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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

Krzysztof Narkiewicz

ESH Newsletter Editor 2000–2005

ESH Newsletter Editor 2005–2011
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 (chlo+thiazide) was found to be effective compared with standard therapy 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) [7]. 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 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/b-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 event 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 12,963 patients (36%) with diabetes were compared to diabetes without treatment and with diabetics that were treated with chlorthalidone, amlodipine, or losinopril. 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 [16].

The Anglo-Swedish Cardiac Outcomes Trial (ASCOT) has shown substantial benefits in patients randomised to a treatment based on amlopidine, 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 intervention prematurely became of the difference in all-cause mortality, indicating the benefits of an amlopidine-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 amlopidine-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 andamlodipine 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 4,733 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, 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%) 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 level 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.

References

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 $\geq 140$ mm Hg or diastolic blood pressure $\geq 90$ 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 $\geq 140/90$ 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 $\geq 3$ 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 at reducing the risk of developing severe hypertension.

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

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Normal/Abnormal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin and haematocrit</td>
<td>Haemoconcentration supports diagnosis of gestational hypertension without proteinuria. Levels may be low in severe cases because of haemolysis.</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Low levels $&lt; 100,000 \times 10^9/L$ 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*</td>
</tr>
<tr>
<td>Serum AST, ALT</td>
<td>Elevated levels suggest hepatic involvement. Increasing levels suggest worsening severity</td>
</tr>
<tr>
<td>Serum LDH</td>
<td>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*</td>
</tr>
<tr>
<td>Proteinuria (24-h urine collection)</td>
<td>Standard to quantify proteinuria. If $&gt; 2$ g/day, very close monitoring is warranted. If $&gt; 3$ g/day, delivery should be considered</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Dipstick test for proteinuria has significant false-positive and false-negative rates. If dipstick results are positive ($\geq 1$), 24-h urine collection is needed to confirm proteinuria. Negative dipstick results do not rule out proteinuria, especially if DBP $\geq 90$ mm Hg</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>Elevated levels aid in differential diagnosis of pre-eclampsia and may reflect severity</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Levels drop in pregnancy. Elevated levels suggest increasing severity of hypertension; assessment of 24-h creatinine clearance may be necessary</td>
</tr>
</tbody>
</table>

*HELLP — Haemolysis, Elevated Liver enzyme levels, and Low Platelet count
Central alpha agonists
- Methyldopa is the drug of choice

\[ \beta \]-blockers
- Atenolol and metoprolol appear to be safe and effective in late pregnancy

Alpha-\[ \beta \]-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 calcium in preventing pregnancy-induced hypertension 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 gestation-associated hypertension. Women with pre-existing hypertension should probably 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 women with pre-existing hypertension.

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 $\geq 170$ or DBP $\geq 110$ 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 considered. Intravenous hydralazine should not 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 volumes are 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.

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. Bromocriptin, 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.

References

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 countries supported the “rule 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 population, the rates of awareness and treatment have increased since the late 1990s, 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 values were higher [18].

The BP CARE Study derived data about hypertensive patients from Eastern European countries (Albania, Belarus, Bosnia, the Czech Republic, Latvia, Lithuania, Poland, Russia, Serbia, and Ukraine), showing that baseline blood pressure values were higher [18].

Inadequate blood pressure control has been 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 drugtherapy and is not a reflection of the white-coat effect [20, 21].

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

Figure 1. Percentage of patients with controlled blood pressure (< 140/90 mm Hg) in different countries around the world [3–4]
Table 1. Percentage of treated hypertensive patients with satisfactory blood pressure control [17, 18]

<table>
<thead>
<tr>
<th>DBP controlled</th>
<th>SBP controlled</th>
<th>SBP and DBP controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 140/90 mm Hg (clinic)</td>
<td>17.5%</td>
<td>12.6%</td>
</tr>
<tr>
<td>&lt; 120/85 mm Hg (24 hour)</td>
<td>26.5%</td>
<td>16.4%</td>
</tr>
</tbody>
</table>

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.

References

Hypertension in chronic renal failure 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal glomerulosclerosis</td>
<td>75–85%</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>65–75%</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>60–70%</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>35–45%</td>
</tr>
<tr>
<td>Mesangio proliferative glomerulonephritis</td>
<td>30–40%</td>
</tr>
<tr>
<td>IGA nephropathy</td>
<td>20–30%</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>10–15%</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>15–25%</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>55–65%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Examination</th>
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</thead>
<tbody>
<tr>
<td>Complementary examinations</td>
</tr>
<tr>
<td>Renal function</td>
</tr>
<tr>
<td>Determination of serum creatinine; cystatin C, creatinine clearance, MDRD or Cockcroft-Gault formulas Urine: quantification of proteinuria; micro- or macroalbuminuria; protein/creatinine ratio Urine sediment, microhaematuria, casts</td>
</tr>
<tr>
<td>Renal morphology: renal ultrasonography</td>
</tr>
<tr>
<td>Renal morphology and function: urography, scintigraphy and isotopic renal flow</td>
</tr>
<tr>
<td>Blood sample determinations: haemoglobin, leukocytes, platelets, urea, uric acid, calcium, phosphorus, transaminases, ionogram and acid-base measurements</td>
</tr>
<tr>
<td>Systemic and viral disease with renal involvement markers: complement, cryoglobulins, ANA anti-DNA, immunoglobulins, ANCAs, viral B and C, and HIV serology</td>
</tr>
<tr>
<td>Renal vascularization: scintigraphy, renal arteriography</td>
</tr>
<tr>
<td>Renal histological study: renal biopsy</td>
</tr>
</tbody>
</table>
Non-pharmacological treatment

- Sodium intake < 60 mmol/day
- Protein intake 0.8–1.2 g/kg/day
- Phosphorus intake < 750 mg/day
- Caloric intake > 35 calories/kg/day
- Increased calcium intake

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 in 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 arterioles and arterioles reducing renal interstitial 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. Dihydropyridines can cause vasodilatation of the afferent arteriole and a decrease in intraglomerular pressure [14]. Diltiazem and verapamil seem to provide greater kidney protection. Mannitol and gynaecomastia.

Combination therapy

- ACEI, ARB or RI + diuretics
- ACEI, ARB or RI + calcium-antagonist
- Beta-blockers + diuretics
- Antihypertensive + statins + antiplatelet treatment

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 diuretic 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.

Alpha-blockers can be used not only for their vasodilator properties but also for their antiproiferative, platelet antiaggregant, and antithromogenic effects. They are indicated in benign prostatic hypertrophy. Alpha-blockers are widely used in indications in these types of patients since they are characterized by sodium and water retention [16]. When

References

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 dilatation). 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, which affects young women (fibrinoidplastic 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 older adult, the renal arteries men over the age of 60 and is more commonly precipitated by a haemodynamically significant stenosis of a renal artery or 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% to patients with coronary disease to 50% in those with diffuse atherosclerotic 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 (fibrinoidplastic 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 older adult, the renal arteries men over the age of 60 and is more commonly precipitated by a haemodynamically significant stenosis of a renal artery or 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% to patients with coronary disease to 50% in those with diffuse atherosclerotic 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].

**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, more than 50% of the renal stenosis is not detected by CTA, due to a mixing of small veins in the renal parenchyma in the early phase of the exam. This manoeuvre does not provide physiological assessment of the severity.

- **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 major drawbacks of DDU are operator-dependence and lack of uniformity in diagnosis. To assess 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 81,471 patients [13]. A peak systolic velocity more 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 (RI > 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)

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td>Abrupt onset at age &gt; 60 years old</td>
</tr>
<tr>
<td>Severe hypertension</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Obstructive vascular disease (cerebrovascular, coronary, peripheral)</td>
</tr>
<tr>
<td>Abdominal bruit, flank bruit or both</td>
</tr>
<tr>
<td>Unexplained azotaemia</td>
</tr>
<tr>
<td>Discrepancy in kidney sizes by more than 1.5 cm with cortical scarring (for unilateral RVH)</td>
</tr>
<tr>
<td>Azotaemia induced by treatment with ACEI/ARB</td>
</tr>
<tr>
<td>Flash pulmonary oedema</td>
</tr>
</tbody>
</table>

**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.

**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, preserve and 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 ACE/ARB in patients with severe and bilateral lesions may cause haemodynamic intraglomerular alterations that determine a loss of renal function. 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 5 years of evolution), especially in patients with renal failures [35].

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 without anticoagulation. A review of the literature [24] conducted a meta-analysis of 600 patients and 100 surgical interventions. A systematic review [21] 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 these controlled studies that there was no difference in mortality at six months with similar results. The angioplasty treatment improved the patient's life affected by renal failure, stroke, and death, doing a better treatment, 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. The CORAL study is a randomized, 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 [10, 19, 20, 27, 30, 31]. The criteria followed to assess the calibre of the artery according to the complexity of their lesions and the experience of each centre.

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

### References

ISOLATED SYSTOLIC HYPERTENSION: CARDIOVASCULAR RISK AND TREATMENT BENEFITS

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2Department of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford, United Kingdom

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 lamina 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 MRHH 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 AT1 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 AT1 receptor antagonists are advised for treatment of patients with ISH [1, 2].
References


15. Koren MJ, Devereux RB, Casale PN, et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Am Intern Med 1991; 114: 345–352.


PATIENT ADHERENCE AND PHARMACOLOGICAL TREATMENT OF ARTERIAL HYPERTENSION

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Introduction
Former US Surgeon General C. Everett 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 [3]. Results from pharmacodynamic and pharmacokinetic 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 stated that compliance could be defined as ‘the degree to which the patient conforms to the 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 prescribed 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 patient’s compliance through pill counts, prescription refills, electronic monitoring of medication use). Each method has its advantages and disadvantages. For example, pill counts and patient diaries allow 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®), 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 methods, 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 phase of 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, if a patient 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.

<table>
<thead>
<tr>
<th>Disease related</th>
<th>Patient related</th>
<th>Physician related</th>
<th>Treatment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic condition</td>
<td>Denial of disease state</td>
<td>Lack of time</td>
<td>Complexity of dosing regimen</td>
</tr>
<tr>
<td>Asymptomatic No immediate consequences of non-persistence or poor execution</td>
<td>Particular beliefs</td>
<td>Failure to increase therapy to reach treatment goal</td>
<td>Duration of treatment</td>
</tr>
<tr>
<td>Low education level</td>
<td>Lack of knowledge of disease</td>
<td>Long waiting time in office</td>
<td>Non-managed side effects</td>
</tr>
<tr>
<td>Male gender</td>
<td>Lack of involvement in treatment plan</td>
<td>Lack of communication and integrated care between physician, patient and pharmacist</td>
<td>Costs of treatment</td>
</tr>
<tr>
<td>Missed appointments</td>
<td>Specificity of care in adherence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Risk factors for non-adherence to antihypertensive treatment [13, 27, 28]
Studies | n | Outcome (persistence) | AT-1 blockers | ACE-inhibitors | Calcium antagonists | Beta-blockers | Diuretics
--- | --- | --- | --- | --- | --- | --- | ---
Jones, 1995 | 10,222 | 6-month persistence | ne | 45% | 41% | 49% | 41%
Bloom, 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% | 58% | 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

References

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. Vasocstriction 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 commonly co-exist. Cyclosporin nephrotoxicity alone does not explain 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.

