CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 24, NO. 12, 2008, 3543–3557

0300-7995
doi:10.1185/03007990802576302

REVIEW

Optimizing the treatment of hypertension and stable coronary artery disease: clinical evidence for fixed-combination perindopril/amlodipine

Roberto Ferrari

Chair of Cardiology, University of Ferrara, Italy and Fondazione Salvatore Maugeri IRCCS, Ferrara, Italy

Address for correspondence: **Prof Roberto Ferrari, Department of Cardiology, University of Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy. Tel.: +39 0532 20 21 43; Fax: +39 0532 24 18 85; fri@unife.it**

Key words: **Amlodipine – ASCOT – Coronary artery disease – Diabetes – Fixed combination – Hypertension – Perindopril**

ABSTRACT

Background: Optimized management of hypertension and coronary artery disease (CAD) improves cardiovascular risk and outcomes, and prevents complications. This article reviews evidence for the fixed combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril and the calcium channel blocker amlodipine.

Methods: A literature search was performed in PubMed/MEDLINE to identify articles published in English between 1988 and March 2008 describing clinical trials, particularly outcome trials, or mechanisms of therapeutic action relevant to the use of combination therapy in patients with hypertension or stable coronary artery disease with an ACE inhibitor (perindopril) and a calcium channel blocker (amlodipine).

Findings: Clinical trials indicate that this combination may have a positive impact on cardiovascular mortality and morbidity in hypertensive individuals. The two complementary mechanisms of action appear to work in synergy, leading to more efficient blood pressure lowering, improved fibrinolytic function, and reduction of secondary effects. This also represents a simplified management strategy for stable CAD. Perindopril has proven efficacy in the prevention of cardiovascular events and mortality in CAD patients, while amlodipine is widely used in the symptomatic management of CAD. Both aspects of guideline-recommended management of CAD are therefore addressed in a single tablet.

Conclusions: The clinical evidence for fixed-combination perindopril/amlodipine indicates it as a credible option for the optimization of the management of hypertension and CAD.

Introduction

Hypertension is an extremely important health-care burden. More than a quarter of the world's population suffers from the condition, with the prevalence rising well above a third in the developed world[1]. Despite this, the management of hypertension remains suboptimal. About 30% of hypertensive individuals are unaware of their condition and receive no treatment at all. Of the remaining 70% who do, only 34% achieve the recommended target of systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg[2]. These data are of concern because of the proven benefits of reducing blood pressure (BP), which translate into reductions in the incidence of myocardial infarction (MI) (20–25%), heart failure (>50%), and stroke (35–40%)[2]. The relationships between BP and cardiovascular risk are strong and graded, and individuals with the highest BP are at the highest risk. Optimized treatment can also reduce the

risk of new-onset diabetes, which is 2.5 times more likely in hypertensive individuals[2], and help prevent complications in individuals who already have type 2 diabetes. The shortcomings in management are generally attributed to insufficient treatment in terms of choice of agent or dosage, absence of synergy when more than one agent is administered, and problems with compliance[3].

The administration of fixed combinations can address all of these factors, and is recommended by international guidelines to help optimize the management of hypertension[2,4,5]. Indeed, some combinations have been shown to improve the prognosis of patients with established hypertension with or without comorbidities[6]. However, because physicians currently have a plethora of fixed combinations to choose from (β-blocker/diuretic, β-blocker/calcium channel blocker [CCB], angiotensin-converting enzyme [ACE] inhibitor/diuretic, angiotensin receptor blocker [ARB]/diuretic, ARB/CCB, etc.), one of today's challenges is becoming the selection of the fixed combination with the best evidence for the optimal management of hypertension.

There is already solid proof that the ACE inhibitor perindopril and the CCB amlodipine are effective as monotherapy for hypertension[7–11], and they have been available to physicians for many years. They are frequently prescribed in free combination in hypertension and stable coronary artery disease (CAD), particularly since the appearance of two large clinical trials, the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA)[6], and the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)[12]. A new addition to the antihypertensive therapeutic armamentarium is a fixed combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril arginine[10] and the CCB amlodipine besylate (Coveram; available dosages: 5/5 mg, 5/10 mg, 10/5 mg, and 10/10 mg). This review will examine the rationale and the evidence for the clinical benefits of the fixed combination of these two agents in hypertension and in the protection of the heart.

The fixed combination of perindopril and amlodipine represents a credible option in the management of stable CAD, which will also be discussed here. Patients with stable angina pectoris require a dual management strategy, with one treatment to improve long-term prognosis and another to manage symptoms[13]. By combining two such agents routinely used in CAD, fixed-combination perindopril/amlodipine could simplify the management of these patients. In a single intake, it may fulfil three therapeutic objectives: antihypertensive efficacy, if needed; a reduction in angina; and the secondary prevention of cardiac events.

Relevant studies were identified through a PubMed/MEDLINE search of English-language articles published between 1988 and March 2008. The search strategy included the terms hypertension, coronary artery disease, coronary heart disease, combination therapy, perindopril, and amlodipine. Separate subsearches were also performed using the above terms and a filter of clinical trials, as well as a cross-search using the above terms combined. Overall 2368 articles were considered and 91 of them describing clinical studies – particularly outcome trials, or mechanisms of therapeutic action relevant to the combination therapy of hypertension or stable CAD with an ACE inhibitor (perindopril) and a CCB (amlodipine) – were selected by the author for inclusion in this review.

Evidence from large-scale clinical trials: ASCOT

The rationale for fixed-combination perindopril/amlodipine comes directly from the results of ASCOT[6], which was the first face-to-face trial to demonstrate a difference in total mortality and cardiovascular morbidity between two antihypertensive regimens. ASCOT included 19 257 hypertensive patients, who had at least three other cardiovascular risk factors, but no cardiac disease. The subjects were randomized to one of two stepwise management strategies: a 'newer' regimen in which patients received amlodipine, plus perindopril as required; or an 'older' regimen in which they received atenolol, plus bendroflumethiazide and potassium as required[6]. The target BP was $<140/90$ mmHg, or $<130/80$ mmHg in patients with diabetes mellitus.

The difference between the two regimens in terms of cardiovascular and total mortality was in favour of amlodipine/perindopril, and ASCOT was stopped early, after a median of 5.5 years. At this point, there was an 11% difference in all-cause mortality, in favour of the amlodipine/perindopril group ($p = 0.0247$) (Figure 1). For the other secondary end-points, there was a 24% difference in cardiovascular mortality ($p = 0.001$), a 13% difference in all coronary events ($p = 0.007$), and a 23% difference in fatal and non-fatal stroke ($p = 0.0003$). Stable angina was a criterion for exclusion from ASCOT, hindering assessment of the effects of the combinations on the symptoms and prognosis of stable CAD. However, the 13% reduction in coronary events and the 32% difference in the tertiary end-point of unstable angina

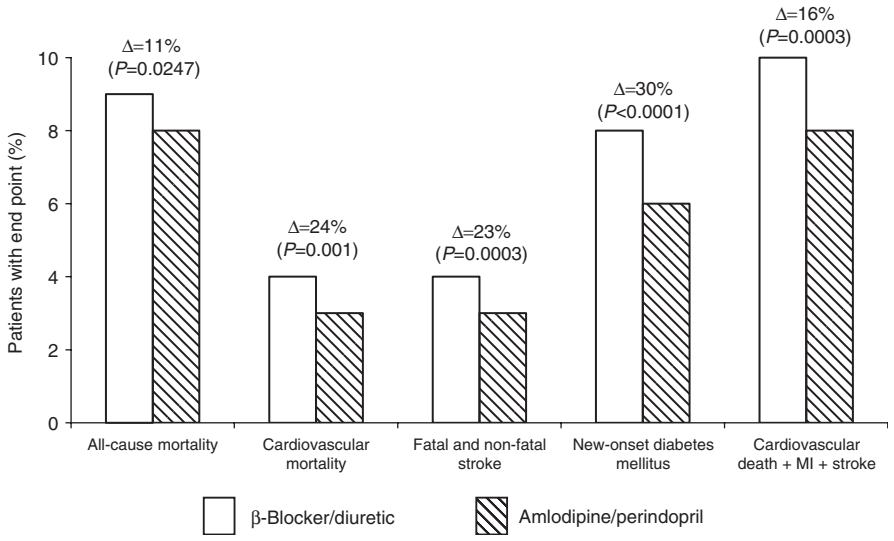

Figure 1. *Results from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) at the study end (median of 5.5 years' treatment) with either amlodipine (5–10 mg/day) plus perindopril (4–8 mg/day) (hatched bars) or atenolol (50–100 mg/day) plus bendroflumethiazide (1.25–2.5 mg/day) (white bars)[6]. Percentage of patients with the secondary end-points of all-cause mortality, cardiovascular mortality, and fatal and non-fatal stroke, the tertiary end-point of new-onset diabetes mellitus, and the post-hoc end-point of cardiovascular death, myocardial infarction (MI), and stroke. Δ, between-group difference*

