AJH 2005; 18:142S–154S

Specific Properties and Effect of Perindopril in Controlling the Renin–Angiotensin System

R. Ferrari, G. Pasanisi, P. Notarstefano, G. Campo, E. Gardini, and C. Ceconi

Perindopril is a long-acting, once-daily lipophilic angiotensin-converting enzyme inhibitor with high tissue angiotensin-converting enzyme affinity, lowering angiotensin II and potentiating bradykinin. Its efficacy, safety, and tolerability are well established in the treatment of hypertension and heart failure. Moreover, large morbidity–mortality trials, such as the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) and Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS), have shown that antihypertensive treatment with perindopril reduces and prevents cardiovascular disease in a large range of patients with vascular diseases, whether or not they are hypertensive. Thus, the outcomes of these and other trials support the concept of cardiovascular protective properties of angiotensin-converting enzyme inhibition with perindopril in addition to the obvious blood-pressure–lowering effect. Considering its properties and the clinical evidence on efficacy and tolerability that has been gathered, perindopril fulfils the criteria of the latest guidelines for hypertension and cardiovascular disease management and should therefore be considered as a first-line antihypertensive agent, forming a consistent part of the comprehensive strategy against hypertension and related cardiovascular complications. Am J Hypertens 2005;18:142S–154S © 2005 American Journal of Hypertension, Ltd.

Key Words: Angiotensin II, angiotensin-converting enzyme inhibition, bradykinin, cardiovascular disease, perindopril.

In the 1970s, based on a series of observations, it was reported that angiotensin II had deleterious effects on the heart, vessels, and kidney. Then came the discovery and development of drugs blocking the renin–angiotensin system (RAS), which clarified the role of this system in several pathologic conditions and led to the widespread use of angiotensin-converting enzyme (ACE) inhibitors in the treatment of cardiovascular and renal disease. Originally, these drugs were developed as therapeutic agents targeted to treat hypertension, but several clinical conditions were subsequently identified. The ACE inhibitors exert their pharmaceutical benefits primarily by blocking angiotensin II formation. However, in addition to inhibiting angiotensin II formation, ACE inhibitors also increase the levels of bradykinin, primarily at tissue level. Both inhibition of angiotensin II formation and increase in bradykinin are believed to contribute to the beneficial effects of ACE inhibitors[1] (Fig. 1). The ACE inhibitors may be less specific in their blockade of angiotensin II than angiotensin II type 1 receptor blockers (ARB), but they confer valuable cardiovascular protection by increasing the availability of bradykinin. If anything, the bradykinin effect compensates for the incomplete blockade of angiotensin II. Currently, ACE inhibitors are not only recognized as having the broadest impact of any drug in cardiovascular medicine—reducing mortality and morbidity from myocardial infarction (MI), heart failure, coronary artery disease (CAD), stroke, diabetes mellitus, and diabetic and nondiabetic nephropathy,[2,3] but they also benefit from very solid data regarding their safety and tolerability profiles.

The ACE inhibitors thus remain the gold standard RAS blocker. However, it should be remembered that among the available ACE inhibitors, important differences exist in chemical structure, potency, bioavailability, plasma half-life, distribution, elimination, and, more importantly, in affinity for tissue-bound ACE.[4]

Pharmacologic Effects of ACE Inhibitors

The ACE inhibitors can be classified into three groups according to their chemical structure. Some contain a sulfhydryl group, captopril being the prototype. In vitro data suggest that the presence of the sulfhydryl group may confer additional properties on ACE inhibition such as

Received May 10, 2005. Accepted May 27, 2005.