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 myocardial 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.

References
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 than 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 LVH is induced.

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 LVH 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 than 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, 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 necropsy. Measurements of LV internal 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 threshold of LVH is somewhat arbitrary and is considered to be averaged LV mass of 150 g/m² in men and 110 g/m² in women [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 remodeling 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 inappropriate) 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.

**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 and observational studies [5].

Despite the fact that echocardiography 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 g/m² (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...
antihypertensive treatment, and were followed according to a clinical prospec-
tive 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 to assess if greater incidence of cardiac events and higher mortality or worsening of cardiac failure can be predicted. In patients at lower CV risk (based on risk factor evaluation and EKG), echocardiography can modify the therapeutic strategy in patients at increased risk. A reduction of blood pressure values, may determine a significant reduction, and 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 persistence or the development of traditionally defined LVH during treatment is associated with an improvement in prognosis, and the persistence or the development of traditionally defined LVH during treatment should be considered at high risk even if the patient is in clinical control for blood pressure and other risk factor assessment. At the present time regression of LVH represents the most clinically useful intermedi-
ate end-point, together with proteinuria, for the evaluation of the efficacy of antihypertensive treatment.

Conclusions
Patients with LVH at baseline and in whom CV risk reduction has not been reached during antihypertensive treatment should be considered at high risk for cardiovascular events and 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.
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-observer 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 was 0.875 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])

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% confidence intervals)</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age and sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.15</td>
<td>1.05–1.17</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.18</td>
<td>1.16–1.21</td>
</tr>
<tr>
<td>Adjusted for age, sex, and other cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.1</td>
<td>1.08–1.13</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.13</td>
<td>1.10–1.16</td>
</tr>
</tbody>
</table>
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 thickness. 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 hypercholesterolaemic 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 the effect of 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 angiotensin 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 ladinipine or atenolol in patients participated into the ELSA study, suggesting that treatment with a calcium antagonist may slow IMT progression without influencing the characteristics of plaque tissue [25].

Conclusions
An ultrasound examination of the common, bifurcation, and internal carotid arteries should be performed in hypertensive patients with comitant 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.

References

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

<table>
<thead>
<tr>
<th>Antihypertensive treatment</th>
<th>Comparison</th>
<th>Change IMT μm/year (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Placebo</td>
<td>–6 μm (–12 to 0.4)</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>Placebo</td>
<td>–10 μm (–33 to 13)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Diuretics/β-blockers</td>
<td>–3 μm (–5 to –0.3)</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>Diuretics/β-blockers</td>
<td>–5 μm (–9 to –1)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Calcium-antagonists</td>
<td>–1 μm (–5 to 2)</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>Calcium-antagonists</td>
<td>–23 μm (–42 to –4)</td>
</tr>
</tbody>
</table>
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)

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

Patient seated for at least 5 min, with higher 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].

References


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 end 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/114/2/5255). 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 ≥ 95th percentile, measured on at least three separate occasions with the auscultatory method. Children with average of systolic or diastolic BP ≥ 90th but < 95th percentile are classified 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 measurements have 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-diAPAping 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 hypertension), clinical trials; other clinical conditions (autoimmune dysfunction, suspicion of catecholamine-secreting tumours). Concerning home BP measurements, evidence in children and adolescents is promising but limited.

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.

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].

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

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.

Evaluative measurements
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.
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 hindered the planning of randomized controlled 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, leads to death 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 body fat mass in children with renal disease.

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 dysplasia, 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 treatment should first target BP 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 or renal outcomes, 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 should be initiated. When BP does not respond adequately or significantly to non-pharmacological treatment, a second step is to lower BP, aiming for a 24-hour target below the 50th percentile, contrasting with significantly higher levels observed in children and adolescents [4].

In children with chronic kidney disease, there is preliminary evidence that a 24-hour target below the 50th percentile, contrasting with significantly higher levels observed in children and adolescents [4].

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 may be administered. The antihypertensive response from the prospective randomized ESCAPE trial that strict BP control aiming for a 24-hour target below the 50th percentile of mean arterial pressure with the addition of a diuretic and a β-blocker therapy during 2 years is better 5-year renal survival, despite a return of proteinuria prior to treatment [22]. Analysis by achieved BP levels shows similar renal outcomes with achieved BP levels of a 75th percentile with significantly higher achieved BP levels of a 75th percentile is associated with an attenuated 24-hour BP above the 90th percentile.

The role of a target BP of a 75th percentile is that it represents an appropriate BP level in children with even mild baseline proteinuria, whereas no benefit of more intense BP lowering is found in children with non-proteinuric disease.

Combination therapy

In children with renal disease, monotherapy is often not sufficient to achieve adequate BP control. Therefore, early 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 blood pressure reduction and a better 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 combination of two drugs are usually used in children, since individual-based contributions are preferred, but fixed-dose 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 at-risk 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, obesity, and other cardiovascular risk factors. Furthermore, r habilization of apoB and high level of apoprotein B to cholesterol (apoB/cholesterol × 100%) has appeared to be associated with the progression of early atherosclerotic plaques, and the long-term effects of statins in children are unknown. The use of ezetimibe is approved in the USA (but not in Europe) only for those rare children with familial hypercholesterolaemia or with sitosterolaemia. Bile-acid sequestrans are difficult to tolerate over the long term. Fibates 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% have impaired fasting glucose tolerance (IGT), 1% impaired glucose tolerance to normal. Metformin is the only oral medication in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of childhood and adolescent obesity. Evaluation of the evidence supporting the use of metformin in children with type 2 diabetes, 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 regular physical activity) is probably the best treatment choice for children with type 2 diabetes, with 60% of cases of type 2 diabetes and 5% have impaired glucose tolerance (IGT), 1% impaired glucose tolerance to normal. Metformin is the only oral medication in children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of childhood and adolescent obesity. Evaluation of the evidence supporting the use of metformin in children with type 2 diabetes, 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 regular physical activity) is probably the best treatment choice for children with type 2 diabetes, with 60% of cases of type 2 diabetes and 5% have impaired glucose tolerance (IGT), 1% impaired glucose tolerance to normal. Metformin is the only oral medication in children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of childhood and adolescent obesity. Evaluation of the evidence supporting the use of metformin in children with type 2 diabetes, and 0.2% type 2 diabetes [11].

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 and health care providers. It is therefore important to educate school 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 councils.

References

**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 clinic 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 peripheral 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 hyperinsulinaemia 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 therapeu tic 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 in patients with coronary artery disease (CAD) or left ventricular hypertrophy (LVH) are multiple and are not simply limited to the effects of blood pressure per se. 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.

References

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 resistant ≥ 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 controlled 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 SBP and non-evidence of improvement of hypertension control 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 study by Tanigawa 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 125I 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/m²) 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- to 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 increases in 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

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<tr>
<th>Causes of resistant hypertension</th>
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<td>Poor adherence to therapeutic plans</td>
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<td>Failure to modify lifestyles, including:</td>
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<tr>
<td>• weight gain</td>
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<td>• high alcohol intake (NB: binge drinking)</td>
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<tr>
<td>Continued intake of agents that raise blood pressure (liquorice, cocaine, glucocorticoids, non-steroidal anti-inflammatory drugs, etc.)</td>
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<tr>
<td>Obstructive sleep apnoea</td>
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<tr>
<td>Unsuspected secondary cause</td>
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<td>Irreversible or minimally-reversible organ damage</td>
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<tr>
<td>Volume overload due to:</td>
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<tr>
<td>• inadequate diuretic therapy</td>
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<tr>
<td>• progressive renal failure</td>
</tr>
<tr>
<td>• high sodium intake</td>
</tr>
<tr>
<td>• hyperaldosteronism</td>
</tr>
</tbody>
</table>

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 criteria of the patients, target-organic 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 to the treatment of RH patients to improve blood pressure control [49–51]. 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 25 mg/d) is considered in all RH 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]. The addition of target-organic blockers permanent-

References


2. McGovern FJ, Wright JT, Bener DJ, Kahl H. Results of a retrospective, observa-


5. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovas-


8. Park J, Campese V. Clinical characteristics of resistant hypertension: The importance of

9. Burnier M, Schneider MP, Chioléro A, Stubi CLF, Brunner HR. Electronic compliance moni-


12. Mejia AD, Egan BM, Schork NJ, Zweifler AJ. Artefacts in measurement of blood pressure

13. Alderman MH, Budner N, Cohen H, Lamport B, Ooi WL. Prevalence of drug resistant hyper-


15. Schlaich M, Grötzinger S, Inagaki K, Vijaykumar N, Weber M. Renal sympathetic denerva-


17. Schlaich MP, Sobotka PA, Krum H, Lambertz J, Wieland E, et al. Renal sympathetic denerva-


20. Burnier M, Schneider MP, Chioléro A, Stubi CLF, Brunner HR. Electronic compliance moni-

21. Liu W, Xu T, Su CH, Zhang T, Zhao X, et al. Sympathetic nervous system predominance such as obesity [61], obstructive sleep apnoea


24. Management of patient compliance in the treatment of hypertension: report of the NHLBI Panel on...
Introduction
The prevalence of type-1 diabetes has 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 5% per year [14]. 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 enzymoimmunonassay 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].

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 between-time BP and urinary albumin excretion has been previously documented, and the 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 re-illumination 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 age, sex, 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–aldosterone 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 increase 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 DRECT 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.