($p = 0.01$) with amlodipine/perindopril indicate a beneficial effect in CAD populations. There was a 30% difference in the tertiary end-point of new-onset diabetes ($p < 0.0001$) and a 16% difference in the *post-hoc* combined end-point of cardiovascular death, MI, and stroke ($p = 0.0003$)[6]. These values are both greater than the corresponding significant risk reductions of 25% and 13% reported with an ARB/diuretic combination versus β-blocker/diuretic in the Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE), despite this being a higher-risk population[14].

At study end, 78% of the total population were receiving combination therapy, and only 15% of the subjects in the amlodipine arm were still on monotherapy[6]. While similar BP reductions were reported for the two groups, there was an average difference of 2.7/1.9 mmHg between the regimens over the duration of the study ($p < 0.0001$). Multivariate analysis of the ASCOT data demonstrated that the advantage of the amlodipine/perindopril regimen in terms of reduction in coronary and stroke events is not entirely explained by the difference in BP between the two groups[15]. Finally, while both treatment regimens in ASCOT were well tolerated, there was a significant difference in the proportion of dropouts due to serious adverse events in favour of the amlodipine/perindopril group (2% for amlodipine/perindopril versus 3% for β-blocker/diuretic, $p < 0.0001$)[6].

The results of ASCOT demonstrate that the perindopril/amlodipine combination provides efficient BP lowering and better protection against cardiovascular events and new-onset diabetes than a β-blocker/diuretic combination. These cardioprotective effects are not entirely due to the difference in BP between the two groups, but may be linked to other differences between the two regimens[15,16]. There have been many reviews and much speculation regarding the results of ASCOT and other head-to-head trials in hypertension[17,18]. For example, in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT)[19] and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE)[20], there were no major differences in cardiovascular outcomes between the monotherapy treatment arms in either trial, despite a significant difference in BP lowering. This suggests that the ASCOT results may be largely due to the combined presence of a CCB and an ACE inhibitor. Furthermore, the International Verapamil-Trandolapril Study (INVEST)[21], which compared the verapamil/trandolapril combination with atenolol/hydrochlorothiazide in 22 576 hypertensive patients with CAD, failed to find additional benefits of that particular CCB/ACE inhibitor combination over β-blocker/diuretic, indicating that the ASCOT results may not be due to a class effect.

The implications of the results of ASCOT are already being felt in terms of changes to clinical practice guidelines[5]. The fixed combination of perindopril and amlodipine reproduces the combination that led to the results of ASCOT. It can therefore be confidently predicted to combine efficient BP lowering and good tolerability with a reduction in total and cardiovascular mortality and morbidity.

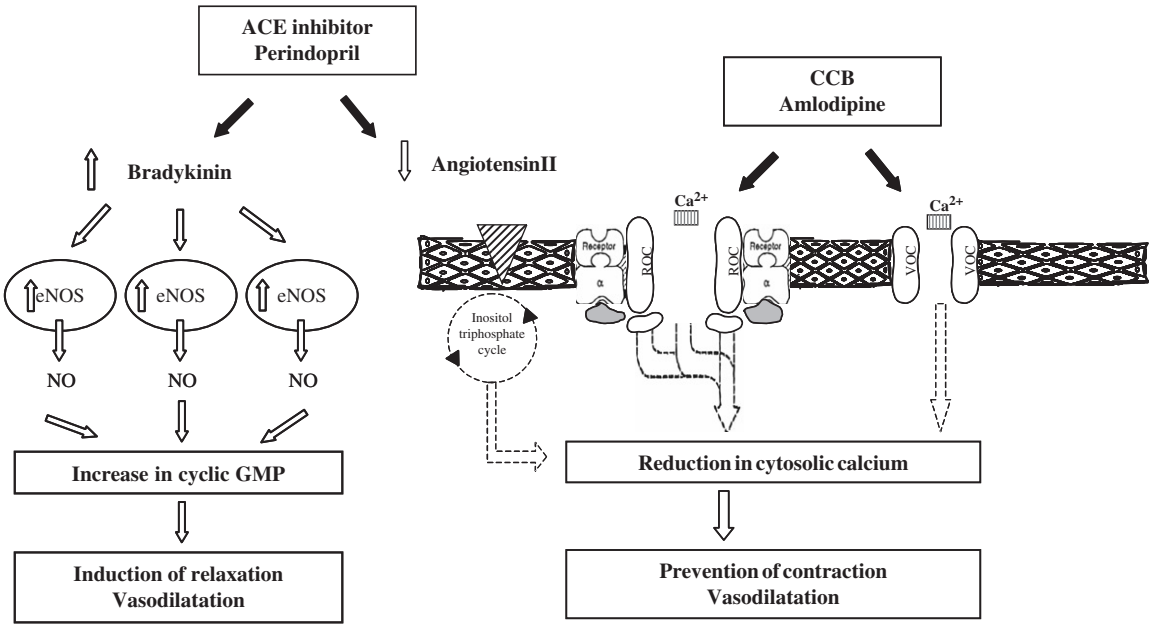

Figure 2. *Antihypertensive mode of action of angiotensin-converting enzyme (ACE) inhibition and calcium channel blockade. eNOS, endothelial nitric oxide synthase; NO, nitric oxide; ROC, receptor-operated channel; VOC, voltage-operated channel. Adapted from Ferrari, 1997*[22]

Fixed-combination therapy: synergy of two complementary mechanisms

Judicious combination of agents from two different classes provides the advantage of applying two complementary mechanisms of action, which can work in synergy. ACE inhibitors and CCBs have complementary actions in reducing BP (Figure 2)[22]. CCBs counteract excess calcium entry through the voltage- and receptor-operated calcium channels of the vascular smooth muscle[23]. ACE inhibitors reduce the vasoconstrictive properties of angiotensin II by preventing its conversion from angiotensin I. These properties are related to: (1) a reduction in the sodium reabsorption and water retention promoted by aldosterone, the synthesis and release of which is stimulated by angiotensin II; and (2) a direct effect of angiotensin II on vascular smooth muscle, which is mainly mediated by the intracellular inositol-triphosphate cycle[24]. In addition, perindopril increases nitric oxide (NO) production via a bradykinin-mediated increase in endothelial NO synthase (eNOS)[25]. Thus, in the vascular smooth muscle, amlodipine causes dilatation by reducing external calcium entry, while perindopril does so by reducing internal calcium release and improving NO release (Figure 2, Table 1)[22].

The two classes of agents also have synergistic cardioprotective effects. At the molecular level, CCBs maintain the viability of the myocytes and delay the occurrence of irreversible ischaemic damage[26]. These effects usually require prophylactic administration, and rely on the ATP-sparing capacity and a reduction in cytosolic calcium overload due to ischaemia[26,27].

ACE inhibitors have also been proven to be cardioprotective in isolated heart preparations. This cardioprotection is independent of the reduction due to ATP-sparing activity or calcium overload, and appears to be related to a reduction in adrenaline release and of the rate of apoptosis[28]. This effect does not require prophylactic administration. Thus, the protective mechanism of the myocytes at the molecular level is different from and complementary to that of calcium antagonists.

