**New markers of hypertensive disease**

**Focus on arterial stiffness**

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**Introduction**

Despite compelling evidence for the efficacy of primary prevention, cardiovascular disease (CVD) remains the main cause of mortality in Europe. The EURIKI study, a cross-sectional study conducted simultaneously in 12 European countries during 2009, demonstrated that many patients with treated CVD risk factors remained inadequately controlled. In fact, of 4,407 patients with dyslipidaemia, 74.4% were treated with lipid-lowering drugs, but target total and LDL cholesterol levels were reached only by 41.2% of treated patients. Among 2,046 patients with type 2 diabetes, 87.2% were treated with antidiabetic drugs, but the recommended HbA1c level of 6.5% was reached by 36.7% of treated patients only. Of 3,324 patients with a diagnosis of obesity prior to study enrolment, 92.2% were on lifestyle treatment (weight reduction advice) and the target of BMI<30 kg/m² was reached by 24.7% of these patients. Finally, the percentage of treated patients with 1, 2, or the 3 main CVD risk factors (hypertension, dyslipidaemia, diabetes) at goal was 41.3, 18.6, and 3.7%, respectively. There were a substantial proportion of patients remaining at high CVD risk (35–39% for the different individual risk factors) among those who achieved specific treatment goals, probably because of under consideration of other risk factor other than the main one.

The most recent US survey data shows that high BP awareness, treatment, and control rates have improved from 69%, 53%, and 26%, respectively, at the time of the 1988 to 1994 Nutrition Health and Examination Survey to 76%, 65%, and 37% between 2003 to 2004. Anyway, despite the greater availability of effective antihypertensive agents, about 65% of patients with hypertension receive the indicated care and only 50% of patients for whom drug treatment is initiated persist on treatment 1 year later.

The consequences of nonadherence are serious because of the resulting poor clinical outcomes and preventable health care costs. Results from a meta-analysis by Di Matteo showed a 27% difference in clinical outcome between patients with low vs high adherence. Cherry and colleagues assessed the benefit of ‘ideal’ vs ‘typical’ adherence in patients with hypertension and hyperlipidemia and found a nearly double relative risk (13.3 vs 25 events per 100 patient-years over 3 years) of myocardial infarction, angina, and stroke in patients who showed no adherence vs those who showed ideal adherence (figure 1).

In addition to gold standard therapy, improvement in smoking cessation strategies, effective healthy diet advice, weight reduction advice in obese patien-
ts, and physical activity advice may substantially increase risk factors control1.

The role of emerging markers

Hypertension, defined as sustained elevation of brachial blood pressure, is a major risk factor for cardiovascular disease, and reduction of brachial blood pressure decreases cardiovascular events, particularly stroke6. But to stratify CVD risk, we have to consider many other risk factors. In hypertensive individuals, renal subclinical organ damage is associated with a 10-year risk of cardiovascular events of 20% or more. Data from the ELSA7 have shown that baseline carotid intima–media thickness (IMT) predicts cardiovascular events independent of BP. Even asymptomatic peripheral vascular disease as detected by a positive ankle-brachial index has prospectively been found to be associated in men with an incidence of cardiovascular events approaching 20% in 10 years89. Among these traditional risk factors, pulse wave velocity (PWV) and central aortic pressure (CAP) are gaining importance. Pulse wave velocity, a measure of vascular stiffness, has been related to cardiovascular risk11 in hypertensive patient10, in the elderly11, in patients with end-stage renal disease12, and in population-based samples13. CAP can be measured by noninvasive techniques14 and potential evidence of greater prognostic importance of central aortic than brachial pressures has been obtained in treated hypertensive patients15. Increased arterial stiffness causes a premature return of reflected waves in early systole, increasing central PP and systolic BP, leading to an increased load on the left ventricle and greater myocardial oxygen demand. Arterial stiffness, wave reflections, and central pressure can serve in clinical practice as “intermediate” or “surrogate” end points for cardiovascular events.