References


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 receive a 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

<table>
<thead>
<tr>
<th>Drugs (class)</th>
<th>Interaction with</th>
<th>Mechanism</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Verapamil, diltiazem</td>
<td>Additive effects</td>
<td>A-V conduction impaired; risk of A-V block</td>
</tr>
<tr>
<td></td>
<td>Oral antidiabetics</td>
<td>Beta-receptor blockade</td>
<td>Symptoms of hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>Broncho-spasmolytic agents</td>
<td>Beta-receptor blockade</td>
<td>Suppression of the bronchospasmodic effect</td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td>Beta-receptor antagonism</td>
<td>The inotropic action of dobutamine is inhibited</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Enzymatic inhibition (CYP-450)</td>
<td>Accumulation of metoprolol</td>
</tr>
<tr>
<td></td>
<td>Propafenone, amiodarone, dronedarone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Digoxin</td>
<td>Hypokalaemia</td>
<td>Digoxin becomes more toxic (arrhythmogenic)</td>
</tr>
<tr>
<td></td>
<td>Lithium ions</td>
<td>Renal excretion of lithium ions impaired</td>
<td>Accumulation of lithium ions</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>Noradrenaline</td>
<td>Alpha-receptor blockade</td>
<td>Noradrenaline shows less vasoconstrictor activity</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td>Alpha-receptor blockade</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>PDE5-inhibitors (sildenafil, tadalafil, vardenafil)</td>
<td>Increased cGMP availability</td>
<td>Severe hypotension</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Verapamil, diltiazem</td>
<td>Beta-blocker</td>
<td>Additive effect</td>
</tr>
<tr>
<td></td>
<td>Azole antimycotics</td>
<td>Enzymatic inhibition (CYP-450)</td>
<td>Accumulation of DHP Ca-antagonist</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Renal excretion of digoxin</td>
<td>Digoxin may accumulate; arrhythmogenic effect</td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors (HIV-treatment)</td>
<td>Inhibition of hepatic degradation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>Ibid.</td>
<td>Ibid.</td>
</tr>
<tr>
<td>Dihydropyridine Ca-antagonists</td>
<td>Beta-blocker</td>
<td>Beta-receptor blockade</td>
<td>Suppression of reflex tachycardia (favourable)</td>
</tr>
<tr>
<td></td>
<td>Beta-blocker (sildenafil)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Beta-blocker</td>
<td>Additive effect</td>
<td>A-V conduction impaired; risk of A-V block</td>
</tr>
<tr>
<td></td>
<td>Diuretics (thiazide)</td>
<td>Enzymatic inhibition (CYP-450 system)</td>
<td>Accumulation of febuxostat, verapamil</td>
</tr>
<tr>
<td></td>
<td>Diuretics (K+-sparing)</td>
<td>Reduced renal excretion of K+</td>
<td>Strong hypotensive action</td>
</tr>
<tr>
<td></td>
<td>NSAID’s including high dose ASA</td>
<td>Retention of Na+ and H2O</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Lithium ions</td>
<td>Reduced excretion of lithium ions</td>
<td>Reduced antihypertensive effects</td>
</tr>
<tr>
<td>AT1-receptor antagonists</td>
<td>DPP4-inhibitor (vildaglaptin)</td>
<td>Inhibition of substance-P degradation [12]</td>
<td>Increased risk of angioedema</td>
</tr>
<tr>
<td></td>
<td>Virtually the same as ACE-inhibitors (except of DPP4-inhibitor)</td>
<td>Interactions as ACEIs (see above)</td>
<td>Described before</td>
</tr>
<tr>
<td>Centrally acting antihypertensives</td>
<td>Alpha-methyl-DOPA</td>
<td>Fe2+-ions</td>
<td>Enteral absorption of α-methyl-DOPA</td>
</tr>
<tr>
<td></td>
<td>Clonidine</td>
<td>Tricyclic antidepressants</td>
<td>Antagonism of central α2-adrenoceptors</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td>Beta-blockers</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Both clonidine and α-methyl-DOPA</td>
<td>Centrally acting depressant agents (hypnotics, tranquillizers, anoreleptics, anti-epileptics, some anti-depressants, H1-anti-histaminic agents, alcohol)</td>
<td>Additive effect, non-specific</td>
</tr>
</tbody>
</table>
Pharmacokinetic interactions
The interaction in intestinal absorption is best illustrated by an example: tetracyclines and other broad-spectrum antibiotics may impair the absorption of oral contraceptives (in particular those with low-dose progesterones 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, phenytoin, 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 tranquilizers), antipsychotics (neuroleptics, major tranquilizers), 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-methyl-dopa, 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 AT1-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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Increase in BP</th>
<th>Interferes with anti-hypertensive effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetics</td>
<td>Sodium retention</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Erog alkaloïds</td>
<td>Sodium retention</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Sodium retention</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Estrogens and progesterone</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Sodium retention</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Psychotropes</td>
<td>Chlorpromazine, tricyclics, MAO-inhibitors etc.</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Increase in blood viscosity</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Hypothetical (via NO)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Resin</td>
<td>Inhibition of GI, absorption of anti-HT drugs</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Sodium retention</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

References
BENEFICIAL COMBINATIONS OF TWO OR MORE ANTIHYPERTENSIVE AGENTS

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2Cardiometabolic Centre, St. Imre Hospital, Budapest, Hungary

Introduction

In a preceding communication we described the most relevant interactions between antihypertensive drugs and other therapies [1]. In the present paper we will deal with the combination of different types of antihypertensive agents. Only combinations half of which are present in our daily practice and 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 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 mmHg in nephritic hypertension;
• < 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 beta-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 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 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-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) receptor agonists

This combination, which has not been studied on a 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, sympathetic 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, 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 CHF can be treated by this combination. Both types of drugs, as well as being efficacious antihypertensives, are known to display beneficial activity in CHF 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-isaemic 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], amiodipine 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 amiodipine–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 end-point (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-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-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 not only additive but also interactive effects. 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 aldoso-
terone system (RAAS) and the sympathetic nervous system (SNS). The metabolic syndrome has been proposed as a target for SNS-suppressant drugs such as monoamine or rilmenidine, since this syndrome is believed to be partly the result of SNS-hyperactivity.

**AT-**-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 favor 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.

### Drugs

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Potential use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers + diuretics</strong></td>
<td>Hypertension + congestive heart failure (CHF)</td>
</tr>
<tr>
<td><strong>Diuretics + ACE-inhibitors</strong></td>
<td>Hypertension + CHF, Isolated systolic hypertension (ISH), hypertension in the elderly ISH or CHF, ISH</td>
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<tr>
<td><strong>Diuretics + AT-</strong>-blockers</td>
<td>Hypertension + CHF, ISH or CHF</td>
</tr>
<tr>
<td><strong>Diuretics + imidazoline (I1)-receptor agonists</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
</tr>
<tr>
<td><strong>Diuretics + calcium-antagonists (dihydropyridines)</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>Beta-blockers + c- blockers</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>Beta-blockers + ACE-inhibitors</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>Ca-antagonist + j- blockers</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>Ca-antagonist + ACE-inhibitors</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>Ca-antagonists + AT-</strong>-blockers</td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>ACE-inhibitors + AT-</strong>-blockers</td>
<td>Hypertension + CHF, ISH or CHF</td>
</tr>
<tr>
<td><strong>ACE-inhibitors + imidazoline (I1)-receptor agonists</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>Diuretics + beta-blockers + calcium antagonists</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
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<tr>
<td><strong>Diuretics + calcium antagonists + ACE-inhibitors</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
</tr>
<tr>
<td><strong>Diuretics + calcium antagonists + AT-</strong>-antagonists</td>
<td>Hypertension + CHF, ISH or CHF</td>
</tr>
<tr>
<td><strong>ACE-inhibitors + a- blockers + imidazoline (I1)-receptor agonists</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
</tr>
<tr>
<td><strong>ACE-inhibitors + Ca-antagonists + j- blockers</strong></td>
<td>Hypertension + CHF, ISH or CHF</td>
</tr>
</tbody>
</table>

### References

THE CLINICAL VALUE OF AMBULATORY BLOOD PRESSURE MONITORING

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Introduction

In order to facilitate 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 as it is more acceptable to patients [3]. A small number of devices 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 24-h 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 a new patient it is recommended that three nocturnal BP recordings are performed to assess the interval that best reflects 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 position/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] and to a greater extent than general population studies. Furthermore, 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 BP [16]. This has justified the increasing use of ABPM for diagnostic purposes [17]. However, it should be kept in mind that in the general patient population 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 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 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].

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 explain the ability 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 without full recovery during the night, a condition known as morning BP surge, has been investigated in many studies, based on the reports that a pronounced morning BP surge might predict exacerbation of 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 reveals the “dipping” pattern—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 fall of more than 10% of daytime values, respectively [56, 57]. The main limitations of this classification are that nocturnal BP variability is 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 [70]. 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 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]. 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.

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 using ambulatory measurements. 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.
Conclusions

ABPM has opened new horizons for hypertension research, and its pro-
gressively greater use has had a positive impact on clinical practice. Its adap-
tion can therefore be recommended, when facilities are available, in a large
number of patients, as compared to what was indicated in previous rec-
ommendations. The usefulness of ABPM is particularly evident in pa-
ients with consistent discrepancies between clinic and home BP levels, in
those with elevated clinic BP but no evidence of organ damage, in patients
with atypical cardiovascular signs and symptoms, and in patients with 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 poorly understood topics 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.

References

31. Polonia JJ, Santos A, Gama GM, et al. Follow-up clinic and ambulatory blood pressure in untreat-
ed white-coat normotensive patients (evaluation after 2–5 years). Blood Press Monit 1997; 2:
333–338.
33. Wing LMH, Brown MA, Beilin LJ, Ryan P, Reid CM; on behalf of the ANBP2 Management Commit-

34. Mancia G, Parati G. Ambulatory blood pressure monitoring and organ hypertension. Hypertension
38. Pierdomenico SD, Lapenna D, Bucci A, et al. Blood pressure variability and prognosis in uncompli-
40. O’Brien E, Waeber B, Parati G, Staessen J, Myers MG; on behalf of the European Society of
Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25:
1105–1187.
41. Han SH, Kario K, Matsuo T, Kobayashi H, et al. Nocturnal fall of blood pressure and silent cerebrovascular
damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme
by ambulatory blood pressure monitoring. The Multicenter White-coat Hypertension Study. J Hu-
43. O’Brien E, Tilioua R, Metoki H, et al. Progress of “masked” hypertension and “white-coat” hy-
pertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the
44. Fagard RH, Comelli VN. Incidence of cardiovascular events in white-coat, masked and sustained
46. Motschou K, Tilioua R, Metoki H, et al. Progress of “masked” hypertension and “white-coat” hy-
pertension detected by 24-h ambulatory blood pressure monitoring. 10-year follow-up from the
47. Mallon JM, Clerson P, Bobbio G, et al. Predictive factors for masked hypertension within a popu-
by ambulatory blood pressure monitoring. The Multicenter White-coat Hypertension Study. J Hu-
50. Ohkubo T, Kikuya M, Metoki H, et al. Progress of “masked” hypertension and “white-coat” hy-
pertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the
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 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].

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 1. Cardiovascular consequences of smoking

<table>
<thead>
<tr>
<th>Cardiac effects</th>
<th>Coronary arteries:</th>
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<tbody>
<tr>
<td></td>
<td>• atherosclerosis in native circulation</td>
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<td></td>
<td>• restenosis after angioplasty</td>
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<td></td>
<td>• atherosclerosis in bypass grafts</td>
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<tr>
<td></td>
<td>• vasoconstriction</td>
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<tr>
<td>Arrhythmias and sudden death</td>
<td>Left ventricular hypertrophy</td>
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<tr>
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<th>Stroke</th>
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<tr>
<td></td>
<td>TIA</td>
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<td></td>
<td>Recurrent carotid artery stenosis after endarterectomy</td>
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<table>
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<tr>
<th>Other arterial pathology</th>
<th>Aortic atherosclerosis</th>
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<td></td>
<td>Iliofemoral atherosclerosis</td>
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<tr>
<td></td>
<td>Intermittent claudication</td>
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<td></td>
<td>Lower limb ischaemia and amputations</td>
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<td>Recurrent atherosclerosis of bypass grafts</td>
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<td></td>
<td>Abdominal aortic aneurysm</td>
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<td></td>
<td>Renal artery stenosis</td>
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<td></td>
<td>Failure of skin grafts</td>
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<td></td>
<td>Uteroplacental arterial hyperplasia</td>
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<td></td>
<td>Diabetic microangiopathy</td>
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</table>

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

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Rises with smoking</th>
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</thead>
<tbody>
<tr>
<td>Hypertensive smokers:</td>
<td>• are harder to achieve optimal BP control in</td>
</tr>
<tr>
<td></td>
<td>• have a worse prognosis</td>
</tr>
<tr>
<td></td>
<td>• are more likely to have atherosclerotic renovascular hypertension</td>
</tr>
<tr>
<td></td>
<td>• are more likely to develop malignant hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum lipids</th>
<th>Increased levels of LDL-cholesterol, free fatty acids, and triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased HDL-cholesterol level</td>
<td></td>
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</tbody>
</table>

| Obesity | As a rule, smokers have lower body weight |

<table>
<thead>
<tr>
<th>Hemorrheology</th>
<th>Increased fibrinogen, blood viscosity, leukocyte count, haematocrit, and platelet aggregation</th>
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<tbody>
<tr>
<td>Decreased platelet survival and bleeding time, erythrocyte</td>
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<thead>
<tr>
<th>Oral contraceptives</th>
<th>Substantial increase in risk of MI, stroke and thromboembolic events</th>
</tr>
</thead>
</table>

| 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]).
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 assess the readiness of every patient who asks about 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 lay health workers, 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 cardiac vascular event rate increases [19–21].