From the Division of Cardiology, University Hospital of Ferrara, Ferrara, Italy; and Cardiovascular Research Center "Salvatore Maugeri ICCRS," Gussago, Brescia, Italy

Address correspondence and reprint requests to Professor Roberto Ferrari, Arcispedale S. Anna, Divisione di Cardiologia, Corso Giovecca 203, 44100 Ferrara, Italy; e-mail: fri@dns.unife.it

0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2005.05.037

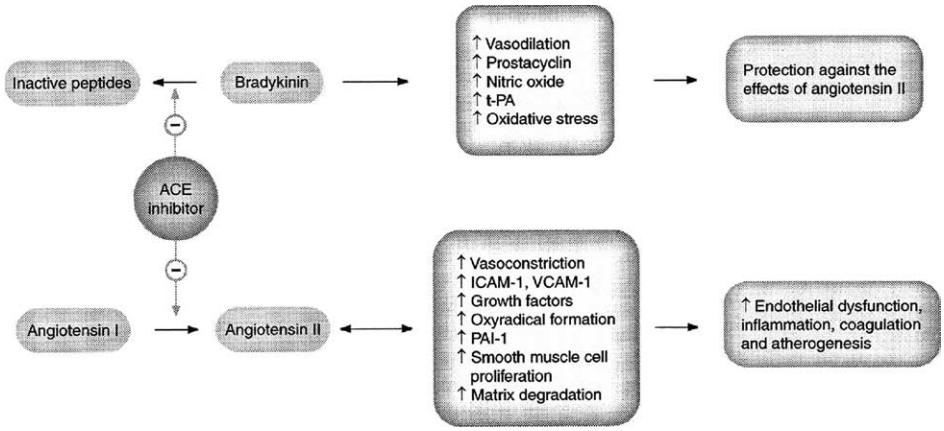

FIG. 1 Atherosclerosis-promoting actions of angiotensin II and protective effects of bradykinin. Angiotensin-converting enzyme (ACE) inhibition blocks the production of angiotensin II and the breakdown of bradykinin. ICAM-1 = intracellular adhesion molecule–1; PAI-1 = plasminogen activator inhibitor–1; tPA = tissue plasminogen activator; VCAM-1 = vascular cell adhesion molecule–1. Adapted from Ref. 1.

free radical scavenging and effects on prostaglandins.[5] However, the clinical relevance of these actions has never been demonstrated. Fosinopril is the prototype of ACE inhibitors that contain a phosphinyl group as their reactive moiety. Other ACE inhibitors contain a carboxyl moiety.

This review will focus on the benefits of perindopril and its cardiovascular protective properties beyond blood pressure (BP) reduction in the treatment and prevention of hypertension and cardiovascular disease.

Perindopril

Perindopril, discovered in 1982 by Les Laboratoires Servier,[6] is a prodrug ester (Fig. 2) converted, in the liver and plasma, to perindoprilat, a potent, long-lasting lipophilic inhibitor of ACE.

An overview of the pharmacokinetic effects of perindoprilat[7] is given in Table 1.

Perindoprilat has a strong affinity for ACE. In patients with CAD, perindopril has been shown to reduce both plasma and vascular levels of ACE, such as endothelial and adventitial ACE, and to increase the expression of endothelial nitric oxide synthase (eNOS) in the endothelium and in vascular smooth muscle cells.[8] In healthy volunteers, it inhibits 50% of ACE activity at a lower concentration than enalaprilat (3.6 *v* 117 nmol/L).[9] The relative tissue affinity of perindoprilat compares favorably with other ACE inhibitors.[10] The onset of activity is slower than that of many other ACE inhibitors: maximal inhibition occurs approximately 8 h after a single oral

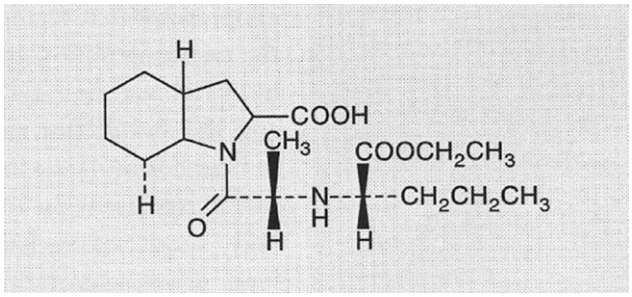

FIG. 2 Chemical structure of perindopril.

