Contribution of perindopril to cardiology: 20 years of success

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Cardiovascular risk factors such as hypertension and diabetes are known to initiate a chain of events that include oxidative stress, endothelial dysfunction, and vascular remodelling, and that if left to progress unchecked, will eventually culminate in end-stage cardiovascular disease. Perindopril is a long-acting lipophilic inhibitor of tissue angiotensin-converting enzyme (ACE) that has been studied in a variety of patient populations, ranging from those with hypertension to more advanced-stage cardiovascular disease. Although the role of ACE inhibitors is well established for patients with hypertension or heart failure, large morbidity–mortality trials have proved the efficacy of perindopril in a comparatively wide range of patients at risk of cardiovascular events, including patients with a history of stroke or transient ischaemic attack, irrespective of whether hypertension was present, and patients with stable coronary artery disease without heart failure or substantial hypertension. In addition, relative to a standard antihypertensive regimen based on a β-blocker/diuretic, a calcium antagonist/perindopril-based regimen has been shown to provide more effective broad-spectrum prevention of cardiovascular events in hypertensive patients. Early studies revealed that, in addition to sustained 24 h antihypertensive activity with once-daily dosing, perindopril is able to reverse arterial remodelling in hypertensive patients. Furthermore, subanalyses of data from morbidity–mortality trials have shown that reversal of abnormal endothelial function and reductions in central aortic pressure may help to account for benefits observed with perindopril that extend beyond those expected from reductions in brachial blood pressure alone. In summary, although it is already a well-established antihypertensive drug, pivotal clinical trials are still helping to unravel the true potential of perindopril across the cardiovascular continuum.

Introduction

Angiotensin-converting enzyme (ACE) plays a key role in hypertension and is induced in virtually every model of cardiac injury, and, as a class of agents, ACE inhibitors are recognized as representing one of the most comprehensive approaches to the treatment and prevention of cardiovascular disease. Among the available ACE inhibitors, important structural and pharmacokinetic differences exist, which may prove to have clinically significant ramifications.

Perindopril, discovered in the early 1980s, is one of the best studied ACE inhibitors in both preclinical and clinical settings. Originally developed for the treatment of hypertension, a number of morbidity–mortality trials have now revealed that perindopril benefits patients with a wide range of cardiovascular conditions, from hypertension, which is an important cardiovascular risk factor, right through to the end stages of cardiovascular disease (Figure 1). In this article, we document the history of perindopril from development to the present day.
Perindopril development studies

Perindopril is a third-generation ACE inhibitor that was created with the aim of providing all the benefits of ACE inhibition, including cardiovascular protection beyond blood pressure (BP)-lowering alone, together with excellent tolerability (low incidence of cough and absence of first-dose hypotension), and true 24 h efficacy with once-daily dosing.4

Vascular and cardiac remodelling studies

In hypertension, vascular remodelling of the arteries may have adverse effects on end organs such as the brain, heart, and kidney. In addition to effectively reducing BP, treatment strategies should, therefore, help to normalize vascular structure. Accordingly, a substantial component of the perindopril development process has been devoted to studying the effects of the drug on cardiovascular remodelling and revealing the ability of the drug to reverse abnormalities in the structure and function of small and large arteries.

When administered for 3 months, perindopril significantly improved the diameter and compliance of the brachial artery in patients with sustained essential hypertension.5 Furthermore, despite similar reductions in BP, treatment strategies should, therefore, help to normalize vascular structure. Accordingly, a substantial component of the perindopril development process has been devoted to studying the effects of the drug on cardiovascular remodelling and revealing the ability of the drug to reverse abnormalities in the structure and function of small and large arteries.

At the site of small resistance arteries, long-term treatment with perindopril resulted in normalization of increased media-to-lumen ratios in hypertensive patients.8,9 When perindopril was compared with atenolol, both drugs significantly reduced BP, but only perindopril led to normalization of small artery morphology.9 A reduction in the left ventricular (LV) mass has been seen to occur in parallel with normalization of resistance artery structure in hypertensive patients treated with perindopril.8

Studies of antihypertensive efficacy

Use of long-acting formulations that provide 24 h antihypertensive effect should ideally be used in the treatment of hypertension. A common indicator of sustained BP control is provided by the trough:peak BP ratio. Myers10 reported that the ratio of changes in placebo-corrected diastolic BP at 24 h vs. 6 h after dosing with perindopril 2–8 mg ranged between 0.97 and 1.0. Perindopril compares favourably with other ACE inhibitors in this regard.11,12