Perindopril has also been shown to protect the endothelium of CAD patients, thus preventing the onset and progression of endothelial dysfunction and atherosclerosis. This, in turn, results in a significant reduction of acute coronary events[12]. The protective effects on the endothelium are related to a specific slowing of the rate of endothelial apoptosis and to an increase of expression and activity of eNOS[29,30]. While the latter effect is common to all ACE inhibitors, the antiapoptotic effect appears, at least experimentally, to be unique to perindopril[31]. It has been shown to be related to maintenance of the angiotensin (which is proapoptotic) and bradykinin (which is antiapoptotic) balance with a relatively strong affinity for bradykinin enhancement versus angiotensin II reduction[32]. CCBs have no effects on the bradykinin/angiotensin II

Table 1. *Comparison of the effects of the angiotensin-converting enzyme (ACE) inhibitor perindopril and the dihydropyridine calcium channel blocker amlodipine, and the synergy between the effects in the clinical setting (see text for references). eNOS, endothelial nitric oxide synthase; NO, nitric oxide; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; SMC, smooth muscle cell*

Perindopril	Amlodipine	Clinical advantage of synergy
↑↑ Vasodilatation	↑↑ Vasodilatation	↑↑↑Enhanced BP lowering
↓ Vasoconstriction	↑ Reflex vasoconstriction	
↑ Antioxidant effect (eNOS expression, NO)	↑ Antioxidant effect (NO)	
↑ Antiremodelling effect		
	↑ Activation of sympathetic nervous system	
↑ Endothelial function		
	↑ Coronary flow	
↑ Increased postcapillary vasodilatation	↑ Increased precapillary vasodilatation	↓ Decreased lower limb oedema
↑ t-PA activity	↑ t-PA activity	
↓ PAI-1 levels		
↓ SMC growth, proliferation and migration	↓ SMC proliferation	↑ Improved fibrinolytic balance
↓ Matrix degradation		
↓ Adhesion of monocytes		

balance, and exert little action on the endothelium, which is lacking in calcium channels. However, a modest effect on endothelial apoptosis has been documented for some calcium antagonists, possibly via a reduction of the apoptotic process as a consequence of a calcium-mediated reduction of the activity of the various caspases[33]. It follows that there is a synergy between ACE inhibitors and CCBs, even in terms of the protection of the endothelium.

In *in vivo* preparations, ACE inhibitors appear to have additional cardioprotective properties due to their ability to interfere with the central and peripheral nervous systems, such as the kallikrein–kinin system, prostaglandin levels, and sympathetic nervous system. Furthermore, ACE inhibitors, but not CCBs, have been repeatedly shown to slow the progression of post-ischaemic ventricular remodelling[34,35]. Thus, the combination of amlodipine with an ACE inhibitor such as perindopril may be useful, not only for the treatment of hypertension, but also for ischaemic heart disease. Together they will also improve fibrinolytic function, inflammation, coagulation and atherogenesis, thereby improving prognosis in CAD[11,29]. On the other hand, CCBs cause coronary vasodilatation and relief of exercise-induced vasoconstriction[3,36]. The mechanisms of action of ACE inhibitors and CCBs work in synergy leading to more efficient reduction of BP, improved fibrinolytic function, and reduction of secondary effects (Table 1).

Synergy leading to more efficient BP lowering

The more efficient reduction in BP with an ACE inhibitor/CCB combination is explained by the vasodilatory action of each agent. CCBs cause a vasodilatation that stimulates both the renin–angiotensin system (RAS) and the sympathetic nervous system, which can lead to reflex vasoconstriction and tachycardia. The vasodilatation brought about by ACE inhibition counteracts this effect, increasing the BP-lowering effect[37,38].

The antihypertensive efficacy of fixed-combination perindopril/amlodipine has been tested in an open-label, multicentre clinical trial in 500 eligible patients lasting for 8 weeks[39]. At baseline, the population had moderate-to-severe hypertension (mean BP 166/100 mmHg), and 12% had severe hypertension (SBP >180 mmHg). BP gradually decreased over 8 weeks to 132/83 mmHg ($p < 0.0001$), and a significant mean reduction of 34/17 mmHg was observed at the end of the study[39]. Target BP (<140/90 mmHg)[2] was achieved in 67% of patients at 4 weeks. The fall in BP in the subgroup with severe hypertension was even greater (–58/22 mmHg), and was highly significant ($p < 0.0001$). Fixed-combination perindopril/amlodipine was well tolerated. Adverse events were rare (1%); dry cough was reported in 0.4% of the population.

Further support for the antihypertensive effect of fixed-combination perindopril/amlodipine comes

from ASCOT, in which it was demonstrated to be an effective BP-lowering regimen[6]. However, this effect may not necessarily extend to all ACE inhibitor/CCB combinations. For example, in INVEST, the verapamil/trandolapril combination was not significantly different in terms of BP lowering from that of atenolol/hydrochlorothiazide over 2 years' treatment[21].

Synergy leading to improved fibrinolytic balance

Hypertensive and CAD patients often have impaired fibrinolytic function, as evidenced by elevated plasma plasminogen activator inhibitor type–1 (PAI-1) and decreased activity of tissue plasminogen activator (t-PA). This may contribute to the increased risk of atherosclerosis and cardiovascular disease in these patients[40]. ACE inhibitors improve fibrinolytic balance by increasing t-PA activity and decreasing PAI-1 levels, while CCBs increase t-PA activity (Table 1)[41]. When agents from the two classes are administered simultaneously, they act in synergy and improve fibrinolytic balance more than either agent alone.

This has been investigated in a 6-week study comparing the effect of combining an ACE inhibitor and CCB (benazepril/amlodipine) with that of each agent administered separately in 38 hypertensive diabetic patients, a population known to have impaired fibinolysis[42]. The ACE inhibitor alone significantly reduced PAI-1, but did not influence t-PA, while the CCB alone significantly reduced t-PA, but did not influence PAI-1. The same significant changes in PAI-1 and t-PA were observed with the combination and, notably, there was a more significant reduction in the PAI-1/t-PA ratio[42]. This synergetic effect appears to be independent of BP lowering, since no significant correlation has been reported between PAI-1 or t-PA and the reduction in BP[41].

Perindopril is already known to have a positive impact on fibrinolytic balance[43,44]. While the effect of amlodipine on fibrinolysis is also established[45], its mechanism is unknown, although it may involve an action on the vascular endothelium[41]. Plasma levels of PAI-1and t-PA were not measured in ASCOT, but the significant reductions in cardiovascular mortality, coronary events, and fatal and non-fatal stroke with this combination may be regarded as indirect evidence for the synergy of the effect of fixed-combination perindopril/amlodipine on fibrinolytic balance[6].

Synergy leading to reduced secondary effects

Dihydropyridine CCBs can cause peripheral oedema because they increase capillary hydrostatic pressure due to the occurrence of more pronounced vasodilatation in the precapillary than in the postcapillary resistance vessels[46]. In the case of amlodipine, this occurs in about 22% of patients[47], with a higher frequency in women than in men. ACE inhibition is known to reduce this secondary effect of CCBs, most likely due to the ACE inhibitor's ability to dilate venous capacitance vessels, hence normalizing intracapillary pressure and reducing fluid exudation into the interstitium (Figure 3). In the trial described above in 500 hypertensive patients treated with fixed-combination perindopril/amlodipine, there were no reports of ankle oedema.

