biological effects of uric acid

Several pathophysiological mechanisms linking serum uric acid to cardiovascular damage at the cellular and tissue levels have been proposed. Soluble uric acid (urate) is not an inert molecule, but possesses several biological actions that could be either beneficial or detrimental [5].

Antioxidant properties

One of the beneficial properties of urate is its ability to act as an aqueous antioxidant. Along with ascorbate, urate may be one of the most important antioxidants in the plasma, reacting with a variety of oxidants. In particular, by scavenging superoxide anions, it blocks the reaction of superoxide with nitric oxide and prevents the formation of peroxynitrite, which is a very toxic product to the cells [8, 9].

Uric acid may also prevent the degradation of extracellular superoxide dismutase (SOD3), an extracellular enzyme which is critical in blocking the reaction and inactivation of nitric oxide by superoxide anions [5].

It has been postulated that the ability of urate to react with oxidants may be an attempt of the host to maintain integrity and function of vascular cells in conditions associated with oxidative stress [5].

Deleterious effects

In contrast to its beneficial actions, uric acid has also been found to have a wide variety of deleterious effects on vascular cells.

Endothelial dysfunction. Uric acid may contribute to endothelial dysfunction. Uric acid infusions in healthy humans result in impaired acetylcholine induced vasodilatation in the forearm, documenting impaired endothelial nitric oxide (NO) release. In experimental animals, mild hyperuricaemia inhibits the NO system in the kidney [10].

The mechanism by which uric acid impairs endothelial function may be related to a pro-oxidative action under certain conditions.

Proliferation of vascular smooth muscle cells. Uric acid also stimulates proliferation of vascular smooth muscles cells by activating intracellular protein mechanisms resulting in proliferative and proinflammatory phenotypes, which produce growth factors, vasoconstrictive and proinflammatory molecules [11].

Pathophysiological significance of hyperuricaemia

Epidemiological studies have reported a relation between serum uric acid and a wide spectrum of cardiovascular disease (CVD) (Figure 1) [12]. This relation is not limited to frankly elevated serum uric acid levels, but has been reported with uric acid levels within the high normal range [3].

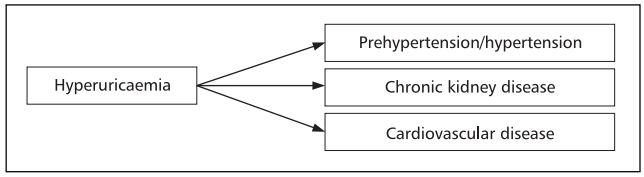

Figure 1. Links between hyperuricaemia, risk of hypertension, CKD, and CVD; CKD — chronic kidney disease; CVD — cardiovascular disease

Hypertension

Hyperuricaemia is very common in hypertension. It has been reported in 25–40% of untreated hypertensive individuals, in 50% of those treated with diuretics, and in over 80% of those with malignant hypertension [3]. The high serum uric acid levels in hypertension have been attributed to several mechanisms: 1) the reduced renal blood flow that often accompanies the hypertensive state stimulates urate reabsorption in the proximal tubule [3]; 2) the hypertensive microvascular disease leads to local tissue ischaemia, the release of lactate that blocks urate secretion in the proximal tubule and increases uric acid synthesis [13]. Tissue ischaemia leads to ATP degradation to adenosine and xanthine oxidase. Both increased xanthine and xanthine oxidase result in increased generation of uric acid and oxidant (O_2^-) formation; and 3) additional factors can contribute to hyperuricaemia in hypertension such as alcohol abuse, lead intoxication, and diuretic use.

During the past few years, several clinical and experimental studies have indicated that uric acid might be an important factor in the development of primary hypertension.