Perindopril has been established as an effective and well-tolerated antihypertensive agent.13–15 Indeed, in a large community-based clinical trial, monotherapy with perindopril 4–8 mg/day was associated with a clinically and statistically significant reduction in BP of −19.7/10.5 mmHg in the overall population and −14.9/8.4 mmHg in hypertensive patients who were non-responsive to previous antihypertensive therapy.13,14 Previous antihypertensive agents used in non-responsive patients included ACE inhibitors, diuretics, calcium channel blockers, β-blockers, angiotensin receptor blockers, and α-blockers. The authors of the study suggested that a number of factors may have contributed to this antihypertensive effect of perindopril in this group of otherwise non-responsive patients, including the relatively consistent 24 h antihypertensive efficacy of...
perindopril and unique effects of the drug on arterial compliance, as described earlier. Compared with other antihypertensive agents, including calcium channel blockers, angiotensin receptor antagonists and β-blockers, in a relatively recent study, perindopril was the only agent to normalize brachial artery endothelial function in hypertensive patients. It is therefore possible that the antihypertensive efficacy of perindopril in patients non-responsive to other agents may, in part, be a result of perindopril-induced improvements in endothelium-dependent vasodilation in peripheral conduit arteries.

First morbidity–mortality data

The beneficial effects of perindopril on mortality were first demonstrated in a study of patients with end-stage renal failure (ESRF). In this study, 150 ESRF patients were randomized to receive perindopril 4–8 mg/day every 48 h or nitrendipine 10–20 mg/day. If target BP was not achieved, atenolol 10–20 mg/day was also prescribed. Over a mean 51 months of follow-up, use of perindopril, either alone or in combination, had a favourable impact on all-cause and cardiovascular mortality [relative risk reduction (RRR) 81 and 82%, respectively; \( P < 0.005 \)] that was independent of changes in BP. LV hypertrophy was an independent predictor of mortality in this patient population. Prior to publication of this study, it was reported that perindopril, but not nitrendipine, induced a pressure-independent decrease of LV hypertrophy in ESRF patients that was associated with reduction of LV diameter and cavity volume.

Pivotal morbidity–mortality trials

In general, ACE inhibitors have been extensively studied in patients with hypertension, heart failure (HF), or impaired LV function after myocardial infarction (MI). Pivotal studies involving perindopril have, however, involved a wide range of patients, including patients without hypertension and patients without apparent LV dysfunction. Acronyms of major studies, and substudies thereof, discussed in this review are explained in Table 1.

PROGRESS

Although the value of antihypertensive therapy is unequivocal with regard to the primary prevention of stroke, the PROGRESS study was conducted in an effort to resolve clinical uncertainty regarding the utility of perindopril-based therapy in patients who had previously experienced a stroke or transient ischaemic attack. Patients (\( n = 6105 \)) who were randomized to active treatment (perindopril 4 mg/day + indapamide 2.5 mg/day when needed) or placebo were required to have no definite indication for treatment with an ACE inhibitor, and there were no BP entry criteria. It was recommended that patients with uncontrolled hypertension received antihypertensive therapy with agents other than ACE inhibitors prior to the study. The effects of therapy on cardiovascular outcomes are illustrated in Figure 2. Over the mean 3.9 year follow-up period, active treatment significantly reduced the risk of the primary outcome (28% reduction in the relative risk of stroke vs. placebo; \( P < 0.0001 \)). This included a 50% reduction in haemorrhagic stroke and a 24% reduction in ischaemic stroke. Active treatment also reduced the risk of major cardiovascular events (non-fatal MI or death from cardiovascular disease) by 26%, and the risk of non-fatal MI was reduced by 38%. With regard to the risk of stroke and major cardiovascular events, benefits associated with perindopril-based therapy were similar in hypertensive (mean baseline BP 159/94 mmHg) and non-hypertensive patients (mean baseline BP 136/79 mmHg). There were only small differences in BP reductions observed for patients classified as hypertensive or non-hypertensive at baseline (\(-9.5/3.9 \) and \(-8.8/4.2 \) mmHg, respectively).