Two final considerations are related to harm reduction strategy and frequent relapse. Concerning the latter, 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—the poorer 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].

References

3. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of population. It was also observed that the application of nicotine replacement 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.

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

![Figure 2](image_url)
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/systolic 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 anti-hypertensive 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 systolic 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), post-dialysis systolic blood pressure lower than 110 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].

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 definitions 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 1. Aetiology of hypertension in dialysed patients

<table>
<thead>
<tr>
<th>Disease/complication</th>
<th>Hypertension risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium and volume excess due to diminished sodium excretory capacity of kidney</td>
<td>Activates the renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>Increased activity of the sympathetic nervous system</td>
<td>Increased endogenous vasocostructor (endothelin-1, Na-K-ATPase inhibitors, adrenomedullin), and decreased vasodilator (nitric oxide, prostaglandins) compounds</td>
</tr>
<tr>
<td>Frequent administration of erythropoietin</td>
<td>Increased intracellular calcium content, induced by parathyroid hormone excess</td>
</tr>
<tr>
<td>Hyperparathyroidism and hypercalcaemia</td>
<td>Use of recombinant human erythropoietin</td>
</tr>
<tr>
<td>Use of recombinant human erythropoietin</td>
<td>Calcification of arterial tree, arterial stiffness</td>
</tr>
<tr>
<td>Pre-existent hypertension</td>
<td>Nocturnal hypoxaemia, frequent sleep apnoea</td>
</tr>
</tbody>
</table>

Table 2. Algorithm for blood pressure control in dialysis patients

<table>
<thead>
<tr>
<th>Step</th>
<th>Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate dry weight</td>
<td>Determine Hypertension Severity Index</td>
</tr>
<tr>
<td>Initiate non-pharmacological treatment</td>
<td>Initiate non-pharmacological treatment</td>
</tr>
<tr>
<td>Attain dry weight</td>
<td>Start or increase the dose of antihypertensives to maintain blood pressure below 150/90 mm Hg</td>
</tr>
<tr>
<td>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</td>
<td>If blood pressure remains uncontrolled, consider: evaluating for secondary forms of hypertension; peritoneal dialysis bilateral nephrectomy (exceptional)</td>
</tr>
</tbody>
</table>

All Table references are to the editors of the European Society of Hypertension Newsletter: Update on Hypertension Management 2011; 12: No. 21 revised version.
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 in patients with 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 occurrence of intradialytic hypotension [16].

Table 3 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 dialysed patients, even in those who are volume expanded. They are useful in patients with left ventricular hypertrophy, diastolic dysfunction, and stable 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 dialysed 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 dialysers. There is only limited experience with angiotensin II receptor blockers (ARBs) in end-stage renal disease. Losartan does not enhance the risk of 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 dialysers.

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 hypertensive 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 dialysed 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].
### Appendix. Features of frequently used antihypertensive drugs in haemodialysis patients

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

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

HIGH BLOOD PRESSURE, ALCOHOL, AND CARDIOVASCULAR RISK

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\(^1\)Institute of Internal Medicine, Hospital Clinic (IDIBAPS), University of Barcelona, Spain
\(^2\)Faculty of Medicine, Complutense University, Madrid, Spain

Introduction
Several cross-sectional and prospective epidemiological studies have established an empiric alcohol and hypertension link. This observation has been made in Europe, North American, Australian, and Japanese populations and seems independent from adiposity, salt intake, education, cigarette smoking, and other indirect explanations [1–3]. A fair 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].

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 alcoholic 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 dyslipidaemia; 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 not included. In addition, if ethanol withdrawal was 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.

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 myocardopathy 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 pharmaco logical 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 [3]).

<table>
<thead>
<tr>
<th></th>
<th>Sensitive (n = 18)</th>
<th>Non-sensitive (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>39.8 ± 7.1</td>
<td>39.5 ± 8.0</td>
</tr>
<tr>
<td>Daily ethanol intake (g)</td>
<td>219 ± 86</td>
<td>214 ± 72</td>
</tr>
<tr>
<td>TLED (kg/kg)</td>
<td>21.9 ± 13.3</td>
<td>19.3 ± 10.7</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>122 ± 7</td>
<td>121 ± 10</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>92 ± 5</td>
<td>91 ± 7</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>78 ± 6</td>
<td>77 ± 7</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
<td>52.4 ± 2.7*</td>
<td>50.5 ± 3.5</td>
</tr>
<tr>
<td>End-systolic diameter (mm)</td>
<td>34.2 ± 3.0</td>
<td>32.8 ± 3.4</td>
</tr>
<tr>
<td>Interventricular thickness (mm)</td>
<td>10.4 ± 2.2*</td>
<td>8.2 ± 0.8</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>9.8 ± 1.2*</td>
<td>8.5 ± 0.7</td>
</tr>
<tr>
<td>Left ventricular mass (g/m²)</td>
<td>132 ± 23.2*</td>
<td>95 ± 17</td>
</tr>
<tr>
<td>Shortening fraction (%)</td>
<td>34.8 ± 3.8</td>
<td>35.7 ± 4.7</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>52.6 ± 6.11**</td>
<td>57.8 ± 4.9</td>
</tr>
<tr>
<td>m — cortisol (nmol/L)</td>
<td>451 ± 162</td>
<td>513 ± 155</td>
</tr>
<tr>
<td>e — cortisol (nmol/L)</td>
<td>206 ± 108</td>
<td>246 ± 138</td>
</tr>
<tr>
<td>PRA (pmol of angiotensin I h¹ ml¹)</td>
<td>0.68 ± 0.99</td>
<td>0.68 ± 0.66</td>
</tr>
<tr>
<td>Aldosterone (ng/dL)</td>
<td>402 ± 280</td>
<td>460 ± 272</td>
</tr>
<tr>
<td>ANP (fmol/mL)</td>
<td>18.1 ± 22.5</td>
<td>14.1 ± 13.4</td>
</tr>
<tr>
<td>Noradrenaline (pg/mL)</td>
<td>260 ± 137</td>
<td>246 ± 80</td>
</tr>
<tr>
<td>Adrenaline (pg/mL)</td>
<td>71 ± 36</td>
<td>61 ± 33</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>112 ± 71</td>
<td>120 ± 75</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>59.7 (15–357)*</td>
<td>33.1 (9–101)</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>47.9 (15–128)</td>
<td>39.3 (8–79)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>199 (108–855)</td>
<td>116 (21–600)</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; TLED — 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

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 teetotalers [20, 21]. Patients who have one to two glasses of alcohol per day had fewer myocardial infarctions and an improved survival compared to teetotalers. 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 25% 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 glycemic 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.
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 [12].

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 = PMHR-resting HR * [% HR] + resting HR). Moderate intensity is defined as that eliciting 64 to 76% of PMHR, or 40 to 59% HR. 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 < 15 METs-hr/day [25]. There is evidence of cardioprotective and antiatherosclerotic effects of exercise. 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 NO33 activity and increases NO release through the augmentation of shear stress, and thereby is considered generally to lower BP. Kimura T.
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 of 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 less 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 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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**References**

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 CHADS2 or CHA2DS2-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). Anti-hypertensive 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, anti-thrombotic 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 ECGs and ultrasound [23]. Asymptomatic 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 postcharge [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 extrasystoles, ventricular doublets, and salvos. 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.

References
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 morbidity-mortality, even when the number of nocturnal respiratory episodes is lower. Pathophysiological mechanisms are suggested to explain morbidity 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 men [4]. The clinical picture includes four main symptoms: diurnal hypertension, 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 the abnormalities 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 airflow (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: O2 desaturation, increase in Pco2, 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 microcirculatory 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 hypertensinolism [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 AHI was associated with a 1% increase in the relative risk of hypertension, and any 10% fall in nocturnal O2 saturation increases the risk of hypertension by 10%. Another study, the Wisconsin Sleep Cohort Study, with subjects free from cardiovascular 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 detect a clinical BP that 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 more pronounced, and the extent 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 other cardiovascular complications.

Left ventricular hypertrophy and diastolic function in OSA

Left ventricular hypertrophy (LVH) seems to be more pronounced 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 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 explain 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 other cardiovascular complications.

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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 proposed for OSA pathophysics, mainline devices, and upper airway surgery 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 [55–58]. The mean BP reduction with active treatment vs. placebo was 8/4 mm Hg. Three meta-analyses using 19 randomized controlled trials were published in 2007 [56–58]. The mean BP reduction with active treatment vs. placebo was 8/4 mm Hg.

References


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 arterial 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 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 homocysteine [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 to 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 nifedipine [13], which also improves the quality of life [14], and clopidozol, 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 factors 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 [19].

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.

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 antiplatept agents; 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.

References

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 greater importance.

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], whereas new antidiabetic medication, increased glycated haemoglobin (HbA1c), and self-reported diabetes criteria in the LIFE study [13, 14] and both WHO criteria in the HOPE study [15]. It is at present unclear whether such differences are due to specific drug 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.

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

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.

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 disposal by enhancing the effects of insulin. The risk-lowering effect of insulin and preventing hypoglaemia. We may preserve the insulin secretory response of pancreatic beta cells to glucose, which is decreased during hypoglaemia [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], 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 blockers (CCBs). However, in the V-HeFT II trial new-onset diabetes was reduced with ARBs compared with CCBs from 16.4% in the amlo-dipine 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 amiodipine-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 effect [5]. Small doses, however, seem most likely 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 hypoglaemia 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 hypoglaemia 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].

Summary of findings in trials
The majority of hypertensive patients require multiple pharmacological 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-onset 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 blocker (ARBs) may increase insulin resistance, while antagonists such as A2-blockers may 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.