Table 1. Overview of the pharmacodynamic effects of perindoprilat

Inhibits ACE in plasma and tissue, including blood vessels
Reduces plasma aldosterone levels
↓ SBP and DBP in patients with hypertension
↓ Aortic carotid-femoral PWV in patients with hypertension
↓ Systemic vascular resistance in patients with hypertension
↑ Arterial diameter, compliance, and blood flow in patients with hypertension
Normalizes arterial media-lumen ratio in patients with hypertension
↓ LVMI, diastolic wall and intraventricular septal thickness in patients with hypertension
Does not affect heart rate or cardiac output
↓ Albuminuria in patients with hypertension and nephropathy, diabetes mellitus, or post–renal transplant
↓ Uric acid levels in plasma in patients with hypertension
Normalizes hypofibrinolysis in patients with hypertension
↓ Kallikrein activity in plasma in patients with hypertension
Does not adversely affect plasma glucose, fructosamine, and glycosylated hemoglobin levels in patients with diabetes mellitus
Does not adversely affect plasma lipid profiles

ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure; LVMI = left ventricular mass index; PWV = pulse wave velocity; SBP = systolic blood pressure.

↓ and ↑ Represent significant ($P < .05$) decreases and increases, respectively, versus baseline or placebo.

Adapted from Ref. 7.

8 mg dose and is still greater than 70% at 24 h; furthermore, these parameters are not affected by age or sex.[11]

According to data from animal studies, renal ACE is inhibited more rapidly and to a greater extent than endothelial or aortic ACE.[12,13] In the rat stroke model, perindopril appeared to exert a greater effect on brain ACE than other ACE inhibitors.[14–17]

As an ACE inhibitor, the main pharmacologic effect of perindopril is a reduction in systemic vascular resistance with little or no change in heart rate. No reflex tachycardia is observed, in contrast to other vasodilator classes.

Perindopril exerts very limited hemodynamic effects in salt-replete healthy normotensive volunteers.[18–21]

In normotensive subjects, administration of oral perindopril (2.5, 5, or 10 mg) led to a significant attenuation (30% to 90%) of the pressor response to angiotensin I at 4 to 6 h.[22]

Administration of oral perindopril therapy for 8 days did not have any significant effects on resting heart rate or hemodynamic response to exercise in normotensive or hypertensive individuals.[23–26]

Effects Beyond Lowering of BP

Clinical studies have demonstrated the therapeutic efficacy of ACE inhibition in many cardiovascular disorders. It has repeatedly been shown that these benefits extend beyond BP–lowering effects. Understanding these effects is a major objective of research efforts. The current state of knowledge is summarized in this section.

The use of ACE inhibitors plays an essential role in the restoration of the balance between angiotensin II and bradykinin (Fig. 1). Bradykinin, which counteracts the harmful effects of angiotensin II, contributes to the hemodynamic and other therapeutic effects, such as vasodilation and vascular protective effects, and the longer-term anti-ischemic effect of ACE inhibitors. It is known that ACE regulates the breakdown of circulating bradykinin into an inactive peptide.[27] From a pharmacologic viewpoint, it is interesting that the Michaelis-Menten constants for bradykinin inactivation and angiotensin II formation are such that blocking ACE invariably leads to lower angiotensin II and higher bradykinin; among the ACE inhibitors, this bradykinin potentiation is particularly pronounced for perindopril.[28] Use of the bradykinin antagonist icatibant has demonstrated that the BP-lowering effect of perindopril involves bradykinin, suggesting an endogenous role of bradykinin in homeostasis.[29] A recent controlled study showed that dobutamine-induced myocardial ischemia was significantly ameliorated by long-term treatment with perindopril at a dose of 8 mg once daily in patients with CAD. These results were closely correlated with the inhibition of serum ACE activities ($P < .01$) and increase in plasma bradykinin concentrations ($P < .05$).[30] The recent EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) showed that treatment with perindopril reduced the primary end point (combined risk of cardiovascular death, MI, and cardiac arrest) by 20% ($P = .0003$).[31] However, it was suggested that BP lowering alone could not be completely responsible for the observed benefits of perindopril, as a similar result was observed in subjects with stable CAD who had low or high BP at entry into the study, or whose BP did not fall during the study. Therefore, the PERindopril Thrombosis, INflammation, Endothelial dysfunction and Neurohormonal activation Trial (PERTINENT), a substudy of EUROPA, set out to establish whether the benefits achieved by perindopril were due to the effect of the drug on endothelial function and markers of inflammation and thrombosis.[32] The preliminary results demonstrated that perindopril treatment for 1 year resulted in an improvement in endothelial dysfunction. This was achieved by increasing bradykinin levels and decreasing angiotensin II levels, which resulted in the restoration of the angiotensin II/bradykinin balance. There was also a significant correlation between the increased bradykinin levels and the upregulation of endothelial cell nitric oxide (via ecNOS). Tumor necrosis factor–α and endothelial cell apoptosis were both reduced. Furthermore, perindopril reduced the levels of von Willebrand factor, a marker of endothelial cell damage and a predictor of cardiovascular outcomes. Taken together, these results confirm the vascular and antiatherosclerotic effects of the ACE inhibitor perindopril and partly explain the results of EUROPA.