In fact, these parameters have an independent predictive value for cardiovascular morbidity and mortality5. In the Copenhagen County population, an increased pulse wave velocity (PWV >12 m/s) was associated with a 50% increase in the risk of a cardiovascular event16. Independent predictive value of PWV for cardiovascular events has been shown in Japanese men followed for 8.2 years17. The independent predictive value of aortic stiffness has been demonstrated after adjustment to classic cardiovascular risk factors, including brachial PP, suggesting that aortic stiffness adds value to a combination of cardiovascular risk factors19. This finding may be related to the fact that aortic stiffness integrates the damage to the aortic wall of cardiovascular risk factors over a long period, whereas BP, glycaemia, and lipids can fluctuate over time and the values recorded at the time of...
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Risk assessment may not reflect the true damage to the arterial wall. Another explanation may be that the identification of aortic stiffness reveals the translation from risk factors to real risk in any patient. The most important study to date to examine the relative importance of central and brachial blood pressures has been the Conduit Artery Function Evaluation (CAFE) study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) hypertension trial. Although brachial blood pressure was reduced to a similar extent in both the atenolol/thiazide and amlodipine/perindopril arms of the CAFE study, a significantly greater reduction in central aortic pressures and AIx was achieved with the amlodipine regimen than with the atenolol regimen. Furthermore, both brachial and central pulse pressures were similarly to a post hoc-defined composite outcome (new car-

**Figure 2.** Relation between 10-year CVD risk and aortic pulse wave velocity. (From Blacher J et al 1999).

![Figure 2](image)

**Figure 3.** Kaplan-Meier estimates of CHD (top), stroke (middle), and CHF (bottom) by a PWV quartile. (From Sutton-Tyrrel K et al 2005).
vascular events, cardiovascular procedures, renal impairment) independent of other risk factors\(^1\) (figure 2 and figure 3). Although measures of stiffness are useful in predicting the occurrence of cardiovascular events, the value of reduction in arterial stiffness as a measurement of the reduction by treatment of the risk of such events has not yet been unequivocally proven. The only clinical evidence that reducing arterial stiffness is associated with a decreased risk of cardiovascular events was obtained in ESRD patients by Guerin et al\(^2\). In a mean follow-up of 50 months, the absence of PWV decrease in response to BP decrease was one of the predictors of all-cause and cardiovascular mortality, together with increased left ventricular mass, age, and preexisting cardiovascular disease. After adjustment for all confounding factors, the risk ratio for the absence of PWV decrease was 2.59 for all-cause mortality and 2.35 for cardiovascular mortality. However, the effect of aortic stiffness attenuation on cardiovascular morbidity and mortality remains to be established in other populations. Indeed, in the REASON study, the combination of perindopril and indapamide significantly attenuated carotid wave reflections\(^3\), resulting in a selective decrease in central systolic BP and PP, and leading to a related reduction in left ventricular hypertrophy\(^4\). This effect was not observed in the atenolol treatment arm, in which carotid PP was not equally reduced. The results of the CAFE study suggested that the positive effect of renin-angiotensin system blockers beyond BP control could be attributed to a greater effect on reduction of arterial stiffness\(^5\).

**Usual therapies and their limitations**

The 2007 ESH/ESC guidelines underline that, no matter which drug is employed, monotherapy can effectively reduce BP in only a limited number of hypertensive patients, most of whom require the combination of at least two drugs to achieve BP control\(^6\). A meta-analysis of 42 studies has shown that combining two agents from any two classes of antihypertensive drugs increases the BP reduction much more than doubling the dose of a single drug\(^7\). The 2007 ESH/ESC guidelines\(^8\) recommend the combination of two drugs to be considered as initial treatment whenever hypertensive patients have a high initial BP or are classified as being at high/very high cardiovascular risk because of the presence of organ damage, diabetes, renal disease, or a history of cardiovascular disease.