This effect has been explored in more depth in an 8-week study in 707 hypertensive patients, in which 10.8% patients reported peripheral oedema with the CCB felodipine alone compared with 4.1% in those receiving additional ACE inhibition with enalapril[48]. This effect has also been observed using water displacement techniques and tissue pressure measurement for other ACE inhibitor/CCB combinations[49–51]. In one study, ankle oedema was assessed on the basis of ankle-foot volume and pretibial subcutaneous tissue pressure in hypertensive patients receiving the ACE inhibitor delapril or the CCB manidipine or the equivalent ACE inhibitor/CCB combination[50]. The CCB monotherapy was associated with significant increases in both ankle-foot volume and pretibial

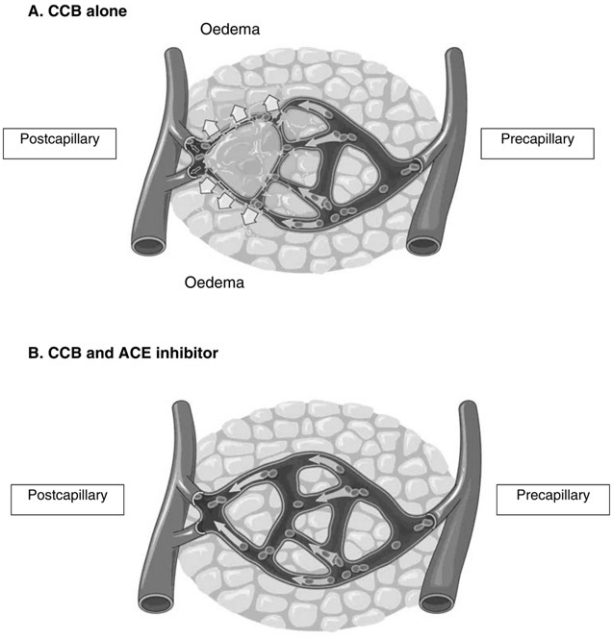

Figure 3. *Explanation for the secondary effect of peripheral oedema with calcium channel blocker (CCB) via precapillary vasodilatation (A), and its reduction by combination with an angiotensin-converting enzyme (ACE) inhibitor (B), which induces postcapillary vasodilatation. Image reproduced with permission from Servier Medical Art*

subcutaneous tissue pressure, which were significantly attenuated when the CCB was combined with the ACE inhibitor.

The vasodilatory properties of ACE inhibitors appear to make them more effective at reducing CCB-related oedema than diuretics, which only diminish fluid retention. It has even been suggested that adding an ACE inhibitor rather than a diuretic to CCB monotherapy is the optimal route to further reduce BP, while attenuating lower limb oedema[51].

Management of hypertension with fixed-combination perindopril/amlodipine

The ASCOT trial has provided evidence for the clinical advantages of fixed-combination perindopril/amlodipine[6]. This combination has proven benefits in terms of BP lowering, reduction in cardiovascular morbidity and mortality and reduction in new-onset diabetes. These benefits may not necessarily extend to other ACE inhibitor or CCB regimens[52].

Perindopril/amlodipine is a combination of two established antihypertensive agents, both of which have been in use for more than 15 years. The antihypertensive efficacy of perindopril was recently reconfirmed in a large trial carried out in more than 13 000 patients treated in general practice[7]. Nearly 50% of the patients achieved BP control after 12 weeks' treatment with perindopril. Subgroup analyses showed that perindopril was effective in different patient groups, divided according to sex, ethnicity, and age. Perindopril has a good tolerability profile, with low rates of cough, hypotension, and withdrawals[7,11,53]. Perindopril also has proven efficacy in cardiovascular disease[11], with additional benefits for coronary patients[12] and in those with stroke[54].

Amlodipine is an excellent antihypertensive, providing BP reductions of similar magnitudes to the other antihypertensive classes[8,9], though it has never been demonstrated to reduce cardiac events more than other antihypertensive agents[19,20]. Its use in hypertension is associated with good tolerability[9]. Of its secondary effects, the most undesirable is peripheral oedema; it can also lead to headache, dizziness, and flushes.

Together the two agents act in synergy, leading to more effective BP reduction and control, and an improved tolerability profile. Another feature of this particular combination is 24-h antihypertensive coverage, which may have contributed to the morbidity and mortality results reported in ASCOT[6]. Current guidelines recommend treatment regimens with a proven ability to lower BP for 24 h, preferably in a single daily dose[4]. A single daily dose of perindopril leads to 24-h BP reduction, as demonstrated by its trough-to-peak ratio of between 75% and 100%, which is the highest in the ACE inhibitor class[11]. Amlodipine, on the other hand, has a long duration of action, with time-to-peak effect of 6–12 h, an elimination half-life of 30–50 h[3], and a trough-to-peak ratio of 80–83%[55].

The most rational antihypertensive combinations, according to the European Society of Hypertension and the European Society of Cardiology guidelines, are those joined by solid lines in Figure 4A[4]. This places ACE inhibitors, CCBs, ARBs, and thiazide diuretics or indapamide – and combinations thereof – as the most appropriate choices for the management of hypertension[4]. The guidelines from the National Institute for Health and Clinical Excellence (NICE) and British Hypertension Society come to the same conclusion (Figure 4B)[5]. Moreover, ACE inhibitors, CCBs, and thiazide-type diuretics form a triangle of solid lines in Figure 4A and are all included as step 3 in Figure 4B. This makes the ACE inhibitor/CCB combination particularly convenient in terms of adherence to guidelines, since the next step in patients requiring triple therapy is logical.

A further advantage of a fixed combination is an expected positive impact on compliance, which in turn would improve long-term clinical outcomes. Compliance can be a problem in hypertension because it is a chronic asymptomatic disease, usually requiring more than one agent to achieve BP targets. A recent meta-analysis found that the use of a fixed combination in hypertension produced a 24% decrease in the risk of noncompliance compared with a regimen of the same two agents separately ($p < 0.0001$)[56]. Fixed combinations improve compliance by simplifying the dosing regimen and improving tolerability.

A pharmacoeconomic analysis has recently been applied to the results of ASCOT. As might be expected, the cost of actual treatment with the 'older' treatment of β-blocker/diuretic was lower than the 'newer' combination of perindopril/amlodipine[57]. However, these lower costs were rapidly offset by increases in other resources with the β-blocker/diuretic, in terms of number of hospitalizations and the cost of procedures, concomitant treatments, and events. Moreover, this analysis failed to take into account costs associated with microvascular complications, excess mortality due to new-onset diabetes, or rehabilitation after stroke. These can all reasonably be predicted to be lower in perindopril/amlodipine-treated patients. The authors' conclusion was that the perindopril/amlodipine combination was cost-effective in patients with moderate hypertension and additional risk factors[57].

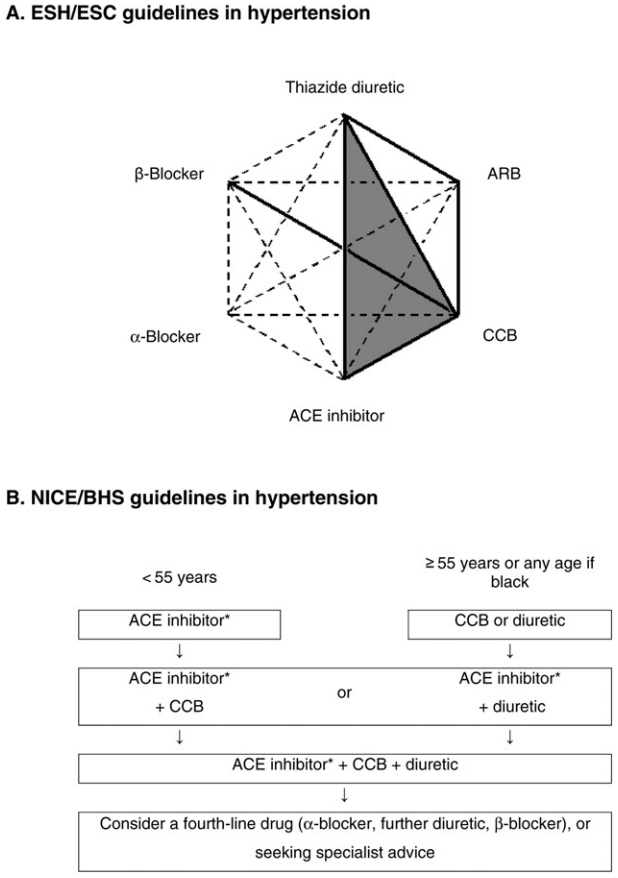

Figure 4. *(A) Possible combinations between the six main classes of antihypertensive drugs, with the preferred combinations in bold, according to the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines[4]. Angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), and thiazide diuretics or indapamide are the only triple combination to form a triangle (grey). (B) Algorithm for the treatment of newly diagnosed hypertension according to the National Institute for Health and Clinical Excellence (NICE) and British Hypertension Society (BHS)[5]. *Consider angiotensin receptor blocker (ARB) if intolerant to ACE inhibition. Modified from Mancia* et al.*, 2007[4] and NICE and BHS, 2006[5]*

Management of stable CAD with fixed-combination perindopril/amlodipine

Fixed-combination perindopril/amlodipine is the first fixed combination in the field of stable CAD, and is a credible option for the management of these patients. Fixed-combination perindopril/amlodipine associates the two parts of a normal management strategy in stable CAD into a single tablet, for use in hypertensive and normotensive individuals alike. The advantages of the fixed combination outlined above for hypertension, in terms of better tolerability, improved compliance, and synergetic effects, such as fibrinolytic function, will also apply in the CAD population. In addition, the complementary actions of perindopril and amlodipine provide secondary prevention of cardiac events and reduction of angina, respectively.