EUROPA

Prior to the EUROPA study, clinical trials had established the efficacy of ACE inhibitors in the reduction of morbidity and mortality among patients with hypertension, HF, or LV dysfunction after MI. The EUROPA study was designed to assess whether the protective effects of ACE inhibition would extend to a relatively low risk general population of patients with stable coronary artery disease (CAD) without HF or substantial hypertension. In addition to the fact that it is a long-acting ACE inhibitor with high lipophilicity, which may facilitate relatively high penetration into the atherosclerotic...
plaque where it may counter the deleterious effects of angiotensin II, improve endothelial function, and hinder the development of atherosclerosis and thrombosis,\(^2\) perindopril was chosen as the ACE inhibitor for the EUROPA trial because of its documented effects on reducing cardiovascular remodelling.\(^{20}\)

During the EUROPA study, 12,218 patients with stable CAD without clinical evidence of HF or uncontrolled hypertension (>180/100 mmHg) were randomized to perindopril 8 mg/day or placebo for >3 years.\(^{20}\) After a mean follow-up of 4.2 years, the relative risk of the primary endpoint (cardiovascular mortality, non-fatal MI, or resuscitated cardiac arrest) was reduced by 20\% with perindopril vs. placebo (\(P = 0.0003\) (\(P = 0.0003\) Table 2)). The beneficial effect of perindopril on the primary endpoint was consistent across predefined subgroups, regardless of age, whether patients had hypertension, diabetes, or previous MI, and in patients receiving lipid-lowering drugs or \(\beta\)-blockers (Figure 3). Most of the EUROPA study population was receiving antplatelet therapy. Post hoc analysis of the EUROPA study data showed that the treatment effect associated with perindopril was constant in patients with high (>3\%), medium (1–3\%), and low (<1\%) level cardiovascular risk per year.\(^{21}\) It has been noted that the 22\% reduction in the risk of MI cannot be explained by the -5/2 mmHg reduction in BP alone, thereby suggesting that a mechanism other than BP reduction was contributing to improved outcome with perindopril.\(^{22,20}\) In relation to the magnitude of the reduction in BP associated with perindopril, it should be borne in mind that baseline BP levels in EUROPA were 137/82 mmHg, that half of the population was normotensive (BP < 140/80 mmHg), that hypertensive patients were already receiving treatment with non-ACE inhibitor antihypertensive agents, and that hypotension was cited as a reason for withdrawal in only 1.0\% of patients.\(^{20}\) Most of EUROPA patients (58\%) had measurements of LV ejection fraction (LVEF) before randomization. The mean LVEF of this population was 57.0 ± 10.4\%, and only 3\% had an impaired LV function, confirming that EUROPA patients did not have asymptomatic LV dysfunction. In patients with preserved LV function (LVEF ≥ 40\%), there was a significant RRR of 16\% of the primary endpoint.\(^{22}\) In a subgroup of EUROPA patients with a previous revascularization (54.9\%), perindopril reduced relative risk of the primary endpoint by 17.3\% (\(P = 0.036\) and risk of MI by 23\% (\(P = 0.015\)). Of note, in the subgroup population of revascularized patients without a history of MI, perindopril was associated with an RRR of 31.7\% for fatal and non-fatal MI (\(P = 0.026\)).

The European Medicines Agency and the US Food and Drug Administration have, after the publication of the EUROPA results, extended perindopril’s indication to include secondary prevention in CAD patients.\(^{24}\) Notably, results from the EUROPA trial have also contributed to the recent European Society of Cardiology recommendation that ACE inhibitor therapy be instigated in all patients with CAD and hypertension, diabetes, previous MI, or LV dysfunction, as well as patients with HF.\(^{25}\)

**Insights into perindopril’s mode of action**

Experimental studies comparing different ACE inhibitors have demonstrated that certain properties of perindopril may contribute to the therapeutic efficacy observed with the drug in trials such as EUROPA. Being lipophilic, perindopril compares very favourably among ACE inhibitors in terms of tissue penetration, which is a factor consistently shown to be correlated with anti-atherosclerotic