Pathophysiological mechanisms by which high levels of uric acid can lead to hypertension have been elucidated in experimental animal studies. Rats rendered hyperuricaemic with oxonic acid, a uricase inhibitor, develop hypertension within several weeks [14]. Blood pressure (BP) elevation was shown to be due to uric acid mediated systemic and renal vasoconstriction as a result of activation of the renin–angiotensin system and a reduction in endothelial nitric oxide levels [14]. Renal arterioles are functionally constricted resulting in a decline in renal plasma flow, but are structurally normal [14]. At this initial stage, controlling hyperuricaemia with allopurinol, a xanthine oxidase inhibitor, or with a uricosuric agent prevents or reverses BP elevation and is associated with reversal of abnormal hormonal changes [14].

With persistent and chronic hyperuricaemia, hypertension is associated with the development of preglomerular arteriopathy and tubulointerstitial disease, reminiscent of the classic lesions of essential hypertension [15]. Controlling hypertension with diuretics does not prevent the development of microvascular disease. Coupled with reported direct actions of uric acid on endothelial and vascular smooth muscle cells, these observations suggest that uric acid may induce microvascular disease independently of hypertension [15]. At this stage, hypertension becomes salt sensitive and can be controlled with salt restriction. In contrast, withholding uricase inhibitor therapy does not reverse the BP elevation [15].

In humans, the link between hyperuricaemia and hypertension has been reported in several studies. Among children newly diagnosed with hypertension, serum uric acid was highly correlated with both systolic and diastolic BP [16]. The Framingham Heart Study indicated that hyperuricaemia preceded the onset of hypertension with an odds ratio of 1.17 for each increase in serum uric acid by 1.3 mg/dl [17]. Similar findings were reported in the Multiple Risk Factor Intervention (MRFIT). In normotensive men without metabolic syndrome, hyperuricaemia (defined as a serum uric acid > 7 mg/dl) was associated with an 80% increased risk of developing hypertension, independent of baseline BP measurements, lipid profile, proteinuria, or renal function [18].

Serum uric acid appears to be a risk, not only for hypertension, but also for milder degrees of elevated BP levels. In a community-based study of 14,451 Chinese subjects, a linear interaction was observed between serum uric acid and risk of prehypertension, especially at serum uric levels between 200 μmol/l (3.4 mg/dl) and 380 μmol/l (6.4 mg/dl) [19]. In contrast, in this study as well as in others, this correlation was lost in subjects older than 60 years of age [19, 20].

Hyperuricaemia is also more common in primary than in secondary hypertension, at least in adolescents [21]. In one study, elevated uric acid levels (> 5.5 mg/dl) were observed in nearly 90% of adolescents with essential hypertension, whereas uric acid levels were significantly lower in those with either secondary hypertension or white coat hypertension. The strength of the relationship between uric acid level and hypertension decreased with increasing patient age and duration of hypertension, suggesting that uric acid may be

a more important pathogenetic factor in younger subjects with early onset hypertension [3]. Hypertension is also common among adults with prehypertension, especially when microalbuminuria is present [22].

Preliminary clinical trials support a role for uric acid in the pathogenesis of early onset primary hypertension. In a double blind, placebo-controlled cross over trial performed in 30 adolescents with hypertension and hyperuricaemia, treatment with allopurinol was associated with a significant fall in both casual (measured at the physician's office) and ambulatory BP, and the reduction was similar in magnitude to that achieved with most antihypertensive agents [18]. For patients in whom uric acid levels decreased to less than 5 mg/dl (300 μmol/l) during allopurinol therapy, BP became normal in 86%, compared with 3% during the placebo phase of the study [23].

Cardiovascular disease

It remains controversial whether uric acid plays a causal role in the development of CVD, or is simply a marker of more traditional CVD risk factors.

Recent reports from the Framingham Heart Study and Atherosclerotic Risk in Communities (ARIC) study, which collectively involve over 200,000 men and women, claim no association between serum uric acid incident CVD in multivariable models [24]. In contrast, other recent studies documented an independent association of uric acid with CVD. In a group of well-treated hypertensive patients, the incidence of CVD was significantly associated with serum uric acid, even with control of other known CVD factors including serum creatinine, body mass index (BMI), and diuretic use [25]. Despite blood pressure control, serum uric acid levels increased during treatment and were significantly and directly associated with cardiovascular events [25].