The efficacy of ACE inhibition with perindopril in the prevention of cardiovascular events in stable CAD was established in EUROPA[12]. Perindopril (8 mg/day) produced a 20% relative risk reduction in the primary end-point of cardiovascular mortality, non-fatal MI, and resuscitated cardiac arrest over 4 years versus placebo ($p = 0.0003$). This effect was independent of BP at baseline. These results were similar to those found for ramipril in the Heart Outcomes Prevention Evaluation (HOPE)[58], and led to the recommendation for the use of these ACE inhibitors as secondary prevention in patients with stable CAD[13]. Preliminary, as-yet unpublished data appear to suggest greater risk reductions in the subgroup of EUROPA receiving perindopril and CCB compared with patients receiving perindopril only or CCB only. This constitutes further support of a synergistic effect of perindopril and CCB in CAD patients. We should also note that CCBs are widely used for symptomatic relief in angina[13], and the efficacy of amlodipine in CAD is well established[59], even in normotensive individuals[60].

The selection of perindopril and amlodipine for a fixed combination in stable CAD appears particularly appropriate, since both agents have solid evidence for efficacy in this population. This is in contrast with the verapamil/trandolapril combination, for which no advantage was found versus β-blocker/diuretic in the INVEST trial[21]. This result most likely depends on the agents themselves, and implies the absence of pure class effects. For example, the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial[61] failed to find a significant effect of trandolapril in a CAD population, which has been linked to underlying differences in binding affinities of the various ACE inhibitors[32]. Also, verapamil is a nondihydropyridine CCB, which may explain the difference between its impact and that of amlodipine. In this context, we should also note that the NORDIL (Nordic Diltiazem) failed to detect a benefit in terms of cardiovascular outcomes for another nondihydropyridine CCB, diltiazem[62]. The results with perindopril/amlodipine also contrast with those of the ACTION (A Coronary Disease Trial Investigating Outcome with Nifedipine GITS)[63] and the INSIGHT (International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment)[64] trials, which found no advantage on long-term outcome with the

CCB nifedipine. Finally, a preliminary report from the EUROPA investigators suggested a synergistic effect between the agents in stable CAD patients receiving perindopril and CCB at every visit throughout the 4-year trial, and a significant reduction in total mortality versus patients receiving placebo and CCB at every visit (M. E. Bertrand, Oral communication, ESC Congress, Munich, 2008).

The dual management strategy of fixed-combination perindopril/amlodipine would also be useful for hypertensive patients with comorbid stable angina pectoris, in whom aggressive treatment of hypertension can reduce cardiovascular risk. This triple effect of fixed-combination perindopril/amlodipine (BP lowering, secondary prevention, and symptomatic anti-anginal efficacy) may be advantageous in all CAD patients.

Fixed-combination perindopril/amlodipine and type 2 diabetes

Comorbid diabetes

The relationship between type 2 diabetes mellitus and hypertension is well known, and the comorbid presence of the two diseases can profoundly affect prognosis[2]. Aggressive management strategies can reduce renal and other organ damage, and improve cardiovascular risk[2]. Combination therapy is frequently required to achieve the more stringent diabetic BP targets (<130/80 mmHg), and ACE inhibitors are strongly recommended as part of the management of these patients since they delay the progression of nephropathy[4]. CCBs remain a logical second choice when combination therapy is required[8].

ASCOT included a large subpopulation with type 2 diabetes mellitus ($n = 5137$), in whom there was a 14% difference in the end-point of major cardiovascular events (coronary events, stroke, and coronary intervention) ($p = 0.026$) in favour of the amlodipine/perindopril group[65]. This was accompanied by a 25% lower incidence of fatal and non-fatal stroke ($p = 0.017$), 48% less peripheral artery disease ($p = 0.004$), and 57% fewer non-coronary revascularization procedures ($p < 0.001$)[65]. These results are in line with other studies of ACE inhibitor/CCB combinations in hypertensive patients with diabetes. Notably, one study in 214 patients receiving either ACE inhibitor/CCB or ACE inhibitor monotherapy for 3 months concluded that the fixed combination was more effective than the monotherapy in achieving diabetic BP goals[66].

Fixed-combination perindopril/amlodipine can therefore be predicted to reproduce the positive results of ASCOT in diabetic hypertensives, providing additional reductions in total and cardiovascular mortality.

New-onset diabetes

Some antihypertensive agents or classes are recognized as increasing the risk of new-onset diabetes in nondiabetic individuals, particularly those with impaired glucose tolerance, insulin resistance, or obesity[4]. A recent network meta-analysis of 22 clinical trials evaluated the rate of new-onset diabetes according to antihypertensive class in nearly 150 000 patients[67]. This meta-analysis concluded by ranking the anti-hypertensive classes as follows[67]:

- *ACE inhibitors and ARBs*. These agents have the lowest association with new-onset diabetes, and even appear to reduce the risk of onset. They could therefore be described as having a positive effect on the risk of onset of diabetes. Several explanations for the protective effect of RAS inhibition have been advanced, including actions on circulating kinins, pancreatic insulin release, and the peripheral effect of insulin[67,68].
- *CCBs*. These agents, like placebo, are neutral with regard to the new-onset of diabetes.
- *β-Blockers and thiazide diuretics*. Treatment with one of these classes, particularly thiazide diuretics, has a negative effect and may actually increase the risk of new-onset diabetes. Thiazide diuretics induce hyperglycaemia via reduction in total body potassium, leading to a reduction in insulin secretion. The thiazide-like diuretic indapamide appears to be metabolically neutral[69]. The effect of β-blockers is less clear, but may be linked to reduced pancreatic insulin release[70].

These effects have been reported in a number of clinical trials, including ASCOT, in which the incidence of new-onset diabetes was 30% lower in the amlodipine/perindopril group than in the β-blocker/diuretic group (Figure 1)[6]. This observation is in line with the above ranking of the agents in terms of the risk of onset of diabetes[67], since ASCOT compares a combination of a 'positive' agent (an ACE inhibitor) and a 'neutral' agent (a CCB) with a combination of two 'negative' agents (β-blocker and thiazide diuretic). It has recently been suggested that the differing effect of the two ASCOT regimens is due to a composite of the adverse effects of the β-blocker/diuretic and the protective effects of perindopril, with amlodipine most probably playing a neutral role[71].

The role of ARBs in new-onset diabetes is surrounded by some controversy. For example, in

VALUE[20], only 13.1% of patients became diabetic in the valsartan arm versus 16.4% in the amlodipine arm. Considering that both arms were also receiving diuretic (hydrochlorothiazide), which increases the risk of diabetes, and also that the amlodipine arm had a greater BP reduction, the difference in new-onset diabetes may be due to the greater number of patients with high-dose hydrochlorothiazide in the amlodipine arm or to a beneficial effect of valsartan on new-onset diabetes. Moreover, surprisingly, telmisartan failed to reduce new-onset diabetes in the recent trials PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) and TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease)[72,73].