**Figure 2** Effects of perindopril-based treatment on stroke subtypes and major vascular events in patients with history of stroke or transient ischaemic attack participating in the PROGRESS study.\(^{19}\) Black squares indicate point estimates, with area proportional to number of events; horizontal lines, 95\% confidence intervals; diamonds, point estimates and 95\% confidence intervals for overall effect; vertical dashed line, point estimate for overall effect. MI, myocardial infarction. Adapted from *Lancet* 2001;358:1033–1041 (Figure 4 on p. 1037).
effects. Potentiation of bradykinin, which counteracts the harmful effects of angiotensin II and contributes to the longer term anti-ischaemic effects of ACE inhibitors, is also particularly pronounced for perindopril. The PERTINENT substudy of EUROPA 20 is offering important new insights into mechanisms that could have contributed to the beneficial effects of perindopril on mortality and morbidity in patients with stable CAD. Results demonstrating that after 1 year of treatment, improvements in endothelial function occurred in patients receiving perindopril, have been published. Analysis of blood drawn from more than 1000 EUROPA participants revealed that perindopril independently and significantly reduced levels of von Willebrand factor (P < 0.001 vs. placebo), a procoagulant product of the endothelium and marker of endothelial damage, high levels of which were associated with cardiovascular events at baseline (P = 0.013). Endothelial function was also investigated more directly, at the cellular level, by cultivating human umbilical vein endothelial cells with serum taken from 87 EUROPA patients, revealing a 27% upregulation of endothelial nitric oxide synthase activity—which plays a pivotal role in the maintenance of endothelial function—after 1 year of treatment with perindopril, as well as a 31% reduction in the rate of apoptosis (Table 3). Levels of tumour necrosis factor-α,
an inducer of apoptosis and negative modulator of endothelial nitric oxide synthase, were reduced by 13% from baseline during treatment with perindopril. Perindopril also helped to restore the balance between angiotensin II (27% reduction; \( P < 0.05 \)) and bradykinin (17% increase; \( P < 0.05 \)) (Table 3). The only significant correlation was between bradykinin and endothelial nitric oxide synthase activity (\( r = 0.43; \ P < 0.05 \)), indicating that the bradykinin pathway is instrumental in facilitating perindopril-induced improvements in endothelial function.

### ASCOT-BPLA

In order to reach target BP, it is agreed that two or more antihypertensive agents will be required in most patients, but the issue of as to which antihypertensive agents should be used in first-line treatment is controversial. The ASCOT-BPLA trial was the first to investigate whether a modern antihypertensive treatment regimen based on amlodipine and perindopril could provide further benefits in terms of reducing cardiovascular events beyond those provided by standard therapy with atenolol and a thiazide diuretic in hypertensive patients.28 A total of 19,257 patients with untreated or poorly controlled hypertension (BP > 160/100 mmHg or > 140/90 mmHg, respectively) and at least three other cardiovascular risk factors were randomized to amlodipine 5–10 mg/day, adding perindopril 4–8 mg/day as needed, or atenolol 50–100 mg/day, adding bendroflumethiazide 1.25–2.5 mg/day and potassium as needed. After 5.5 years, median follow-up, the study was stopped prematurely because, compared with patients treated with atenolol/bendroflumethiazide, all-cause mortality was reduced by 11% in the amlodipine/perindopril group (\( P < 0.05 \)) (Table 4). At the end of the study,

### Table 3  Effects of perindopril on markers of endothelial function in patients with stable coronary artery disease assessed as part of the PERTINENT\(^{26}\) substudy of EUROPA\(^{20}\)

<table>
<thead>
<tr>
<th>Markers</th>
<th>Baseline</th>
<th>Placebo (n = 44)</th>
<th>Perindopril (n = 43)</th>
<th>One year</th>
<th>Placebo (n = 44)</th>
<th>Perindopril (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Perindopril (n = 43)</td>
<td></td>
<td></td>
<td>Placebo (n = 44)</td>
<td>Perindopril (n = 43)</td>
</tr>
<tr>
<td>eNOS expression (arb. units/mg protein)</td>
<td>7.4 ± 2.9</td>
<td>7.6 ± 4.9</td>
<td>8.7 ± 3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eNOS activity (pmol/min/mg protein)</td>
<td>2.5 ± 1.0</td>
<td>2.9 ± 1.0</td>
<td>3.3 ± 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apoptosis (%)</td>
<td>7.8 ± 2.9</td>
<td>7.0 ± 2.6</td>
<td>4.7 ± 2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin II (pg/mL)</td>
<td>15.8 ± 7.7</td>
<td>14.4 ± 5.5</td>
<td>12.5 ± 5.2</td>
<td></td>
<td></td>
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<tr>
<td>Bradykinin (pg/mL)</td>
<td>12.4 ± 6.0</td>
<td>12.3 ± 6.6</td>
<td>17.7 ± 6.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-(\alpha) (pg/mL)</td>
<td>27.7 ± 4.4</td>
<td>28.9 ± 5.9</td>
<td>24.6 ± 11.4</td>
<td></td>
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</tbody>
</table>

Data are expressed as mean ± standard deviation.
eNOS, endothelial nitric oxide synthase; TNF, tumour necrosis factor.
\(*P < 0.05\) for change associated with perindopril vs. placebo.