In a population based study, the NHANES I Epidemiologic Follow Up Study, for each increase of 59.5 μmol/l (1 mg/dl) in uric acid the hazard ratios of CVD mortality and ischaemic heart disease were 1.09 and 1.17 for men and 1.26 and 1.3 for women, respectively. The results of the LIFE Study provided additional support for an association between baseline uric acid and increased risk of CVD events [26]. Attenuation of the increase in serum uric acid by Losartan over 4.8 years reduced CVD events in this high-risk population.

Chronic kidney disease

Hyperuricaemia is highly prevalent in patients with chronic kidney disease (CKD), reflecting reduced efficiency in renal excretion of uric acid and associated with hypouricosuria.

The role of uric acid in the initiation and progression of CKD remains controversial. Recent epidemiological and experimental evidence suggests a role for uric acid not only as a marker of reduced kidney function but also as a causal risk for the development and progression of renal disease.

In experimental studies, oxonic acid-induced hyperuricaemia in rats caused the slow development of albuminuria, preglomerular arteriopathy, glomerulosclerosis, and tubulointerstitial disease [14]. Controlling hyperuricaemia with hypouricosuric agents in these animals prevented renal microvascular and histopathological injury and preserved renal function [14].

Several epidemiological surveys and prospective studies have documented an association between hyperuricaemia and risk of new onset kidney disease. In the Okinawa General Health Maintenance Association study, which included 6400 Japanese participants with normal renal function at baseline, uric acid levels > 8 mg/dl were associated with a 2.9- and 10-fold increased risk of developing CKD (defined as serum creatinine levels > 1.4 mg/dl in men and > 1.2 mg/dl in women) within 2 years in men and women, respectively [27]. The relationship between serum uric acid levels and incident kidney disease (defined as GFR decrease of 15 ml/min/1.73 m^2 with final GFR < 60 ml/min/1.73 m^2) was also evaluated in over 13,000 participants with intact kidney function in two community based cohorts. During a follow-up period of 8.5 years, each 1 mg/dl greater uric acid level at baseline was associated with an approximately 10% increase in risk of kidney disease in multivariable adjusted models.

Chronic use of diuretic therapy has been cited as a possible risk factor for hyperuricaemia-induced CKD. Clinical and population based studies have indicated that diuretic usage often accelerates progression to CKD in hypertensive subjects. The use of diuretics in the Syst-Euro, SHEP, INSIGHT, and ALLHAT studies was associated with a greater decline in renal function compared with other treatment groups [3].

In a randomized clinical trial in 54 hyperuricaemic patients with stage 3 or 4 CKD, allopurinol therapy, compared to placebo, during a 1-year follow-up was associated with a significant reduction in serum uric acid levels and delay in progression of CKD (defined as an increase in serum creatinine level > 40% of baseline or the need for replacement therapy) [28]. These interesting observations give support to the hypothesis that hyperuricaemia maybe nephrotoxic in CKD, accelerating progression to ESRD.

In contrast, two other studies failed to substantiate a relationship between serum uric acid levels and CKD. In a separate analysis of 5800 participants from the Cardiovascular Health Study (CHS) there was no association between serum uric acid levels and incident CKD defined as eGFR < 60 ml/min/1.73 m^2. Likewise, in a cohort of patients with predominantly nondiabetic stages 3 to 4 CKD, hyperuricaemia was not an independent predictor of progression to end stage renal failure [29].

In gout, whether or not gouty nephropathy or chronic uric acid nephropathy exist as a specific entity resulting from the direct renal injury from uric acid deposition in renal parenchyma remains controversial but appears to be unlikely. Prior to the advent of hypouricosuric therapy, patients with gout exhibited evidence of CKD (albuminuria, renal functional impairment), hypertension, and histological renal lesions which included arteriolosclerosis, glomerulosclerosis, and tubulointerstitial disease with or without patchy deposition of uric acid crystals in the outer medulla, and were attributed to coexistent hypertension and aging independent of crystal deposition [3].