Vascular remodeling of the arteries in hypertension, even at early stages, may affect one or several end organs such as the brain, heart, and kidney. Vascular remodeling has been established as a major contributor to cardiovascular morbidity and mortality in hypertension.

Therefore, modern treatment strategies should target BP reduction, but should also have vascular effects leading to normalization of the vascular structure. Despite similar effects on BP, evidence from pharmacologic trials has shown that antihypertensive treatments have unequal efficacies in vascular remodeling. Among antihypertensive drugs, ACE inhibitors have been shown to effectively reduce BP in hypertensive patients and to reverse vascular remodeling.

The remodeling effects of ACE inhibitors, responsible for the long-term effects of this class, take place at the level of the small-resistance and large arteries, and the heart. A recent report demonstrated that, among antihypertensive drugs, only ACE inhibitors had an effect on aortic stiffness that was significant and independent of BP lowering.[33] From both short- and long-term trials in patients with essential hypertension, a large body of evidence has been collected for the ACE inhibitor perindopril. Perindopril administered for 3 months significantly improved the diameter and compliance of the brachial artery in patients with sustained essential hypertension, an effect that was treatment related and independent of BP reduction ($P < .01$).[34]

When comparing perindopril with a β-blocker (atenolol), both drugs significantly reduced BP, although only perindopril led to normalization of small artery morphology, but also significantly reduced left ventricular (LV) mass and improved impaired coronary reserve to normal levels compared with the effects in healthy control subjects.[35,36] Similarly, in

another trial, both perindopril and a diuretic combination (amiloride plus hydrochlorothiazide) significantly reduced BP in hypertensive patients, but only perindopril induced an increase in distensibility of the common carotid artery.[37] Perindopril has also been shown to repair the coronary arterioles by inducing regression of periarteriolar and interstitial collagen of coronary arterioles, thereby leading to a 54% increase in coronary blood flow ($P = .001$), a 67% increase in coronary reserve ($P = .001$), and a 33% reduction in coronary vascular resistance ($P = .001$).[38]

In addition, the effect of perindopril on reversing vascular remodeling has recently been shown in patients with end-stage renal disease. In this population, perindopril significantly decreased pulse-wave velocity (PWV) independently of BP changes, resulting in a highly significant relative risk reduction (RRR) in all-cause mortality by 81% and cardiovascular mortality by 82%.[39]

With regard to the reversal of cardiac remodeling, perindopril significantly reduces the left ventricular mass index in hypertensive patients.[23–26,36,39] This occurs within a few months and to a greater extent than with either calcium channel blockers[40] or β-blockers.[23]

The link between CAD and ACE activity has been under intense study, which was given added impetus after the demonstration of increased expression of ACE and angiotensinogen in proliferating tissue of balloon-injured vessels of mice[41] and human beings.[42] Around the same time it was shown that ACE accumulates in regions of inflammatory cells in the human atherosclerotic plaque.[43]

Currently it is generally believed that ACE activity in the heart and the vessels contributes both to the development and the progression of CAD. In animal models and later in clinical studies, ACE inhibitors were shown to delay the development and progression of atherosclerosis.