References
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 aneurysms, 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

<table>
<thead>
<tr>
<th>Hypertensive encephalopathy</th>
<th>Severe hypertension associated to acute target organ damage:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• acute coronary syndromes</td>
</tr>
<tr>
<td></td>
<td>• pulmonary oedema</td>
</tr>
<tr>
<td></td>
<td>• acute aortic dissection</td>
</tr>
<tr>
<td></td>
<td>• intracerebral haemorrhage, subarachnoid haemorrhage</td>
</tr>
<tr>
<td></td>
<td>• acute brain infarction</td>
</tr>
<tr>
<td></td>
<td>• acute or rapidly progressing renal failure</td>
</tr>
<tr>
<td>Severe hypertension after thrombolysis for ischaemic stroke</td>
<td></td>
</tr>
</tbody>
</table>

| Pheochromocytoma crisis |

| Guillain-Barré syndrome |

| Spinal cord injury |

| Drugs related hypertension (sympathomimetics, cocaine, phencyclidine, phentolamine, 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 continuous BP monitoring. Cautious 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 antplatelet effect and intracranial pressure increase. The risk of cyanate toxicity is greater when the
drug is used for long periods (days) or in patients with hepatic or renal dysfunction. With nitrprusside, SBP should be cautiously monitored intra-
arterially; hypotension can, however, be managed in most cases by discon-
inuing the infusion. Nitroglycerin is a venous and, to a lesser degree, arteri-
olar dilator, particularly indicated in acute coronary syndromes and pulmo-
nary 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 intracerebral haemorrhage. It may be given also before 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),
also looks promising because it induces vasodilatation without
out 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, myocardiak ischemia may also be in-
duced by acute elevations in BP in patients without haemodynamically re-
levant coronary artery disease through an increase in left ventricular wall stress and
myocardial oxygen consumption. In this setting intravenous vasodilators, such as nitroglycerin and nitrprusside, should be the initial drugs, in combi-
nation 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
nitrprusside in combination with loops diuretics for volume overload con-
rol. 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 prevent arrhythmia and cardiac mortality with the aim of reduc-
ing the risk of major complications. In this preparation is not recommended [14].

Table 4. Drugs for hypertensive urgencies

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

References

5. International Society of Hypertension Working Group. International Society of Hyperten-
7. Goldblatt LB. Blood pressure management in patients with acute ischemic stroke. Hyper-
tension 2004; 43: 137–141.
 receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, place-
11. Anderson CS, Haas CE, Leblanc JM; on behalf of the ACCESS Study Group. Acute postoperative hyperten-
sion is uncommon, particularly after cardiac, 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), nitrprusside, nitro-
glycerin, or fentolapom 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 be achieved by orally administered drugs without hospital admission and with close ambulatory follow-up. Clin-
ical surveillance is advisable during the first few hours after drug administra-
tion. Blood pressure lowering should be gradual: there is no proven benefit from a rapid reduction in BP in asymptomatic patients who have no evi-
dence 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
may further reduce the likelihood of effective BP reduction. The degree of BP reduction induced by sublingual nifedipine can never 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 pres-
sure should be the initial goal of treatment.
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 oscillometric 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 when to start drug treatment if 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 study [40] the angiotensin receptor blocker valsartan and the calcium antagonist amlopidine 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 amlopidine 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 amlopidine-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 angiotensin receptor blocker losartan over the beta-blocker atenolol combined with bendroflumethiazide, but the blood pressure was slightly higher in the latter treatment arm. However, in the ACCOMPLISH trial a fixed amlopidine-ACEI combination was superior to diuretic-ACEI in reduction of endpoints irrespective of age despite little blood pressure difference between the treatment arms [43].
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, convertase enzyme inhibitors, and angiotensin-II-receptor blockers.

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.

References

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 intrinsinc myocardial contractility, adverse chamber remodeling and left ventricular hypertrophy, coronary myocardial 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 myocyte width, which in turn increases wall thickness, and the development of concentric remodelling or hypertrophy [7]. Myocyte 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, and cardiotoxin-1, and growth factors, such as insulin like growth factor, have profibrotic effects and favour perivascular and interstitial fibrosis. Myocyte 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].

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 physiologic 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 function, 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 transmural flow combined with pulsed wave Doppler 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 1. Characteristics of patients with systolic or diastolic heart failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diastolic heart failure</th>
<th>Systolic heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Frequently elderly</td>
<td>All ages, typically</td>
</tr>
<tr>
<td></td>
<td>50–70 yr</td>
<td>40–90 yr</td>
</tr>
<tr>
<td>Sex</td>
<td>Frequently female</td>
<td>More often male</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preserved or normal, approximately 40% or higher</td>
<td>Depressed approximately 40% or lower</td>
</tr>
<tr>
<td>Left ventricular cavity size</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal, often with concentric left ventricular hypertrophy</td>
<td>Dilated</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually present</td>
<td>Sometimes present</td>
</tr>
<tr>
<td>Chest radiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congestion with or without cardiomegaly</td>
<td>Congestion and cardiomegaly</td>
</tr>
<tr>
<td>Gallop rhythm present</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fourth heart sound</td>
<td>Third heart sound</td>
</tr>
</tbody>
</table>
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 amlopidine 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 in diabetics with left ventricular hypertrophy, the effect of treatment with an angiotensin II receptor antagonist (ARB) 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 followings of antihypertensive therapy. The SOLVD study [25] has already showed a beneficial effect of treatment with ACE inhibitors in comparison to a placebo in hypertensive patients, superimposable to that obtained in normotensive subjects.

The 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 peripheral 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 CHARMI (Cardiac Insufficiency Bisoprolol Study: Assessment of Reduction in Mortality and Morbidity) study [26] showed that in patients with diastolic dysfunction (Preserved group) treated with carvedilol 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 (L-Prevent) evaluated the effect of an ARB (irbesartan) in patients with diastolic dysfunction, and did not show a significant benefit with 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 aldosterone blocker 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 by 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, beta-blockers, calcium antagonists, and alpha-blockers. Angiotensin II 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.

### References

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. Measuring 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 mechanical analysis 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 endpoint 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.

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

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-

HYPERTENSION AND MACROVASCULAR DISEASE

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-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.

### 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]).

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

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

### References

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 ago, 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 sub-study 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 differenties 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. 19.9% 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].

Pathophysiological pathways in hypertension leading to sexual dysfunction

Penile erec tion 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 atherosclerotic 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 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 definitive conclusions, particularly in regard to the newer generation antihypertensive agents. Indeed, the beneficial effects of ADE on erectile dysfunction was recently questioned by the outcomes of the study of the ONTARGET–TRANSCEND trials, in which ARB administration neither significantly improved nor impaired erectile function [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 medications 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 evaluating effects of different antihypertensive drugs on sexual dysfunction emerges as extremely important.

Sexual dysfunction and hypertension: a mutual target for S-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 therapeutic 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 adds to the initiation rather than reinitiation of sexual 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, the novel, long-acting PDE-5 inhibitor vardenafil 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 hypertension. This 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.

References

DISCOVERING THE GENETIC DETERMINANTS OF HYPERTENSION

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Hypertension (HTN) and blood pressure (BP) are examples of complex (polygenic) traits. Progress in the genetic dissection of these traits is challenging, but the era of GWAS has dramatically increased the prospect and obstacles to future progress in blood pressure genetics.

Gene mapping studies in hypertension

There are some key points 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. Most GWAS results are due to rare variants with large effect sizes and these account for less than 1% of human HTN. The high prevalence of essential HTN and the rare diseases that map to the BP phenotype suggest that these trends can 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 complex traits such as blood pressure or hypertension. The current popular method to observe 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 observe P-values to be corrected because highly significant results can occur by chance given the number of tests performed in GWAS.

Linkage and candidate gene studies

Initial approaches to each of identifying gene 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 is the candidate gene study that relies 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 relation to the inheritance patterns. Each independent marker in genetic 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. Linkage mapping is used in linkage disequilibrium (LD) maps to identify genetic markers that have low LD between each other and have a very small fraction of the overall BP variation. Attempts have been made to develop a risk score that estimates the conjoint effect of the top hits to be several mm Hg [28].

Genome-wide association studies

The CD:CV framework requires population-wide genotyping of very large numbers of individuals to identify disease-associated genetic variants. The GWAS almost always 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, independent of the causal gene. This results in an LD peak, which is identified by the GWAS hits. The GWAS hits, only two loci contained known BP genes. The SNP rs17367504 is correlated with plasma atrial natriuretic peptide in hypertension and hypokalaemia, making this a more likely candidate gene than the other causal BP genes.

The effect sizes of all the variants listed in Table 1 are modest, with a per SNP effect of 0.5–1.0 mm Hg SBP and 0.3–0.6 mm Hg DBP. One study suggested that the apparent association is not due to genotyping artefacts is the presence of multiple correlated SNPs at a locus with comparable association. Techniques that account for genetic and environmental factors. The strength of the evidence for all of the genetic variants involved in HTN should provide new insights into the disease susceptibility, progression, and severity, leading to novel pharmacological targets.

Hypertension (HTN) and blood pressure (BP) are examples of complex (polygenic) traits. Progress in the genetic dissection of these traits is challenging, but the era of GWAS has dramatically increased the prospect and obstacles to future progress in blood pressure genetics.
**Table 1. Genome-wide association studies: replicated findings for BP and HTN**

<table>
<thead>
<tr>
<th>Chr</th>
<th>SNP</th>
<th>Position</th>
<th>Ethnicity</th>
<th>N</th>
<th>Phenotype</th>
<th>Risk allele</th>
<th>Risk allele frequency</th>
<th>OR or β</th>
<th>p</th>
<th>Nearest gene</th>
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<td>1</td>
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<td>0.49</td>
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<td>1017</td>
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<td>T</td>
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<td>C10orf107, TMEM65D, RKHB1, ARID8, CYP11A1</td>
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<td>6 × 10^-10</td>
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<td>0.31</td>
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<td>ZNF562, PHB</td>
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</table>

**References**

2. Palmer LJ, Cardon LR. Shaking the tree: mapping complex disease genes with linkage disequi-
5. Pilia G, Chen WM, Scuteri A et al. Heritability of cardiovascular and personality traits in 6,148 
6. Newton-Cheh C, Hirschhorn JN. Genetic association studies of complex traits: design and 
8. Ji W, Foo JN, O’Roak BJ, et al. Rare independent mutations in renal salt handling genes con-
9. Ji W, Foo JN, O’Roak BJ, et al. Rare independent mutations in renal salt handling genes con-
10. Geoﬀrey NN, Terwilliger JD, Blangero J. Large upward bias in estimation of locus-specific effects 
    using 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 undervariable phenotypes such as sodium homeostasis, endothelial func-
    tion, 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.
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 which study microcirculation in humans. One area of advancement has been in vivo capillaroscopy of the nailfold [17]. Furthermore, increased wall-to-lumen ratio of retinal arterioles 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.