Fructose consumption, metabolic syndrome, and risk of cardiovascular disease

The past few decades have witnessed a major increase in the prevalence of obesity, hypertension, diabetes mellitus, and metabolic syndrome. There is evidence that serum uric acid levels are rising as well. These observations have been associated with a large increase in fructose intake. Fructose is an isomer of dextrose synthesized from corn syrup and is currently used as a sweetener in preference to naturally occurring sucrose [30]. Fructose is unique among sugars in that it rapidly causes depletion of ATP and increases both the generation and the release of uric acid.

Experimental observations support a link between fructose intake, hyperuricaemia, and hypertension. Rats fed with fructose develop hyperuricaemia, hypertension, metabolic like syndrome, and renal haemodynamic and histological changes very similar to those observed with hyperuricaemia [3]. Controlling hyperuricaemia with xanthine oxidase inhibitors in these rats partially prevented these changes (Figure 2).

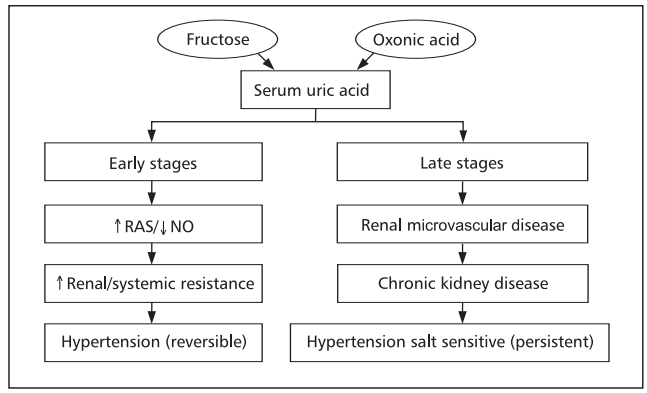

Figure 2. Relationship between oxonic acid/fructose induced hyperuricaemia, hypertension, and CKD; RAS — renin–angiotensin system; NO — nitric oxide

Similarly, epidemiological studies have linked fructose intake with increased prevalence of hyperuricaemia, obesity, hypertension, and CKD; features common to metabolic syndrome. There is strong evidence associating fructose intake with hyperuricaemia and increased incidence of gout [31]. However, it is unclear whether fructose intake is causally related to incident hypertension and CKD. Although higher serum uric acid levels are associated with an increased risk of hypertension in younger individuals, several lines of evidence suggest that uric acid may only be a marker of hypertension risk in humans [32]. Large prospective studies in males and females found no association between fructose intake and risk of incident hypertension [32].

An association between fructose intake, hyperuricaemia, albuminuria, and chronic kidney disease has been well documented in several studies. However, a causal relationship between fructose intake and incident CKD remains controversial. Recent analysis of the data of the Atherosclerosis Risk in Communities Study (ARIC) has provided possible answers to these queries. These data suggest that increased fructose consumption is associated with an increased prevalence of CKD mainly in participants with serum uric acid > 9 mg/dl. However, there was no evidence of increased incidence of CKD. These data cast some doubt over the association of fructose intake with the development of hypertension and chronic kidney disease [33].

Conclusions

Serum uric acid, the major metabolite of purine nucleotides, is a recently recognized risk factor for hypertension, CVD, and CKD and may act as a link between metabolic syndrome and the increasing incidence of the newly recognized associated nephropathy.

Reduction of elevated serum uric acid levels may reverse hypertension in adolescents with new onset hypertension and may delay the progression of renal dysfunction in patients with established CKD.

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HYPERTENSION AND AORTIC DISEASE

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Introduction

Hypertension has long been recognized as a major cardiovascular (CV) risk factor. It promotes the formation of atheromatous lesions in the large arteries, including the aorta. Increased stiffness of the aortic wall — which can be non-invasively investigated by measuring the carotid-to--femoral pulse wave velocity (PWV) — can lead to systolic hypertension, especially in the elderly. Hypertension may also be secondary to aortic coarctation, in which case it affects the upper limbs even though there is hypoperfusion downstream of the aortic lesion, which is usually isthmic.