The ability of ACE inhibitors to reduce ischemic events is a result of their effects on BP and hemodynamics and, in the longer term, on the prevention of progression of coronary atherosclerosis or stabilization of the atherosclerotic plaque.

The endothelium maintains normal vascular tone and structure, local homeostasis, and vascular wall proliferation via the reactive release of vasoactive substances, among which nitric oxide (NO) has a predominant role. The effects of NO are well characterized: relaxation of vascular smooth muscle, inhibition of platelet aggregation and of expression of adhesion molecules on monocytes and neutrophils, and inhibition of growth and migration of smooth muscle cells. Oxidative stress mediated by angiotensin II impairs the activity of NO, thus constituting the primary theoretic basis for the improvement of endothelial function by ACE inhibitors.

The ACE inhibitors reduce endothelial dysfunction in normotensive patients with CAD, hypertension, type 2 diabetes, and congestive heart failure (CHF). Coronary flow reserve, measured by normal flow-dependent and cold pressor test–induced dilations, was improved in a group of 10 patients with hypertension and left ventricular hypertrophy (LVH) and angiographically normal coronary arteries—an improvement likely to be mediated by an improvement in endothelial function.[44]

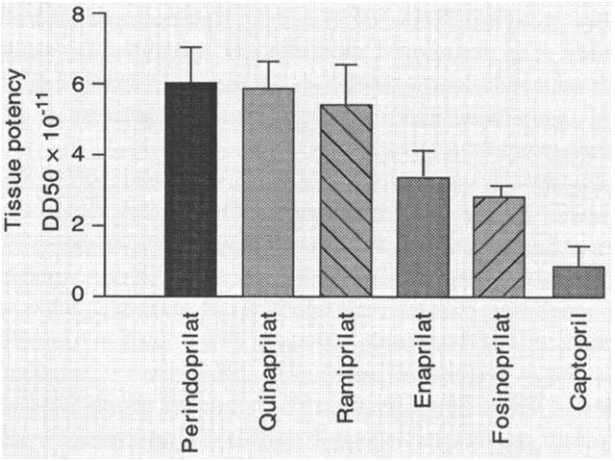

FIG. 3 Relative tissue affinity of various angiotensin-converting enzyme inhibitors. Adapted from Ref. 5.

Experimental data are yielding valuable insights into the antiatherogenic effects of ACE inhibitors.[45] In one model, perindopril was shown to reduce the progression of atherosclerosis and to prevent the accelerated development of atherosclerotic lesions.[46] The underlying mechanisms are wide ranging, including protection of the endothelium, antimitogenetic, antithrombotic, and plaque-stabilizing actions, and possibly antioxidant action; they are largely mediated by angiotensin II and bradykinin. Lowering angiotensin II reduces vascular smooth muscle cell growth, which, in turn, restores endothelial function and reduces the propensity for plaque rupture. The bradykinin-mediated increases in NO and prostacyclin maintain endothelial function and integrity and could help to prevent the development of proliferative atherosclerotic lesions. The critical role of endothelial NO in preventing the development of atherosclerotic lesions is supported by findings from knockout experiments in mice.[41]

Perindopril, being lipophilic, compares very favorably among ACE inhibitors in terms of the tissue penetration of its active metabolite—a factor consistently shown to correlate with antiatherosclerotic effects[5] (Fig. 3). Lipophilicity also confers a distinct advantage when the atherosclerotic plaque is the target.