**Strategies to improve both efficacy and adherence to treatment**

The combination of an ACE inhibitor, perindopril, and the diuretic indapamide had already been shown in the PROGRESS study to have a greater BP lowering effect than the ACE inhibitor alone and, in parallel, a much greater preventive effect on recurrent stroke\(^9\). In ADVANCE\(^10\), the combination of indapamide and perindopril in patients with type 2 diabetes (on top of preexisting therapy) for more than 4 years was followed by a significantly greater antihypertensive effect than administration of placebo. A combination of an ACE inhibitor and a dihydropyridine calcium antagonist was the most widely used combination therapy in Syst-Eur and Syst-China\(^11\), as well as in the HOT study\(^12\) in order to achieve lower BP goals. The combination amlodipine-perindopril was widely used in the ASCOT study, being more effective in lowering BP and cardiovascular events than the combination of a ß-blocker with a thiazide\(^13\).

In the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial\(^14\), more than 11,000 hypertensive patients with a relatively elevated cardiovascular risk were randomized, after stopping previous treatment, to receive benazepril plus either the calcium antagonist amlodipine or hydrochlorothiazide. Over the 3 years of follow-up, both treatments reduced BP very effectively, and the rate of serious side effects was limited and similar between the two groups. In the group receiving the benazepril-amlodipine combination, however, the incidence of the primary endpoint (a composite of several cardiovascular fatal and nonfatal events) was 20% less than in the group receiving the benazepril-hydrochlorothiazide combination, with a significant reduction also in cause-specific events such as myocardial infarction.

In the STAR study\(^15\), hypertensive patients with an impaired fasting glucose exhibited a worse metabolic response to the glucose load test (as well as a greater rate of new-onset diabetes) if treated with a combination of a blocker of the renin–angiotensin system and a diuretic than if treated with the combination of a renin–angiotensin system blocker and a calcium antagonist\(^16\). The combination of a calcium channel blocker (CCB) and an ACE inhibitor is especially effective because of their comple-
mentary mechanisms. Moreover, lower amounts of each component drug are necessary to effectively decrease BP, thereby preventing dose-dependent adverse effects\textsuperscript{35}, and compound-specific adverse effects can be limited by supporting the physiological actions of the other component. For example, peripheral oedema, a characteristic adverse effect of calcium channel antagonists, is less common when a CCB is administered in combination with an ACE inhibitor or an angiotensin II type-1 receptor antagonist (angiotensin receptor blocker - ARB)\textsuperscript{36-38}. In addition, the combination of an ACE inhibitor and a calcium channel antagonist has synergistic potential in terms of renal, cardiac and vascular effects. The objective of fixed-dose combination antihypertensive therapies is to achieve better BP control in a cost-effective way while minimizing adverse effects\textsuperscript{39} (table 1).

**The lercanidipine/enalapril fixed dose combination**

Lercanidipine is a third-generation dihydropyridine calcium channel antagonist that inhibits calcium entry through L-type calcium channels in smooth muscle cells of the cardiovascular system, leading to peripheral vasodilatation and reducing BP\textsuperscript{40-42}. It has high lipophilicity, enabling a slower and smoother onset and longer duration of action than other dihydropyridines\textsuperscript{43}. Lercanidipine may have antatherogenic effects beyond BP reduction\textsuperscript{40}, reducing levels of low-density lipoprotein cholesterol oxidation by 35% in hypertensive patients with diabetes\textsuperscript{44}, and reducing signs and symptoms of ischaemia, and improves heart function in patients with angina\textsuperscript{45}. Lercanidipine has also been reported to have renoprotective effects\textsuperscript{46,47}, and improves the lipid profile and glucose tolerance\textsuperscript{48}. Unlike other dihydropyridine calcium channel antagonists, lercanidipine has renoprotective effects because it induces both afferent and efferent arteriolar vasodilatation\textsuperscript{47}.