**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.
References


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 110 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 Brisighella 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 (a systolic BP 8–13 mm Hg; a 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 PHARYLIS (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 dolichol, geranylgeranoc acid, and farnesylnarsenioic 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 reendothelialisation, 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 ischemic attacks [19]. The benefit of lowering both BP and cholesterol was evaluated in two large-scale trials, ALLHAT [20] and ASCOT-LA [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 hypercholesterolemia, 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 (5%) and LDL-cholesterol (16.2%) 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, the rate of nonadherence increased from 8% at year 2 to 17% by year 4. This increase continued at year 5 by a further 8% of 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 pravastatin (5–10 mg/d), a perindopril (4–8 mg/d) or to atenolol (50–100 mg/d) and bendroflumethiazide (12.5–2.5 mg/d) monotherapy [21]. 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 significant. The compliance rate for pravastatin vs. usual 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 in clinical practice. Patients adherence to medications and thus improve the simultaneous management of hypertension and dyslipidemia, which may also improve clinical outcome [26].

References

4. Singh BH, Izzo JL Jr, Wilson MF. Effects of cholesterol on blood pressure response to mental stress. Strazzullo P, Perry SM, Barbatto A, et al. Do statins reduce blood pressure? A meta-analysis 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 significant. The compliance rate for pravastatin vs. usual 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 in clinical practice. Patients adherence to medications and thus improve the simultaneous management of hypertension and dyslipidemia, which may also improve clinical outcome [26].

Conclusions

The 2008 ESC/EAS 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.

19. Amarenco P, Tenke AM. Statins for stroke prevention: disappointment and hope. Circula-
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 mg/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-haemodynamic, 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.

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 the product of hypertension and/or renal risk in non-diabetic subjects [1–11]. Consequently, microalbuminuria is 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 m², 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. Schroeder et al. [13] also showed that normalization of UAE during treatment was associated with a trend towards fewer cardiovascular events as compared with persisting microalbuminuria. Conversely, new-

<table>
<thead>
<tr>
<th>UAE (mg/g)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR stage</td>
<td>Description</td>
<td>[mmol/ L/1.73 m²]</td>
<td>High-normal [15-29]</td>
<td>High ≥ 30-299</td>
</tr>
<tr>
<td>G1</td>
<td>High</td>
<td>&gt; 105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>Optimal</td>
<td>90-105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>Mild</td>
<td>60-90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3a</td>
<td>Mild to moderate</td>
<td>45-90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b</td>
<td>Moderate to severe</td>
<td>30-45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severe</td>
<td>15-29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt; 15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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
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 hypertonics with microalbuminuria may contribute to a better reduction on UAE due to the frequent clustering of cardiovascular risk factors.

References
20. Schmieder (data on file)
HYPERTENSION IN ATHLETES

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Introduction
Blood pressure increases with age. Systolic blood pressure continues to increase through out 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 is 10–25%. WHO defines hypertension as blood pressure that 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 measurement 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 including 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 blood of prohibited substances such as anabolic steroids, erythropoetin, stimulants, and so forth. The uncontrolled use of these agents has been associated with 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 complications, and, accordingly, different groups 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 may be found in hypertensives [12]. Whether or not hypertension in the athlete will trigger or accentuate the cardiac hypertrophy, or athletic exercise in a person with hypertension secondary to hypertension will worsen the hypertension, 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 arthrogenic right ventricular dysplasia, which are 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 sudden death in the young is not known, but hypertensive disease 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 [13]. 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 other cardiovascular conditions by searching for other risk factors, target organ damage and concomitant diseases or accompanying clinical conditions [3]. Diagnostic procedures comprise a thorough history, family and personal 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. Subsequently, additional tests may be ordered, 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 asymptomatic patients with hypertension or hypertension by conventional blood pressure measurements. In patients with hypertension about to engage in hard or very hard exercise (intensity ≥ 60% of maximum) and lower and higher intensity training reduce office and exercise systolic blood pressure by 3.5/3.2 mm Hg [28]. The meta-analysis included nine studies designed to measure the effect of lower and higher intensity training on systolic and diastolic blood pressure. The meta-analysis reported that lower and higher intensity training reduce systolic blood pressure by 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, 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 3.5/0.2 mm Hg [28]. The meta-analysis is based on a study 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 exercise. 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

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

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 risk of cardiovascular complications, close follow-up is recommended. Drug therapy should be considered if blood pressure elevations persist after several months or weeks, respectively, despite appropriate lifestyle changes. The goal of antihypertensive therapy is to reduce blood pressure to at least 130/80 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. Recent 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 [1]. 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. 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 short term [3, 31, 32] but capacity is 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 but also banned because they only have the potential to increase 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 are 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 recommendations to patients who may have hypertension are based on the need or very hard to limit exercise 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.
Concept and definition
Arterial hypertension is often part of a constellation of anthropometric and metabolic abnormalities that include abdominal obesity, characteristic dyslipidemia 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/NHLBI). 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 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.

Mechanisms of hypertension in MS
Mechanisms involved in MS are obesity, IR, and a constellation of independent factors which tend to produce an atherogenic, vasculopathic, and pro-inflammatory condition [3]. Skeletal muscle and the liver, not adipose tissue, are the two key insulin-resistance 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 factors programming. Superimposing upon these are infections and/or chronic exposure to certain drugs which can also make their contributions. 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 case-control 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 CV 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 [11].

MS and hypertension-induced organ damage
Metabolic syndrome is 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 m².

Evidence is available that aortic pulse wave velocity (PWV) is higher in hypertensives with MS, irrespective of age and systolic blood pressure value. Likewise, an
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 hypertensive patients [4]. Overall, the prevalence 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 PPV [19] or IMT [18] has been evaluated. While progression of PPV 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 to reduce the risk of a CV or renal event to levels observed in patients who have developed type 2 diabetes or hypertension. The aim is to also delay or prevent the progression (as well as to favor regression) of the types of organ damage that are frequently present and have an adverse prognostic significance.

Targeting metabolic syndrome mechanisms

Lifestyle measures

Well-controlled studies demonstrating the benefits 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 with borderline elevations but then with 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 calorie reduction (500–1000 cal/day), on the other hand, is usually effective and beneficial for long-term weight control. A 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 increase 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. Low intake of vegetable 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 drug mechanisms interfering with the mechanisms of MS: insulin-sensitizers and endogenous cannabinoid receptor blockers (CB1 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 an improvement of the status of MS and typical of this condition. A promising new type of drug, 11beta-HSD1 enzyme inhibitors, will come in the near future.

References

**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 hypertensive crisis, 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 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.

**Table 1. Mechanisms that increase the risk of cerebrovascular disease**

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**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 28% (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 groups.

**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, multifogenic, 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 strokes 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 the risk of stroke holds over a wide range of pressures, with a 1% decrease in systolic BP for example, a 11% increase in stroke risk and a 16% increase in the risk of all-cause mortality. This 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 SPRINT 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.

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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 (BPLTCT) [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. This notion is supported by the fact that the therapy 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 BPLTCT 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, hypertension patients aged 80 years of age on average, the optimal 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 classes of antihypertensive drugs (and their meta-analysis and meta-regres- sions) 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 from 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 reduc- tion 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, associated with 5 years of age on average, 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 defini- tive clinical data, current evidence-based guidelines suggest pursuing a cautious approach to reducing BP in the acute setting. In many cases, however, it is not clear whether patients with cerebrovascular 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.

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.

References


Dietary salt 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. 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 practices, several nation-wide initiatives, if 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 BP has been reported 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 2-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 across and within populations, as well as its strengthening with age [5, 6]. Of those, 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 or 3 g/24 h for salt) had little BP increase with age. In the EPIC-Norfolk 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 cardiovascular mortality in men, but the association was only observed in overweight men [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 glomerular clearance was two-fold greater in patients on a high sodium intake (> 200 mmol/day) 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 cardiovascular mortality in men, but the association was only observed in overweight men [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. In a recent study, a negative association was found between dietary salt 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, Stassen 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 a significant reduction in salt intake associated with a greater 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-pharmacological interventions in the elderly (TONE) [28] implemented weight loss and/or sodium reduction in obese patients with 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, a large intervention study was designed 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 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 difficulties in achieving long-term changes in dietary habits, future studies should examine the 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 Trial of Hypertension Prevention I (THOP I) 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) to 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 diets 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

References

2. Denton D, Weisinger R, Mundy N, et al. The effect of increased salt intake on blood pressure of chimpanzees. Nat Med 1999; 1: 1009–1010. These participants were 0.64 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 (THOP I), multiple lifestyle changes were implemented 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 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 (THOP 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 would 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 Trial of Hypertension Prevention I (THOP I) 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.

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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 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 difficulties in achieving long-term changes in dietary habits, future studies should examine the 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 Trial of Hypertension Prevention I (THOP I) 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.

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HYPERTENSIVE RETINOPATHY
Roland E. Schmieder, MD
Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Germany

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 funduscopy 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, funduscopic examination by Keith, Wagner, and Barker in 1939, in which they classified hypertensive retinopathy goes back to the pioneering work by Keith, Wagner, and Barker in 1939, in which they demonstrated the prognostic significance of funduscopy 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, funduscopic examination 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 vasconstriction (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, Wagner, 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].

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriolar narrowing</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Retinal haemorrhages</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Micro-aneurysms</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Hard exudates</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cotton-wool spots</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Optic disc swelling</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular oedema</td>
<td>+</td>
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</table>

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>
<thead>
<tr>
<th>Grade 1</th>
<th>Mild retinopathy</th>
<th>Generalised and focal arteriolar narrowing, arteriolar wall opacification, and arteriovenous nicking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Moderate retinopathy</td>
<td>Flame-shaped or blot-shaped haemorrhages, cotton-wool spots, hard exudates, micro-aneurysms, or a combination of all these factors</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe retinopathy</td>
<td>Some or all of these retinopathy signs, as well as swelling of the optic disc</td>
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| Table 2. Classification of hypertensive retinopathy [9] |
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 SLDVF with AFPPIA 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.

References
2. Gunn RM. Ophthalmoscopic evidence of (1) arterial changes with chronic renal diseases and (2) of increased arterial tension. Trans Ophthalmol Soc UK 1892; 12: 124–125.
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 is associated with increased risk of cardiac 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 the evidence 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 new-onset AF in these trials involving 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 was added to the systolic pressure measure [1]. Other known risk factors for AF are left ventricular hypertrophy, left atrial size, heart failure, valvular (in particular mitral valve) and ischaemic heart disease, male gender, diabetes mellitus, hyperlipidaemia, 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].

Several smaller studies have shown the 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 (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, these trials 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, especially as the definitions and evaluations of AF differ between the trials. Annual ECG recordings may underestimate the prevalence of AF, especially as the definitions and evaluations of AF differ between the trials, and no significant effects of RAS-blockade on the effect on AF, and no significant effects of RAS-blockade on the development of AF as a primary endpoint, but there are several secondary analyses of large randomized trials. However, these trials are not designed for increased risk of AF in hypertensives and look into the effect of different antihypertensive treatment regimens.

In the VALUE trial, more than 15,000 high-risk hypertensive patients were treated with amiodarone (calcium channel blocker (CCB)) or valsartan (ARB), and new-onset AF was a secondary pre-specified endpoint. These patients were hypertensive and no statistically significant difference was seen 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 will be 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 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].