This newsletter will not address the above-mentioned abnormalities but will focus on the relationships between hypertension and aortic aneurysm, dissection, and hematoma, all problems which require multidisciplinary care by clinicians, radiologists, and surgeons in concert.

Aortic aneurysm

Abdominal aortic aneurysm

An aneurysm is a localised fusiform or sacciform dilatation of an artery. Aneurysm of the abdominal aorta (AAA) is diagnosed when the greatest aortic diameter reaches 30 mm. Its physiopathology usually involves an atheromatous deposit associated with the usual CV risk factors, including hypertension but most importantly smoking (with prevalence four times higher in smokers) [1]. It is most common in men of over 65 (prevalence about 5%). In the Tromsø Study, the risk factors for AAA within seven years were smoking, hypertension (OR = 1.54), hypercholesterolaemia, age, and male gender [2]. AAA is associated with a combination of multiple factors, including localized haemodynamic biomechanical stress, medial fragmentation, and genetic predisposition through a complex immunologic mechanism. Extracellular matrix abnormalities lead to increased proteolysis, loss of smooth muscle tissue, inflammation, and apoptosis [3]. Interestingly, an experimental/numerical study has shown pronounced arterial wave reflections with AAA [4]. Rarely, infection leads to AAA [5]. An AAA is usually small when discovered but grows in diameter, slowly at first, then later exponentially. Ultrasonography is the reference modality for the diagnosis and monitoring of AAAs. It measures their diameter, analyses the geometry, and detects any mural thrombus that may be present. CT scan (Figure 1) or MRI can also be useful before treatment.

AAA treatment is essentially prophylactic, designed to prevent rupture, which is fatal in some 75% of cases. The time for surgery and its nature will depend on the characteristics of the AAA and the patient's condition. In a non-emergency situation, surgery is indicated once the aortic diameter reaches 55 mm (or 50 mm in women and patients with a family history of aneurysm or if there is evidence of fast expansion) [6]. If the diameter of an asymptomatic infrarenal AAA is below 50 mm, rigorous surveillance is recommended (ultrasonography every three to six months). Aortic repair can be achieved by open surgery (graft-prosthesis) or via an endovascular approach (stent grafting). In patients with AAA, Lantelme et al. showed that both graft-prosthesis and stent graft placements significantly increased the carotid-to-femoral PWV, a recognized marker for CV events [7].

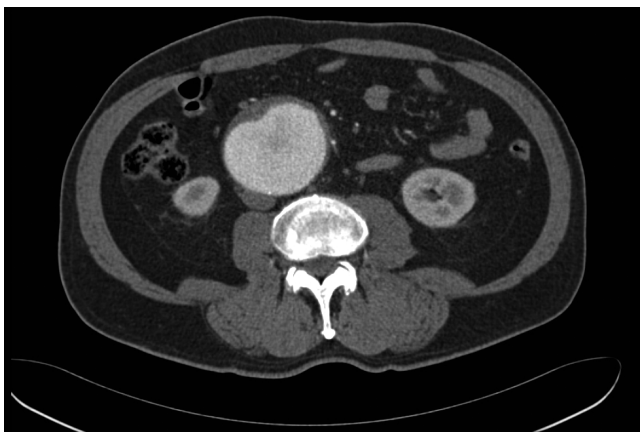

Figure 1. CT scan with contrast injection: voluminous abdominal aortic aneurysm with a mural thrombus

In a patient with an AAA, all CV risk factors should be managed in order to prevent recurrence. Testing for obstructive sleep apnoea (OSA) would seem to be legitimate in this population because severe OSA may accelerate AAA expansion [8]. ESC guidelines on perioperative cardiac management in non-cardiac surgery recommend beta-blockers in patients scheduled for high-risk surgery (i.e. surgery on the aorta or other major vessels, and on peripheral vessels) [9]. Medical treatment of AAA involves strict blood pressure (BP) control. This will not treat the aneurysm *per se* but effective hypertension control may decrease the rate of AAA expansion. The use of beta-blockers in slowing AAA growth is controversial: a meta-analysis suggests that beta-blockers do not appear to significantly reduce AAA growth [10]. In contrast, angiotensin II type 1 receptor antagonists (ARBs) seem to inhibit AAA progression, as has been demonstrated in rats with telmisartan [11]. Statins also seem to be useful because they inhibit the expression of various inflammatory compounds, including MMP [12].