### Table 4  Effects of an amlodipine/perindopril-based antihypertensive treatment regimen vs. an atenolol/bendroflumethiazide-based regimen on cardiovascular outcomes in hypertensive patients participating in the ASCOT-BPLA study\(^{28}\)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Frequency</th>
<th>Amlodipine/perindopril-based regimen (n = 9639)</th>
<th>Atenolol/thiazide-based regimen (n = 9618)</th>
<th>Unadjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI (including silent) + fatal CHD</td>
<td>429 (5%)</td>
<td>474 (5%)</td>
<td></td>
<td>0.90 (0.79–1.02)</td>
</tr>
<tr>
<td>Non-fatal MI (excluding silent) + fatal CHD</td>
<td>390 (4%)</td>
<td>444 (5%)</td>
<td></td>
<td>0.87 (0.76–1.00)***</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>753 (8%)</td>
<td>852 (9%)</td>
<td></td>
<td>0.84 (0.78–0.90)***</td>
</tr>
<tr>
<td>Total cardiovascular events and procedures</td>
<td>1362 (14%)</td>
<td>1602 (17%)</td>
<td></td>
<td>0.89 (0.81–0.99)***</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>738 (8%)</td>
<td>820 (9%)</td>
<td></td>
<td>0.76 (0.65–0.90)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>263 (3%)</td>
<td>342 (4%)</td>
<td></td>
<td>0.77 (0.66–0.89)**</td>
</tr>
<tr>
<td>Fatal and non-fatal stroke</td>
<td>327 (3%)</td>
<td>422 (4%)</td>
<td></td>
<td>0.84 (0.66–1.05)**</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>567 (6%)</td>
<td>799 (8%)</td>
<td></td>
<td>0.70 (0.63–0.78)***</td>
</tr>
<tr>
<td>Development of renal impairment</td>
<td>403 (4%)</td>
<td>469 (5%)</td>
<td></td>
<td>0.85 (0.75–0.97)***</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.
\(*P < 0.05\), **P < 0.001, ***P < 0.0001 vs. atenolol/thiazide.
most patients were taking at least two study drugs (78%). The primary endpoint (non-fatal MI, including silent MI, and fatal coronary heart disease) was lowered by 10% with amlodipine/perindopril (Table 4), but, as a result of loss of power due to early trial termination, statistical significance was not attained. There were, however, significant reductions across a range of other endpoints, including total coronary events, total cardiovascular events and procedures, cardiovascular mortality, fatal and non-fatal stroke, development of diabetes, and development of renal impairment, in the amlodipine/perindopril treatment arm (Table 4).

The CAFE substudy of 2199 patients from the ASCOT-BPLA trial demonstrated that, despite similar effects on brachial systolic BP in the two treatment groups, central aortic systolic BP was 4.3 mmHg lower and central aortic pulse pressure was 3.0 mmHg lower in the amlodipine/perindopril treatment group compared with the atenolol/thiazide group ($P < 0.0001$ for both differences).29 Central pulse pressure was significantly associated with a composite outcome of total cardiovascular events/procedures and development of renal impairment. An analysis of the factors contributing to differential clinical outcomes in ASCOT-BPLA concluded that conventional risk factors and differences in brachial BP may not fully account for the better cardiovascular outcomes observed in the amlodipine/perindopril arm of the study.30 An accompanying editorial speculated that part of the advantage of the new drugs might be due to a reduction in pulse pressure of the central arteries.31 The results of the CAFE study lend credence to this theory.

In the light of the significance of the ASCOT-BPLA findings, the National Institute for Health and Clinical Excellence together with the British Hypertension Society has published a revision to the official treatment recommendations for the pharmacological management of patients with hypertension.32 The revised guidelines recommend an ACE inhibitor as first-line therapy for antihypertensive patients aged <55 years. If initial therapy was with a calcium channel blocker or a thiazide diuretic and a second drug is required, the guidelines recommend adding an ACE inhibitor.