This effect has been examined more specifically in the STAR trial in 240 hypertensive patients with impaired glucose tolerance[74]. The STAR participants were randomly assigned to one of two fixed antihypertensive combinations, ACE inhibitor/CCB or ARB/diuretic. New-onset diabetes was measured over 1 year by a 2-h oral glucose tolerance test and insulin levels. An interim analysis after 12 weeks already showed a significant difference in glycaemic control and insulin sensitivity in favour of the ACE inhibitor/CCB group. After 1 year, the incidence of new-onset diabetes was significantly lower in the ACE inhibitor/CCB group (11.0 vs. 26.6%; $p = 0.002$)[74]. This result can also be rationalized in terms of the above ranking of antihypertensive classes for the risk of new diabetes[67]: STAR compares a 'positive/neutral' (an ACE inhibitor and a CCB) with a 'positive/negative' combination (an ARB and a thiazide diuretic). This indicates that the diabetes-generating effect of thiazide diuretics cannot be alleviated simply by use of low doses or combination with 'positive' agents (in this case ARB)[2,75]. In LIFE, there was a clear superiority of ARB over β-blocker toward decreasing new-onset diabetes[14], despite treatment with a diuretic. It is well known that β-blockers might increase rather than reduce new-onset diabetes. However, it is also possible that ARBs have a specific antidiabetic effect, even though this has been challenged in more recent trials[72,76].

The preliminary results of an extension of STAR have recently been reported[77], in which study participants ($n = 123$) were switched to the ACE inhibitor/CCB fixed combination for a further 6 months, independently of their treatment allocation in the first part of the trial. Fourteen percent of the population had diabetes after 6 months. The group switching from ARB/diuretic to ACE inhibitor/CCB had an improved glucose and insulin response after 6 months. The investigators conclude that the impairment of glycaemic control observed with the ARB/diuretic combination may actually be reversible by switching to an ACE inhibitor/CCB regimen.

While the diabetogenic properties of diuretics are well documented, even at low doses, the STAR study has provided strong evidence for the benefits of switching patients on an antihypertensive combination including a thiazide diuretic to an ACE inhibitor/CCB regimen, such as perindopril/amlodipine.

Fixed-combination perindopril/amlodipine and renal function

Hypertension plays an important role in kidney disease, and microalbuminuria is a clear prognostic indicator of renal and cardiovascular risk[2]. Antihypertensive treatment with ARBs has been shown to reduce microalbuminuria and improve renal function, but this has never been correlated with a reduction in mortality or cardiovascular outcomes[78–81]. On the other hand, antihypertensive treatment with ACE inhibitors and other agents can improve both renal function and long-term prognosis[4]. Meta-analytic techniques have been used to show that the use of ACE inhibitors in hypertensive patients with diabetes and evidence of nephropathy reduces all-cause mortality by 21% (95% confidence interval [CI], 0.63–0.99) compared with placebo[82]. This has been demonstrated for perindopril in a clinical study in patients with type 1 diabetes and microalbuminuria, which demonstrated reversion to normoalbuminuria in half of the perindopril-treated patients, compared with none in the placebo group[83]. In the same study, perindopril also normalized the albumin excretion rate.

The addition of a dihydropyridine CCB to an ACE inhibitor appears to confer a greater antialbuminuric advantage than monotherapy with either agent alone[36,84], which strengthens the recommendation for ACE inhibitor/CCB combinations in diabetic hypertensives. These effects have now been investigated on a large scale, in the ASCOT population, for which there was a significant 15% reduction in renal impairment ($p = 0.019$) in the amlodipine/perindopril group versus β-blocker/diuretic[6]. There is much evidence for renoprotection with perindopril/amlodipine.

Fixed-combination perindopril/amlodipine and cardiovascular risk

One explanation for the difference between the treatment groups in ASCOT is a differential impact of the

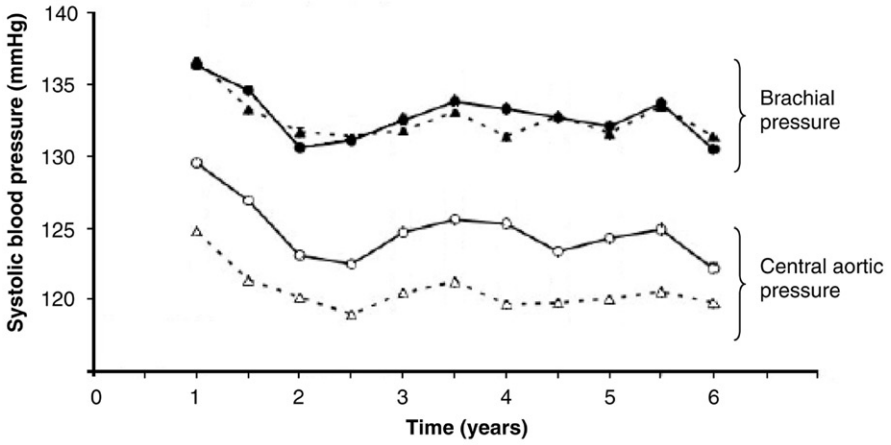

Figure 5. *Differences in brachial and central aortic systolic blood pressure for patients receiving amlodipine/perindopril (triangles) or β-blocker/diuretic (circles) in the Conduit Artery Function Evaluation (CAFE) study. Modified from Williams* et al.*, 2006*[16]

two regimens on central aortic BP. This was analysed in a substudy of ASCOT, Conduit Artery Function Evaluation (CAFE), the results of which were reported in 2006[16].

In the clinical setting, brachial artery BP is considered to accurately reflect central aortic BP. However, brachial BP is principally determined by peripheral vascular resistance and cardiac output. On the other hand, central aortic BP is also affected by the stiffness of the conduit arteries[85]. Stiffer arteries transmit the pulse wave more rapidly, which means that it returns to the heart during contraction, increasing central aortic SBP[86]. Raised central aortic SBP and pulse pressure have the effect of increasing cerebral blood flow and LV load, increasing the risks of stroke and LV hypertrophy, respectively. In addition, because of the decrease in diastolic perfusion pressure, there is an increased risk of coronary events.

In the CAFE study, brachial and central aortic pressures were measured in 2199 patients for up to 4 years (1042 in the amlodipine/perindopril group and 1031 in the β-blocker/diuretic group)[16]. The CAFE population had the same baseline characteristics as the overall ASCOT population, and there were no significant differences between the two groups. Over the duration of the study, there was no significant difference between the two groups in terms of brachial SBP (difference 0.7 mmHg; 95% CI, –0.4–1.7; $p = 0.2$). However, central aortic SBP was significantly lower in the amlodipine/perindopril group (difference 4.3 mmHg; 95% CI, 3.3–5.4; $p < 0.0001$) (Figure 5).

There are known differences in the effect of the various antihypertensive classes on central aortic BP. Brachial BP measurements appear to underestimate the effects of ACE inhibitors and CCBs, but overestimate the effect of β-blockers[86]. Moreover, because central aortic BP is believed to be linked to risk of stroke, LV hypertrophy, and coronary events, then this result can be considered as a potential explanation for the mortality and morbidity results of ASCOT[16]. Further support for the role of perindopril comes from the Regression of Arterial Stiffness in a Controlled Double-Blind study (REASON), which found a greater difference in reductions in central aortic SBP values with a perindopril/indapamide regimen than with the β-blocker atenolol[87].

Type 2 diabetes is also associated with stiffening of the conduit arteries, and should therefore be expected to have an effect on central aortic BP[85]. This hypothesis has been tested for the first time in a substudy of CAFE in 501 diabetic patients and the preliminary results have been presented. In this cohort, brachial BP measurements did not differ substantially between the groups, whereas there were significant differences in the central aortic SBP in favour of the amlodipine/perindopril arm (difference 4.9 mmHg, $p < 0.0001$)[88]. Analysis of variance showed that the difference between the brachial and central aortic pressures was further increased by the presence of diabetes. This suggests that the benefits of fixed-combination perinodopril/amlodipine would be accentuated in diabetic hypertensives.