Thoracic aortic aneurysm

Most thoracic aortic aneurysms (TAA) involve the ascending aorta. The causes are multiple. It is rarely an atheromatous aneurysm essentially affecting the descending intrathoracic or thoraco-abdominal aorta but constitutional abnormalities of the aortic wall are more common, with involvement of the media and connective tissue degradation. This can be genetic in origin and may be part of a syndrome (Marfan, Loeys-Dietz or type IV Ehlers-Danlos syndrome). TAA may also be associated with an aortic bicuspid valve or caused by degenerative or inflammatory pathology. Hypertension — like advanced age and male gender — induces expansion of the diameter of the ascending aorta [13].

A TAA is usually diagnosed by ultrasonography. CT scan or MRI is only usually carried out later to establish a more accurate anatomical evaluation. Ultrasonography is used to measure the four aortic diameters (annulus, Valsalva sinus, sino-tubular junction, and sub-coronary aorta). The aneurysm may be restricted to the Valsalva sinus or segment 1 of the aorta, or it can cause annulo-aortic ectasia. It is often associated with possible major aortic insufficiency. The upper normal threshold aortic diameter at the Valsalva sinus has been defined in both men and women at less than 2.1 cm/m^2 [14]. If ultrasonography shows dilatation of the initial aorta, the examination should be repeated every year (or even every 6 months), depending on the diameter measured.

To reduce the risk of vascular disease in hypertensive patients with thoracic aortic disease, the 2010 ACC/AHA guidelines recommended (class I) administering antihypertensive therapy to bring BP to less than 140/90 mm Hg (130/80 mm Hg if there is intercurrent diabetes or chronic renal disease) [15]. In patients with thoracic aortic aneurysm, BP should be decreased to the lowest point the patient can tolerate, using beta-blockers, ACE inhibitors, or ARBs (class IIa). Unless contraindicated, beta-blockers (class I) should be administered to all patients with Marfan's syndrome who have an aortic aneurysm, to reduce the rate of aortic dilatation. The beneficial effect of beta-blockers in this situation has long been recognized [16]. In Marfan's syndrome, prescribing an ARB (losartan) is reasonable to reduce the rate of aortic dilatation (class IIa). ACE inhibitors (perindopril) also seem to be effective at slowing aortic expansion [17]. It is recommended that the patient stop smoking (class I), and a statin should be prescribed if there is atherosclerosis (class IIa).

The purpose of prophylactic surgical repair is to reduce the risk of aortic rupture. Although not all patients with dissection of the thoracic

aorta may have major dilatation of the initial aorta [18], the risk of rupture increases with aortic diameter. Surgical repair is therefore recommended in patients with asymptomatic TAA in whom the ascending aorta or aortic sinus diameter is 55 mm or greater (class I) [15]. In patients with Marfan's syndrome or other genetically mediated disorders (including a bicuspid aortic valve), or if the aortic growth rate is over 5 mm per year (class I), elective surgery is indicated at smaller diameters (40–50 mm depending on the condition).

Thoracic aortic dissection/haematoma

Aortic dissection (AD) is characterized by the rapid appearance of an intimal flap separating the true aortic lumen from a false channel. This problem is rare with an estimated prevalence of between 0.5–3/100,000 inhabitants per year [19]. ADs are classified in two different types: type A involves the ascending aorta (Figure 2) whereas in type B the ascending aorta is untouched. The main predisposing factors are structural abnormality of the aortic wall — either constitutional (Marfan, type IV Ehlers-Danlos or Loeys-Dietz syndrome) or acquired (atherosclerosis and aortitis) — and hypertension. The prevalence of hypertension is therefore very high in patients with AD: 60–70% of patients with a history of AD had high BP prior to the accident [20]. In patients with thoracic AD, the prevalence of OSA is high and respiratory events are more severe [21]. This has led to a proposal that OSA should be systematically investigated following AD. AD has a very poor prognosis with high morbimortality, not only in the acute phase but throughout follow-up [22].