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Several 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 0.69 (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 amiodarone: 13 patients versus 39 patients, respectively (p < 0.01) [17]. Treatment with ARB also 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 groups (treatment regimens inc.). 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 8,048 patients were included (6 hypertension trials, 2 post-myocardial infarction trials, 3 heart failure trials (primary prevention), 8 studies after cardioversion, and 4 on medical prevention of paroxysmal AF.
(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 [22]. In primary prevention RAS-blockade was most effective in patients with new-onset diabetes mellitus and heart failure [23]. 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 seen with the angiotensin II receptor blocker (ARB) [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 and stress on the heart [21]. Reduction of left ventricular hypertrophy by blockers of RAS may influence 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 dilation, and modulation of sympathetic activity [7]. Blockade of RAS may have anti-inflammatory effects that may reduce the risk of tachyarrhythmia and atrial fibrillation, 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 anti-arrhythmic 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 < 0.0001) [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 antithrombotic 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, but calcium lowerers typically do not significantly attenuate the Ca2+ 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 CCBamlodipine in preventing new-onset AF [12]. Diuretics are often included in antithypertensive treatment regimens, but the effect on new-onset AF has seldom been investigated. In the Veterans 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 consequence. 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.
The term “paraganglioma” identifies a category of tumour arising from neuroendocrine cells from the nerve cell line, that is postulated to result from the neuronal network 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 subjects/year) 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, adrenomedullary masses 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 foods containing tyramine or sympathomimetic parmesan cheese, some red wines, orange juice) and some drugs (opiates, histamine, ACTH, glucagon, methylxypic 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 liability and orthostatic hypotension. Symptoms and signs related to increased metabolic rate (heat intolerance, sweating, weight loss) and to increased glycogenolysis (heat intolerance, sweating, weight loss) and to increased glycogenolysis 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 1 (café-au-lait spots, neurofibromas, Lisch nodules, skin freckling), 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, neurofibromatosis, Marfanoid body habitus), or by familial occurrence of pheochromocytomas-paragangliomas without other features.

In addition, as mentioned above, over the last two decades the widespread use of imaging techniques has frequently led 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 (2-methoxydopamine 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 adenoma tumours that are less intense compared with the liver.

If an abdominal mass is detected, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan is suggested. PET scanning allows for the detection of pheochromocytomas even in the presence of concomitant hypermetabolic incidentalomas, providing a better localization of the tumour (up to 100%). The diagnostic performance of FDG-PET is excellent in many cases, with a sensitivity of 90–95% and specificity of 95–100%. In cases of a strongly suspicious CT scan/PET scan or MRI localization, the diagnostic procedure is concluded and therapeutic options must be considered. If 18F-MIBG scintigraphy is negative, a “third-line” diagnostic option should be considered, such as positron emission tomography with different radionuclides (18F-fluoro-
phaeochromocytoma 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 cases of ascertainment).

Treatment

When the diagnosis of phaeochromocytoma 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 α-blocker phenoxybenzamine is still considered the first 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-receptor blockade to prevent 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 phaeochromocytoma/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 is removed; 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 metabolites 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 1% 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 phaeochromocytoma

The incidence of malignant phaeochromocytoma 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 phaeochromocytoma 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 chomatrin 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 phaeochromocytomas 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 2000 MBq and above) when radiotherapy fails to control the tumour. 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 111indium-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 currently 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.

References

5. Lenders JW. Biochemical diagnosis of phaeochromocytoma and paraganglioma. Ann Endo-

clinic 2009; 70: 161-165.
10. Timmers HJ, Chen CC, Carusoquill JA, et al. Comparison of 18F-fluoro-L-DOPA, 18F-fluoro-
12. Mannelli M, Castellano M, Schiwi F, et al. Italian Phaeochromocytoma/Paraganglioma Net-


Figure 1. Recommended diagnostic flow-chart
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 “Renaisance” 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 confusing 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/ml PRA (or 68 to 338 as PMo/L over mU/L) [7]. Most groups, however, use cut-offs of 20–40 for Aldo in ng/dl over PRA in ng/ml (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) 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, salme infusion, fluorocratic suppression, and captoril 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 {grade B}. 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

![Flowchart](image-url)
compliance, laboratory facilities, and local expertise. The most commonly used test is the saline infusion test (2 L over 4 hrs) with a tentative cut-off for post infusion plasma aldosterone above 7 ng/dl [8]. It should be noted that confirmatory tests requiring oral or intravenous administration of angiotensin II have been administered with caution in patients with a history of hypertension or congestive heart failure. As all these tests rely on the presumed autono-
mus of the aldosterone production from angiotensin II, which is apparently not the case in autonomous aldosterone overproduction, these tests have a large number of false negative and false positive results, and therefore some experts support the view that these tests should not be used as they can lead to curative adrenalectomy not being given to many patients.

Subtype classification

Patients with primary aldosteronism should undergo adrenocortical tomograp-
hy (CT) as the initial subtype study, to exclude large masses that may represent adreno-
cortical carcinoma and to ascertain the right adrenal vein anatomy, which is useful for 
performing 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 adenomas are not uncommon, especially in older patients (> 40 years old) and are indistinguishable from APAs on CT. Unilateral adrenalectomy would be inappropriate. In 
addition, non-functioning unilateral adrenal macroadenomas are not uncommon, espe-
cially in older patients (> 40 years old) and are indistinguishable from APAs on CT. Unilateral UAA (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 useful test for lateralization.

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 are limited for detecting small aldosterone excesses 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 usually difficult to reach), experience in medical treatment of PA (with IV 
venous angiotensin II) has provided useful information. The use of AVS requires 
unilateral adrenal CT, but adrenal vein sampling is usually effective in identifying 
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Testing for familiar forms of PA

• Testing for familial forms of PA (FH-I (GRA))

In the early 1970s, and an improved agent, [131I]19-Iodocholesterol scintigraphy was first used 
in patients with aldosterone-producing adenoma; consequently, this method is useless in interpreting micronodular findings 
but has an advantage over CT in its ability to differentiate adenomas from other adrenal masses. 
This test, developed in the 1970s, was based on the finding that the PAC in patients 
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given to many patients.
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.

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 — Undiscovered 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 across-sectionally with subtle cognitive or 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 infarcts 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 single 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 disease 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 decline in cognitive function and 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 wall thickness, an assumed parameter of microvascular pathology 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 wall pathophysiological change to examine arterial 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 arteries. 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 cm³ versus 2 cm³; p = 0.047). The greatest difference was observed in the group of patients with severe WMH grade. In this group, 6% of new WMH lesions were observed in the treatment arm of the study, whereas the volume of WMH increased by 7.6 cm³ 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 lowering arterial pressure resulted in 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 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.

References

HYPERTENSION AND SLEEP

Introduction

Cardiovascular control is markedly affected by normal sleep with a different autonomic regulation of the cardiovascular system with the different sleep stages [1]. Blood pressure (BP) and heart rate (HR) are linked to sleep/wakefulness phases. This is not a 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 changes 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 syndrome (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. These modifications have an impact on the cardiovascular system resulting 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-activation and thus to the development of the sustained increase in blood pressure (BP) seen in OSA patients. The endothelial dysfunction evidenced in OSA patients also partly explains hypertension, owing to decreased vasodilation and enhanced vasoconstriction, resulting from NO availability reduction. Similarly, the hyperinsulinemia often present in obese 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 OAS has several characteristics: diastolic and nocturnal predominance and commonly encountered masked hypertension with frequent non-diaper status. Furthermore, as OAS 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 OSA, reduces the 24-hour 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 included hypertensive patients. Furthermore, the presence of an antihypertensive treatment was not constant. The range of blood pressure decrease was similar to that achieved with CPAP in the three meta-analyses [4].

The studies differed regarding to the BP parameters used (SBP, DBP, or mean BP), the type of control treatment 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-hour 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 [9] recommended 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 (NHANES) [11] have reported a relationship between self-reported short sleep duration and prevalence and incidence of hypertension. Several studies 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 NHANES who had self-reported less than 5 hours of sleep by night demonstrated a higher incidence of hypertension after 2 to 3 years follow-up [13]. 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 NHANES 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 insomnia 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 increase in the risk of hypertension after 8 to 10 years of follow-up. This association persisted, even though attenuated, when analyses were adjusted for confounders, body weight in particular. This 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 non-insomniac 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-
Hypertension, whatever the cause, and sleep disturbances may increase hypertension severity and limit treatment efficacy. 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 reported 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 characterised by an irresistible urge to move the legs and unpleasant sensations 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). Winkelmann 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 in the elderly. Hypertension 2007; 50: 585–589.

References

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 perioperative health problem in non-cardiac surgery patients, with an overall prevalence of 20–25%. Numerous studies have shown that stage 2 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 the 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 elevated or current cardiovascular risk for cardiac complications? How can we discriminate moderately well between patients at low versus high risk for cardiac arrhythmia, and severe valvular disease. The revised cardiac risk index Previous or current cardiac disease, diabetes mellitus, functional status, body mass index, nutritional status, and renal insufficiency all confer higher risk for perioperative cardiovascular 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 second-ary 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 peroperatively 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 \( \beta \)-blockers and clonidine because of potential heart rate or blood pressure rebound. In patients unable to take oral medications, parenteral \( \beta \)-blockers, including propranolol, atenolol, and metoprolol, are attractive because of their anti-isometric effect. In patients unable to take oral medications, parenteral \( \beta \)-blockers, including propranolol, atenolol, and metoprolol, are attractive because of their anti-isometric effect. In patients unable to take oral medications, parenteral \( \beta \)-blockers, including propranolol, atenolol, and metoprolol, are attractive because of their anti-isometric effect.
pressure treatment also includes the control of pain, anxiety, hypoxia, and depending on the individual needs of the patient [13]. Postoperative blood distention may be preferable. Because of the large volume shifts that occur during the postoperative period; however, agents with slightly longer duration of action are frequently given to reverse the neuromuscular blockade. Anticholinergic agents are frequently given to reverse the neuromuscular blockade, nitroglycerin or nitroprusside, or a combination of the two (Tables 1, 2).

As the patient emerges from surgery, anticholinesterase or anticholinergic agents are usually given to reverse the neuromuscular blockade. 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. Postoperative blood pressure treatment also includes the control of pain, anxiety, hypoxia, and hyperthermia.

Diuretics. Special attention must be paid to the potassium levels of patients receiving diuretics so that they are not administered on the day of surgery because of the potential adverse interaction of diuretic-induced volume depletion and hypokalaemia and the use of anesthetic 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 beta-blockade, especially in patients at low to moderate risk of cardiac events. The specific issue of whether to initiate use of beta-blockers perioperatively in such patients has been extremely controversial. In the past, beta-blockade, mostly due to conflicting data from large, well-controlled clinical trials, POISE and DECREASE-IV. According to recently published 2009 ACC/AHA guidelines [14–15], in patients undergoing surgery who are already receiving beta-blockers for treatment, beta-blockers should be continued perioperatively. The guidelines recommend unloading the beta-blocker in high-risk surgery who are at high cardiac risk, beta-blockers titrated to heart rate and blood pressure and blood pressure are probably recommended (Ila, B). For patients undergoing either intermediate-risk procedure or vascular surgery, the usefulness of initiating beta-blockade is uncertain. The usefulness of beta-blockers is also uncertain in patients undergoing lower-risk surgery. Findings from the POISE trial suggest that starting higher doses of beta-blockers acutely on the day of surgery is associated with risk. When beta-blocker 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 out the perioperative period.