The results of CAFE provide an explanation for the reduction in cardiovascular risk in hypertensive patients with the perindopril/amlodipine combination[6]. Further support comes from the meta-analyses of the Blood Pressure Lowering Treatment Trialists' Collaboration, which found that regimens based on ACE inhibitors and CCBs significantly reduce major cardiovascular events by 22% and 18% versus placebo, respectively[89,90]. Larger reductions in BP lead to larger reductions in risk; a 10-mmHg reduction in BP led to a

15% reduction in the risk of stroke or CHD[91]. There are also differences between classes, for ACE inhibitors are superior to CCBs in the prevention of CHD and heart failure, whereas CCBs are superior to ACE inhibitors in the prevention of stroke[90,91]. ACE inhibition is known to have a positive impact on CHD, but the mechanisms responsible for stroke protection with CCBs remain less clear, though their hypotensive effects may play a role[91]. ACE inhibition may also have a positive impact on stroke risk, considering the results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[54], in which perindopril/indapamide prevented secondary stroke in patients with a history of stroke or transient ischaemic attack. These observations are in line with the broad range of risk reduction observed in ASCOT (Figure 1)[6], and provide further support for protection against cardiovascular risk with fixed-combination perindopril/amlodipine.

Conclusion

Optimized management of hypertension improves cardiovascular prognosis (incidence of MI, heart failure, and stroke) and can help prevent new-onset diabetes in at-risk individuals. Although most hypertensive patients will need at least two agents to achieve the BP targets set by international guidelines[2,4,5], physicians currently have a bewildering array of combinations to choose from, and one of the difficulties is becoming the selection of the most appropriate regimen.

The clinical benefits of fixed-combination perindopril/amlodipine as discussed in this review are summarized in Table 2. Fixed-combination perindopril/amlodipine constitutes a guideline-recommended[2,4,5] combination of two well-known agents with proven efficacy in BP lowering over 24 h. Moreover, this reproduces the ASCOT combination[6], which provides the physician with the opportunity to reproduce the ASCOT results in clinical practice. This can be expected to translate into reduced cardiovascular mortality and morbidity, and improved risk for the incidence of new-onset diabetes[6]. The perindopril/amlodipine combination reduces hypertension via two complementary mechanisms of action working in synergy. This should lead to more efficient BP lowering and better tolerability. Patients with stable CAD could also benefit from fixed-combination perindopril/amlodipine, which combines the symptomatic and prognostic management of stable angina into a single tablet. The reduction in cardiovascular risk is accompanied by reduction in the risks of CHD and heart failure, due to the presence of perindopril[11,12], and in the risk of stroke, due to that of amlodipine[91]. Finally, the efficient BP-lowering effect expected for fixed-combination perindopril/amlodipine should also be of advantage in diabetic hypertensive patients, who require aggressive management of their condition.

Table 2. *Summary of the clinical benefits of fixed-combination perindopril/amlodipine in hypertension and coronary artery disease (CAD) (see text for references). ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BP, blood pressure; CHD, coronary heart disease*

Hypertension	Efficient BP reduction
	Two well-known agents with proven antihypertensive efficacy
	Combination used in ASCOT
	Synergy of two complementary mechanisms of action
	24-h BP control
Coronary artery disease	Prognostic management of stable CAD (perindopril)
	Symptomatic management of stable angina crises (amlodipine)
	Aggressive BP reduction in stable angina pectoris
Type 2 diabetes	Reduction in the risk of new-onset diabetes
	Aggressive BP reduction in hypertensive diabetics
Reduction in secondary effects	Improved tolerability
	Reduction in peripheral oedema due to amlodipine
Cardiovascular risk reduction	Reduction of cardiovascular morbidity and mortality
	Reduction in risk of CHD and heart failure (perindopril)
	Reduction in risk of stroke (amlodipine)
Pharmacoeconomics	Cost-effective in hypertension

The clinical evidence for fixed-combination perindopril/amlodipine indicates it as a viable choice to optimize the management of hypertension and stable CAD. The combination is available as perindopril/amlodipine 5/5 mg, 5/10 mg, 10/5 mg, and 10/10 mg, which allows for flexible dosing. Its addition to the therapeutic armamentarium will facilitate the selection of an effective regimen for these patients.

Acknowledgements

Declaration of interest: This article is supported by Servier. R. F. has received research grants and honoraria from Servier for participating as an executive committee member of the EUROPA and BEAUTIFUL trials. The author takes full responsibility for the contents of this article. The sponsor, Servier, had no form of contribution or input to the contents of the article or its drafting.

References

1. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365:217-23
2. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52
3. Kaplan NM. Clinical Hypertension. Philadelphia, PA: Lippincott, Williams, & Wilkins, 2006
4. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007;28:1462-536
5. National Institute for Health and Clinical Excellence (NICE) – British Hypertension Society (BHS). Hypertension: management of hypertension in adults in primary care. Available from www.nice.org.uk/CG034guidance. [Accessed 12 July 2006]
6. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895-906
7. Julius S, Cohn JN, Neutel J, et al. Antihypertensive utility of perindopril in a large, general practice-based clinical trial. J Clin Hypertens (Greenwich) 2004;6:10-17
8. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. J Am Coll Cardiol 2002;39:315-22
9. Weir MR. Calcium channel blockers: their pharmacologic and therapeutic role in hypertension. Am J Cardiovasc Drugs 2007;7(Suppl 1):5-15
10. Telejko E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. Curr Med Res Opin 2007;23:953-60
11. Ferrari R. Angiotensin-converting enzyme inhibition in cardiovascular disease: evidence with perindopril. Expert Rev Cardiovasc Ther 2005;3:15-29
12. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782-8
13. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. Eur Heart J 2006;27:1341-81
14. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003
15. Poulter NR, Wedel H, Dahlof B, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet 2005; 366:907-13
16. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113:1213-25
17. Brady AJ. Perindopril versus angiotensin II receptor blockade in hypertension and coronary artery disease: implications of clinical trials. Clin Drug Investig 2007;27:149-61
18. Meurin P. The ASCOT trial: clarifying the role of ACE inhibition in the reduction of cardiovascular events in patients with hypertension. Am J Cardiovasc Drugs 2006; 6:327-34
19. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97
20. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022-31
21. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290: 2805-16
22. Ferrari R. Angiotensin converting enzyme inhibitor-calcium antagonist combination: an alliance for cardioprotection? J Hypertens Suppl 1997;15:S109-17
23. Ferrari R. Major differences among the three classes of calcium antagonists. Eur Heart J 1997;18(Suppl A):A56-70
24. Riordan JF. Angiotensin-I-converting enzyme and its relatives. Genome Biol 2003;4:225
25. Wiemer G, Linz W, Hatrik S, et al. Angiotensin-converting enzyme inhibition alters nitric oxide and superoxide release in normotensive and hypertensive rats. Hypertension 1997; 30:1183-90
26. Boraso A, Bernocchi P, Benigno M, et al. Time-dependence of the cardioprotective effects of lercandipine. J Cardiovasc Pharmacol 1997;29:69-77
27. Ferrari R, Visioli O. Protective effects of calcium antagonists against ischaemia and reperfusion damage. Drugs 1991; 42(Suppl 1):14-26
28. Ferrari R. Mechanisms of protective effects of angiotensin-converting enzyme inhibitors in myocardial ischaemia. In: Fox K, Remme W. ACE inhibition and ischaemic heart disease. London, UK: Science Press, 1999:13-23
29. Ceconi C, Fox KM, Remme WJ, et al. ACE inhibition with perindopril and endothelial dysfunction. Results of a substudy of the EUROPA study: PERTINENT. Cardiovasc Res 2007;73:237-46