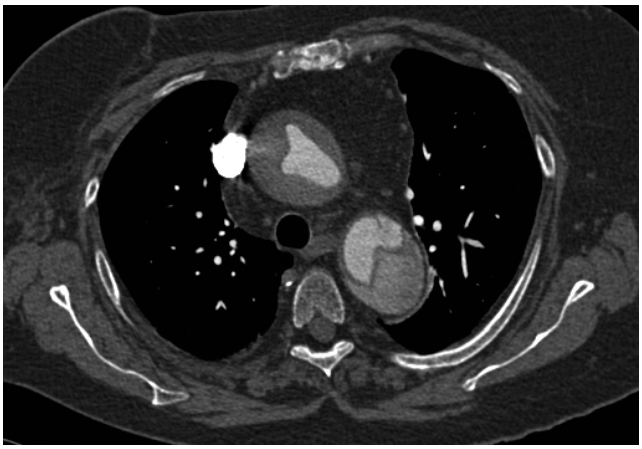

Figure 2. CT scan with contrast injection: type A aortic dissection

Treatment for type A AD is surgical with replacement of the ascending aorta. Most type B ADs are treated with drugs, sometimes with a complementary endovascular or surgical procedure. Although prognosis is more favourable in type B AD, the risks of aortic rupture, visceral ischaemia, and death are still high. These events are all the more common if the false channel remains patent, if the initial aortic diameter is large, if its expansion is rapid, or if BP remains uncontrolled [23, 24].

An intramural hematoma of the thoracic aorta (AH) is a haemorrhage that dissects the aortic wall. An intimal lesion — a tear, ulcer, or ruptured plaque — is often detected. AH tends to strike patients older than those who have had AD and develops at atheromatous lesions, usually against a background of long-standing, uncontrolled hypertension [25]. Type A AH often deteriorates to AD with a high risk of mortality: surgical repair is indicated. Type B AH can be treated with drugs, possibly with a complementary endovascular or surgical procedure.

AD and AH constitute life-threatening emergencies which require immediate, multidisciplinary care [26], always including intravenous antihypertensive medication — often a combination of a beta-blocker (labetalol) and a vasodilator (nitroprusside or nitroglycerin) — to bring systolic BP to less than 100 mm Hg [27].

Patients who have experienced AD or AH — whether or not they have been operated on — should be monitored for a long time to cut down the risk of complications or recurrence [28]. This should include both clinical monitoring and radiology. Despite a clinical consensus on the importance of BP control after AD, only two studies have evaluated the effectiveness of control following AD. The first, conducted in patients with a history of chronic type A AD, showed that close BP monitoring (self-measurement) was associated with better long-term prognosis [29]. The second found a prevalence of uncontrolled hypertension in 60% of 40 patients with chronic AD [30]. To date, there are no specific guidelines for BP monitoring in these very high-risk patients. A threshold of 135/80 mm Hg has been proposed for patients who have had surgery for AD [27]. To achieve this, it is important not to hesitate to prescribe several different classes of antihypertensive drugs, especially beta-blockers. The same is true for AH, in which it has been shown that failure to prescribe a beta-blocker is predictive of poor outcome [31]. Static physical exercise should be limited in the months following AD or AH.

Conclusion

Abnormalities of the aortic wall can promote the development of aneurysms which are very likely to rupture. When such an abnormality is detected, everything must be done to minimize this risk, including drug treatment followed by imaging, surgery, or prophylactic endovascular treatment. In addition to rupture, AD or AH can suddenly develop, necessitating emergency care. All these pathologies — especially AD and AH — are promoted by hypertension. In these situations, drug treatment is based on beta-blockers and/or renin–angiotensin system antagonists.

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