### References


### Table 1. Perioperative use of antihypertensive drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Perioperative use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Not on day of surgery</td>
<td>Potential hypokalaemia, volume depletion</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Avoid starting previous day in high risk patients</td>
<td>With caution in intermediate and low risk</td>
</tr>
<tr>
<td>ACE-I/ARBs</td>
<td>Last dose day before operation</td>
<td>Restart ACE-I/ARBS with caution if the patient is euolemic</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Diltiazem effective in CHF and verapamil in supraventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Continue dose</td>
<td>Withdrawal may cause blood pressure rebound</td>
</tr>
<tr>
<td>Esmolol</td>
<td>May cause bradycardia and pulmonary oedema</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>May cause bradycardia, heart block, and delayed hypotension</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Initial dosing of antihypertensive agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>Intravenous: 0.625–1.25 mg (lower dose if hyponatraemia, possible volume depletion, concomitant diuretic therapy, or renal failure) over 5 min, then double at 4–6 h intervals until desired response, a single maximal dose of 1.25–5 mg, toxicity, or a cumulative dose of 20–40 mg/day</td>
</tr>
<tr>
<td>Esmolol</td>
<td>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, toxicity</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Intravenous intermittent: 3–20 mg slow IV push every 20–60 min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Intravenous: 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 200–400 mg/day</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Intravenous infusion: 5 µg/min initially, then titrate in 5 µg/min increments every 3–5 min until desired response or toxicity</td>
</tr>
<tr>
<td>Nitropresside</td>
<td>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</td>
</tr>
</tbody>
</table>

### Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs)’s.

There is much debate in the literature over the use of ACE-I or ARBs in the perioperative period due to their potential central vagonetic 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-I and ARBs should receive their last dose the day before surgery and withhold the medication 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 euolemic, in order to decrease 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. Diltiazem and verapamil did not decrease the incidence of myocardial ischaemia although verapamil did increase the incidence of supraventricular tachycardia.

### Clonidine.

Clonidine has a favourable sympathetic-mediated effect on blood pressure control (at lower doses central sympathetic tone is increased with a vasodilator 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 an adverse effect profile.

### 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].
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 model 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 moderate; 5–9% as increased, and cardiovascular death < 5%, in addition to not smoking, BMI < 25 kg/m², 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/s 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 many risk factors, 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.
several interacting cardiovascular risk factors, the absolute cardiovascular risk is dependent on all the risk factors; and 3) Treatment indications and goals are determined according to the absolute cardiovascular risk and the secondary prevention 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 advice. However, 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 large risk 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 signs of subclinical cardiovascular damage, lifestyle advice is recommended by the ESC [5] and ESH [2]. In subjects with high normal blood pressure, severe dia-betic nephropathy and diabetes is associated with high normal blood pressure 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 ESC 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 OMTT-study [17] have demonstrated a worse prognosis in patients receiving a very low blood pressure, indicating a target level 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]. 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.

References

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 hyperuricemia was a disease, it was proposed that it had a causal role in cardiovascular and renal conditions, including hypertension, arteriosclerosis (the histological lesion of hypertension), kidney disease, and heart disease [1]. By the 1990s, however, prospective human studies showed that uric acid was 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 in the reproductive age due to enhanced renal urate clearance by oestrogen compounds [3]. After menopause, serum urate values in healthy females increase and approach 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 levels may vary significantly as a result of factors that modify its generation or urinary excretion. High purine or protein diets, alcohol consumption, high coffee turnover, and certain enzymatic defects of purine metabolism enhance generation, whereas those factors associated with inflammation and elevated serum urate levels are increased in disease. On the other hand, drugs that interfere with purine metabolism or enhance increased urinary excretion are associated with a reduction in serum urate levels.

Hyperuricemia is usually defined as serum levels > 6.5-7 mg/dl and > 6 mg/dl in men and women, respectively [3].

Homoeostasis 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 an enzyme complex. In turn, xanthine and hypoxanthine are metabo-
ized 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 [3]. The enzyme xanthine oxidase, responsible for urate turnover, is expressed in almost all tissues except 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 homoeostasis, urate is eliminated by the kidney and the gastrointestinal tract [5].

The remaining 1/3 of urate load is excreted through the proximal convoluted tubule. Four distinct processes are involved in the renal handling of urate: 1) glomerular filtration; 2) peritubular 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].

A urate nor uric acid, 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].

During the past 20 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 hyperten-
sion have been elucidated in experimental animal studies. Rats rendered hyperuricaemic with pterin acid, a uricase inhibitor, develop hypertension with several stages: 1) Blood pressure (BP) elevation was shown to be due to uric acid mediated systemic and renal vasoconstriction as a result of the non-angiotensin system and a reduction in endothelial nitric oxide oxides [14]. Renal arterioles are functionally constricted resulting in a decline in renal plasma flow, but are structurally normal [14]. At this initial stage, controlling hyperuricemia with allapatine, a xanthine oxidase inhibitor, or with a nicotinic acid prevents or reverses BP elevation and is associated with reversal of abnormal hormonal changes [14].

In hypertensive patients, 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 [11]. The Framingham Heart Study indicated that hyperuricemia predicted the onset of hypertension with an odds ratio of 1.17 for each increase in serum uric acid by 1.3 mg/dl [11]. Similar findings were reported in the Multiple Risk Factor Intervention (MRFIT). In normotensive men without metabolic syndromes, hyperuricemia (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, prothrombin, 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 others, this correlation was lost in subjects older than 60 years of age [19, 20].

Hyperuricemia is also more common in primary than in secondary hypertension, at least in adolescents [21]. In 2004, serum 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

Deleterious effects
In contrast to its beneficial actions, uric acid has also been found to have a wide variety of deleterious effects on vascular tissues, resulting in proliferative and proinflammatory phenotypes, which produce growth factors, vascular strictive and proinflammatory molecules [11].

Pathophysiological significance of hyperuricaemia
Epidemiological studies have reported a relation between serum uric acid and a wide spec-
trum of cardiovascular disease (CVD) and hypertension levels to frankly elevated serum uric acid levels, but has been reported with uric acid levels within the high normal range [3].

Hypertension
Hyperuricaemia is very common in hypertensive patients. It has been reported in as many as 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 [2]; 2) the hypertension microvascular disease leads to local tissue ischemia, the release of lactate that blocks urate secretion in the proximal tubule and increases uric acid synthesis [13]. Tissue ischemia leads to ATP degradation to adenosine and xanthine oxide. Both increased xanthine and xanthine oxide result in increased generation of uric acid and oxidant (O2−) formation; and 3) additional factors can contribute to hyperuricemia in hypertension such as alcohol abuse, lead intoxication, and diuretic use.

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sion have been elucidated in experimental animal studies. Rats rendered hyperuricaemic with pterin acid, a uricase inhibitor, develop hypertension with several stages: 1) Blood pressure (BP) elevation was shown to be due to uric acid mediated systemic and renal vasoconstriction as a result of the non-angiotensin system and a reduction in endothelial nitric oxide oxides [14]. Renal arterioles are functionally constricted resulting in a decline in renal plasma flow, but are structurally normal [14]. At this initial stage, controlling hyperuricemia with allapatine, a xanthine oxidase inhibitor, or with a nicotinic acid 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 microalbuminuria. With reported direct actions of uric acid on endothelial and vascular smooth muscle cells, these observations suggest that uric acid might 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 hyperuricemia 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 syndromes, hyperuricemia (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, prothrombin, or renal function [18].

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Health Study (CHS) there was no association between serum uric acid levels and incident CKD. In a separate analysis of 5800 participants from the Cardiovascular disease (28). These interesting observations give support to the hypothesis that hyperuricaemia is associated with an approximately 10% increase in risk of kidney disease in multivariable analysis of the Atherosclerosis Risk in Communities Study (ARIC) has provided possible answers to these queries. 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 6480 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, respectively) over a median 10 years of follow-up (29). In a population based study, the NHANES I Epidemiologic Follow Up Study, for each increase of 5.9 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 Lesanot over 4.8 years reduced CVD events in this high-risk population.

Cardiovascular disease

It remains controversial whether uric acid plays a causal role in the development of CVD, or is simply a marker of metabolic or CVD risk factors (27). Recent reports from the Framingham Heart Study and Atherosclerotic Risk in Communities Study (ARIC) has provided possible answers to these queries. 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 fructose, somewhat like a metabolic like syndrome, and renal haemodynamic and histological changes very similar to those observed with hyperuricaemia were observed in rats fed fructose with xanthine oxidase inhibitors in these rats partially prevented these changes (Figure 2).

Chronic kidney disease

Hyperuricaemia is highly prevalent in patients with chronic kidney disease (CKD), reflecting renal dysfunction or renal excretion of uric acid and associated with hyperuricaemia (98). 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 hypouricase therapy, patients with gout exhibited evidence of CKD (albuminuria, renal functional impairment, hypertension, and end stage renal failure) which were accompanied by hyperuricaemia, glomerulosclerosis, and tubulointerstitial disease with or without patchy deposition of uric acid crystals in the outer medulla, and were attributed to consistent hypertension and independent of crystal deposition (99).

Fructose consumption, metabolic syndrome, and risk of cardiovascular disease

The past few decades have witnessed significant changes 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 fructose, somewhat like a metabolic like syndrome, and renal haemodynamic and histological changes very similar to those observed with hyperuricaemia were observed in rats fed fructose with xanthine oxidase inhibitors in these rats partially prevented these changes (Figure 2).

Figure 2. Relationship between oxonic acid/fructose induced hyperuricaemia, hyperuricaemia, 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 epidemiological evidence that fructose intake 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 debate 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 prevalence of CVD. These last two points add to 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 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.

References

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 atherosomatic 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 hyperperfusion downstream of the aortic lesion, which is usually ischimic.

This newsletter will not address the above-mentioned abnormalities but will focus on the relationships between hypertension and aortic aneurysms, dissection, and dissection, 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 thrombi 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].

In a patient with a 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/m² [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, perindopril or 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

Figure 1. CT scan with contrast injection: voluminous abdominal aortic aneurysm with a mural thrombus
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 OSAH is high and respiratory events are more severe [21]. This has led to the proposal that OSAH 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 in all the cases, or they 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 antiplatelet medication — a combination of a beta-blocker (failing) and a vasodilator (nitrprosulphure 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 outcome [29]. The second found a prevalence of uncontrolled hypertension in 60% of patients with chronic AD [30]. To date, there are no specific guidelines for BP monitoring in these very high-risk patients. A threshold of 150 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 aneurysm 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.

References
9. Kirchler M, Schmutzler R, Laffert PM, et al. 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 outcome [29]. The second found a prevalence of uncontrolled hypertension in 60% of patients with chronic AD [30]. To date, there are no specific guidelines for BP monitoring in these very high-risk patients. A threshold of 150 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.

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