30. Comini L, Bachetti T, Cargnoni A, et al. Therapeutic modulation of the nitric oxide pathway: are all ACE inhibitors equivalent? Pharmacol Res 2007;56:42-8
31. Ceconi C, Francolini G, Bastianon D, et al. Differences in the effect of angiotensin-converting enzyme inhibitors on the rate of endothelial cell apoptosis: in vitro and in vivo studies. Cardiovasc Drugs Ther 2007;21:423-9
32. Ceconi C, Francolini G, Olivares A, et al. Angiotensin-converting enzyme (ACE) inhibitors have different selectivity for bradykinin binding sites of human somatic ACE. Eur J Pharmacol 2007;577:1-6
33. Gao F, Gong B, Christopher TA, et al. Anti-apoptotic effect of benidipine, a long-lasting vasodilating calcium antagonist, in ischaemic/reperfused myocardial cells. Br J Pharmacol 2001;132:869-78
34. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342:821-8
35. Ferrari R. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. Arch Intern Med 2006;166:659-66
36. Weir MR. Targeting mechanisms of hypertensive vascular disease with dual calcium channel and renin-angiotensin system blockade. J Hum Hypertens 2007;21:770-9
37. Rosenthal T, Gavras I. Fixed-drug combinations as first-line treatment for hypertension. Prog Cardiovasc Dis 2006; 48:416-25
38. McInnes GT. Antihypertensive drugs in combination: additive or greater than additive? J Hum Hypertens 2007; 21:914-16
39. Jadhav U. Evaluation of efficacy and tolerability of perindopril and amlodipine combination in the management of patients with moderate-to-severe hypertension in India. Poster presentation at the 23rd Annual Scientific Meeting of the American Society of Hypertension, New Orleans, LA, May 14-17. J Clin Hypertens 2008, Abstract
40. Poli KA, Tofler GH, Larson MG, et al. Association of blood pressure with fibrinolytic potential in the Framingham Offspring population. Circulation 2000;101:264-9
41. Fogari R, Zoppi A. Antihypertensive drugs and fibrinolytic function. Am J Hypertens 2006;19:129-39
42. Fogari R, Preti P, Lazzari P, et al. Effect of benazepril amlodipine combination on fibrinolysis in hypertensive diabetic patients. Eur J Clin Pharmacol 2003;59:271-5
43. Fogari R, Mugellini A, Zoppi A, et al. Losartan and perindopril effects on plasma plasminogen activator inhibitor-1 and fibrinogen in hypertensive type 2 diabetic patients. Am J Hypertens 2002;15:316-20
44. Matsumoto T, Minai K, Horie H, et al. Angiotensin-converting enzyme inhibition but not angiotensin II type 1 receptor antagonism augments coronary release of tissue plasminogen activator in hypertensive patients. J Am Coll Cardiol 2003; 41:1373-9
45. Gleerup G, Winther K. Decreased fibrinolytic activity and increased platelet function in hypertension. Possible influence of calcium antagonism. Am J Hypertens 1991;4:168-71
46. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. Am J Hypertens 2001;14:978-9
47. Fogari R. Ankle oedema and sympathetic activation. Drugs 2005;65(Suppl 2):21-7
48. Gradman AH, Cutler NR, Davis PJ, et al. Combined enalapril and felodipine extended release (ER) for systemic hypertension. Enalapril-Felodipine ER Factorial Study Group. Am J Cardiol 1997;79:431-5
49. Fogari R, Malamani GD, Zoppi A, et al. Effect of benazepril addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. J Hum Hypertens 2003;17:207-12
50. Fogari R, Malamani G, Zoppi A, et al. Effect on the development of ankle edema of adding delapril to manidipine in patients with mild to moderate essential hypertension: a three-way crossover study. Clin Ther 2007;29:413-18
51. Weir MR, Rosenberger C, Fink JC. Pilot study to evaluate a water displacement technique to compare effects of diuretics and ACE inhibitors to alleviate lower extremity edema due to dihydropyridine calcium antagonists. Am J Hypertens 2001;14:963-8
52. Doggrell SA, Wang QH, Yue P, et al. Is amlodipine the best initial a monotherapy for hypertension? Expert Opin Pharmacother 2006;7:829-32
53. Yoshinaga K, Saruta T, Abe K, et al. Clinical evaluation of monotherapy with perindopril, an ACE inhibitor, in the treatment of essential hypertension: double-blind parallel comparison with enalapril. J Clin Ther Medicines 1997; 13:4259-97
54. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41
55. Zannad F, Bernaud CM, Fay R. Double-blind, randomized, multicentre comparison of the effects of amlodipine and perindopril on 24 h therapeutic coverage and beyond in patients with mild to moderate hypertension. J Hypertens 1999;17:137-46
56. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007;120:713-19
57. Lindgren P, Buxton M, Kahan T, et al. Economic Evaluation of ASCOT-BPLA: Antihypertensive treatment with an amlodipine-based regimen is cost-effective compared to an atenolol-based regimen. Heart 2008;94:e4
58. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53
59. Davies RF, Habibi H, Klinke WP, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. J Am Coll Cardiol 1995;25:619-25
60. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA 2004;292:2217-25
61. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058-68
62. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000;356:359-65
63. Poole Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet 2004; 364:849-57
64. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000;356:366-72
65. Östergren J, Poulter NR, Sever PS, et al for the ASCOT investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes . J Hypertens 2008;26:2103-2111.
66. Bakris GL, Weir MR. Achieving goal blood pressure in patients with type 2 diabetes: conventional versus fixed-dose combination approaches. J Clin Hypertens (Greenwich) 2003;5:202-9

67. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 2007;369:201-7
68. Scheen AJ. Prevention of type 2 diabetes mellitus through inhibition of the renin-angiotensin system. Drugs 2004; 64:2537-65
69. Marre M, Puig JG, Kokot F, et al. Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: The NESTOR* study. J Hypertens 2004;22:1613-22
70. Luna B, Feinglos MN. Drug-induced hyperglycemia. JAMA 2001;286:1945-8
71. Gupta AK, Dahlof B, Dobson J, et al. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the ASCOT-BPLA trial and the relative influence of antihypertensive medication. Diabetes Care 2008;31:982-8
72. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174-83
73. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008;359:1225-37
74. Bakris G, Molitch M, Hewkin A, et al. Differences in glucose tolerance between fixed-dose antihypertensive drug combinations in people with metabolic syndrome. Diabetes Care 2006; 29:2592-7
75. Messerli FH, Kuteyeva O. Bashing diuretics or failure of surrogate endpoint? J Hypertens 2007;25:949-50
76. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358:1547-59
77. Bakris G, Molitch M, Zhou Q, et al. Reversal of diuretic-associated impaired glucose tolerance and new-onset diabetes: results of the STAR-LET study. J Cardiometab Syndr 2008;3:18-25.
78. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8
79. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 2002;106:672-8
80. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345:861-9
81. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60
82. Strippoli GF, Craig M, Deeks JJ, et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ 2004;329:828
83. Jerums G, Allen TJ, Campbell DJ, et al. Long-term comparison between perindopril and nifedipine in normotensive patients with type 1 diabetes and microalbuminuria. Am J Kidney Dis 2001;37:890-9
84. Fogari R, Preti P, Zoppi A, et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. Am J Hypertens 2002;15:1042-9
85. Protogerou AD, Papaioannou TG, Blacher J, et al. Central blood pressures: do we need them in the management of cardiovascular disease? Is it a feasible therapeutic target? J Hypertens 2007;25:265-72
86. Morgan T, Lauri J, Bertram D, Anderson A. Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004;17:118-23
87. Asmar RG, London GM, O'Rourke ME, et al. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension 2001;38:922-6
88. Lacy PS, Cruickshank JK, Thom S, *et al.* Diabetes accentuates the differential impact of blood pressure-lowering drugs on central aortic pressure: principal results from CAFE-DIABETES; the diabetic cohort within the Conduit Artery Functional Evaluation (CAFE) study. J Hypertens 2007;25(Suppl 2): S279, Abstract
89. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2000;356:1955-64
90. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. Lancet 2003;362: 1527-35
91. Verdecchia P, Reboldi G, Angeli F, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension 2005;46:386-92

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-4758_4, *Accepted for publication:* 24 October 2008
Published Online: 19 November 2008
doi:10.1185/03007990802576302