In diabetic patients, lercanidipine treatment led to a significant decrease in glycosylated haemoglobin (HbA1c) level, without negatively affecting glucose omeostasis\textsuperscript{49}. In diabetic patients with renal failure, lercanidipine had a good tolerability profile and a neutral effect on plasma lipids, with no impairment in renal function\textsuperscript{50}. In hypertensive patients with the metabolic syndrome, lercanidipine appeared to have a better tolerability profile and was associated with fewer vasodilatation-related adverse effects than other

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**Table 1.** Synergistic possibilities with the combination of an angiotensin-converting enzyme inhibitor (ACE-I) and a calcium channel antagonist (CCA)\textsuperscript{39}.

<table>
<thead>
<tr>
<th>Effect</th>
<th>DHP-CCA</th>
<th>Non DHP CCA</th>
<th>ACE-I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Efferent arteriolar tone</td>
<td>Minimal ↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Afferent arteriolar tone</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Minimal ↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Renoprotection</td>
<td>No</td>
<td>Possibly</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Vasculature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial-mediated vasoconstriction</td>
<td>↓</td>
<td>↓</td>
<td>Minimal effect</td>
</tr>
<tr>
<td>Nitric oxide release</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Arterial compliance</td>
<td>↑</td>
<td>No</td>
<td>↑</td>
</tr>
<tr>
<td>Vascular hypertrophy</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Atherogenesis</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓</td>
<td>No effect</td>
</tr>
<tr>
<td>Left ventricular filling</td>
<td>↑</td>
<td>↑</td>
<td>No effect</td>
</tr>
<tr>
<td>Contractility, unloading</td>
<td>Some effect</td>
<td>No effect</td>
<td>Improvement</td>
</tr>
<tr>
<td>Coronary flow</td>
<td>↑</td>
<td>↑</td>
<td>Mild ↑</td>
</tr>
<tr>
<td>Secondary cardioprotection</td>
<td>No</td>
<td>Some</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ACE= angiotensin-converting enzyme; DHP=dihydropyridine; ↑=increase; ↓=decrease.
dihydropyridine calcium channel antagonists. Enalapril is a prodrug that is hydrolysed to the active form enalaprilat, which decreases plasma levels of angiotensin II by inhibiting ACE, so reducing angiotensin II and leading to peripheral vasodilation and reduced vascular resistance, decreasing BP values. Enalapril has positive effects on cardiovascular risk factors and prevents decline in renal function. A number of clinical trials have demonstrated that the lercanidipine/enalapril combination has better efficacy and tolerability than monotherapy with either agent. In addition, lercanidipine was non-inferior to hydrochlorothiazide as add on therapy to enalapril in diabetic patients with hypertension who had not responded to enalapril alone. The fixed-dose formulation of lercanidipine/enalapril was well tolerated in all clinical trials, with an adverse effect rate similar to the component drugs as monotherapy and showing to effectively decrease BP.

Conclusions
Calcium channel antagonists are associated with reductions in cardiovascular morbidity and mortality; ACE inhibitors lead to a reduction in myocardial infarction and cardiovascular death. Both these kind of drug appear to diminish CVD above that attributable to BP lowering alone. Based on this evidence, a fixed-dose combination of an ACE inhibitor and a calcium channel antagonist may provide effective cardiovascular protection as it has been shown with the fixed-dose combination of the CCB lercanidipine and the ACE inhibitor enalapril. This combination has greater BP lowering efficacy than either component alone, both in the general hypertensive population and in patients with diabetes. Lercanidipine/enalapril is also well tolerated, with similar adverse effect rates to the component drugs as monotherapy. Moreover the association of a CCB/ACE inhibitor was effective in ameliorating central pressure and not only blood pressure. Anyway, we don’t know yet if arterial stiffness and central pressure should become target for therapy or not.

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