### PREAMI and PEP-CHF

The recently published PREAMI33 and PEP-CHF34 studies have helped to fill in gaps in the knowledge regarding the potential benefits of ACE inhibitors in specific groups of post-MI and HF patients. There is a wealth of data showing that ACE inhibitors reduce morbidity and mortality in patients with LV dysfunction after MI, but the PREAMI study has demonstrated that progressive LV remodelling can occur in elderly post-MI patients with preserved LV systolic function, and that it is possible to prevent such remodelling with perindopril 8 mg/day. Most randomized controlled trials of ACE inhibitors in patients with HF have focused on patients with LV systolic dysfunction, however the PEP-CHF study has shown that, although prognosis associated with LV diastolic dysfunction may be more benign than that associated with systolic dysfunction, elderly patients with LV diastolic dysfunction may benefit from treatment with perindopril.

### Tolerability

Perindopril is generally a well-tolerated ACE inhibitor. As with all ACE inhibitors, the side effect most commonly reported with perindopril is a dry cough, believed to be, at least partly, mediated by bradykinin. In large practice-based studies involving patients with hypertension, cough occurred in 8–9% of patients, leading to withdrawal in 3–4%.14,15 Safety data from the PROGRESS and EUROPA studies reported similar low withdrawal rates associated with cough in patients receiving perindopril (2.2 and 2.7%, respectively).19,20 During the PROGRESS and EUROPA studies, only 2.1 and 1.0% of patients, respectively, withdrew from treatment because of hypotension.19,20
Ongoing research and development

Although the presence of diabetes portends a worse clinical outcome in patients with established cardiovascular disease, further analysis of the PROGRESS and EUROPA data has found that reductions in the relative risk of the primary study endpoints obtained with perindopril-based therapy were maintained in diabetic patients. Because the cardiovascular event rate in diabetic patients is higher than the general CAD population, any relative reduction in events will translate into a greater absolute reduction. On the basis of the PROGRESS data, for example, it was calculated that, in order to avoid one stroke, 16 patients (95% CI 9–111) with diabetes would need to be treated for 5 years compared with 34 patients (95% CI 21–83) without diabetes. Following on from these substudies, ADVANCE is an ongoing study specifically aiming to determine the effects of perindopril plus the glucose-friendly diuretic indapamide vs. placebo (BP control arm) and intensive vs. standard glucose control (glucose control arm) on morbidity/mortality primary endpoints among patients with diabetes. The first primary endpoint is the macrovascular composite of non-fatal stroke, non-fatal MI, or cardiovascular death. In line with previous studies in which perindopril has been observed to protect progression of diabetic nephropathy and retinopathy, ADVANCE’s second primary endpoint is the microvascular composite of new or worsening nephropathy, or retinopathy. The ADVANCE trial design is illustrated in Figure 4.

The currently available tert-butylamine salt of perindopril has a shelf life of about 2 years in countries with a temperate climate and requires special packaging in countries with high temperatures and relative humidity. In order to improve the overall stability and shelf life of the product, a new arginine salt of perindopril has recently been developed. At doses of 5–10 mg, perindopril arginine is bioequivalent to perindopril tert-butylamine 4–8 mg, but is 50% more stable and has a shelf life of 3 years.

Conclusion

Compared with other inhibitors of the renin-angiotensin system, perindopril has the richest evidence to support its use along the cardiovascular disease continuum, not only in patients with uncomplicated hypertension, but also in patients with established CAD or previous stroke, whether they have hypertension even in the absence of clinical HF, as evidenced in the EUROPA and PROGRESS studies. In addition, the ASCOT-BPLA trial has provided evidence of the need for evolution of traditional prescribing practices to include first-line ACE inhibition as standard practice in hypertensive patients. It is not yet certain whether improved outcomes observed in conjunction with perindopril in large morbidity/mortality studies are related to a class effect of ACE inhibitors or specifically related to specific properties of perindopril, a long-acting, lipophilic inhibitor of tissue ACE, per se.

Worldwide recognition and use of perindopril in clinical practice is evidence of the success of the perindopril clinical development programme over the past 20 years.

Conflict of interest: Professor Fox has received research grants and honoraria from Servier.

References