Another effect of ACE inhibitors is to shift the fibrinolytic balance, by reducing plasminogen activator inhibitor–l and increasing tissue plasminogen activator via action on angiotensin II and bradykinin, respectively.[47] Impaired fibrinolysis may be associated with chronic hypertension.[48]

The contribution of sympathetic modulation to the clinical effects of ACE inhibitors, especially in patients without CHF, remains unclear. However, inhibition of sympathetic nervous system activity was shown to contribute to the BP-lowering effect of perindopril in hypertensive diabetic individuals with nephropathy.[49]

At some stage during the development of CHF, the com-

pensatory response of the RAS becomes harmful. The beneficial effects of ACE inhibitors in CHF are attributable to their RAS blockade, which leads to vasodilation and improved myocardial function and hemodynamics.[50] The improved prognosis of CHF patients is mainly caused by a reduction in the progression of CHF. Studies with specific ARB indicate that bradykinin is also involved in this process.

In the acute setting, a short-term anti-ischemic effect and a reduction in stress-induced myocardial ischemia via neurohormonal modulation have also been shown.[29,51] Cerebral vasodilation by perindopril is also likely to be caused by improvements in endothelial function, as in other vascular beds, and reduction in cerebral arteriolar remodeling,[52] which may be independent of BP.

Clinical Use

Hypertension

With more than 15 years of clinical experience, the central role of perindopril in the therapeutic armamentarium against hypertension is well established. Efficacy has been shown through numerous surrogate end-point studies.

In most European countries, the initial dose of perindopril for hypertension is 4 mg once daily, titrated upward if necessary to a maximum of 8 mg daily. If response to monotherapy is inadequate, the usual addition is a diuretic.

Clinical trials have shown that perindopril reduces BP in patients with mild-to-moderate hypertension in a dose-dependent manner at doses of 8 mg or less. Postmarketing data have shown that mean BP fell from 173/100 to 145/82 mm Hg (mean absolute reduction: 28/18 mm Hg) in the 43,245 patients who completed 1 year of treatment with perindopril (2 to 8 mg/day).[53]

A community-based, open-label trial involving more than 10,000 patients from the United States with essential hypertension provided valuable real-life data that reinforced the findings from clinical trials. The study included newly diagnosed patients with hypertension, inability to tolerate other antihypertensive medications including ACE inhibitors, ARB, diuretics, and calcium channel antagonists, and a lack of BP control with any prior antihypertensive monotherapy. The mean BP was reduced from 157/95 to 139/84 mm Hg (mean absolute reduction: 18/11 mm Hg) over 12 weeks of monotherapy with perindopril 4 mg once daily (titrated to 8 mg midway, at the physician's discretion). Adequate control (140/<90 mm Hg) was achieved by almost half of the patients; and notably, monotherapy was effective in both men and women across all ethnicities and in high-risk subgroups.[54] One analysis suggested that perindopril is an effective option in patients nonresponsive to previous antihypertensive therapy with ACE inhibitors.[55]

The ACE inhibitors seem to have lower efficacy in African-American patients with hypertension, probably because of lower levels of renin in this patient group.[4] Yet the effect remains significant, as shown by a study with perindopril monotherapy.[56] Furthermore, ACE inhibition is associated with advantages in terms of target-organ protection and arresting disease progression in this patient group.[57]

Most studies comparing perindopril with other ACE inhibitors have involved captopril and enalapril. Data from three large 3-month, randomized, double-blind trials showed that perindopril has better efficacy than captopril, as measured by response rate (67% to 80% *v* 44% to 57% of patients achieving diastolic BP of 90 mm Hg).[24,25,58] Five trials found a similar effect of perindopril and enalapril in terms of systolic and diastolic BP reductions (7% to 15% reduction from baseline), although response rates varied.[59–62] Studies have also compared perindopril with other drug classes. Several trials comparing perindopril against calcium channel blockers (dihydropyridine and nondihydropyridine) show no significant difference in BP-lowering efficacy.[26,40,63,64] Data from comparisons with β-blockers are conflicting; however it is worth highlighting that one study demonstrated that perindopril was better than metoprolol in patients with LVH.[23,65–67] In another comparative study, perindopril and atenolol both significantly reduced BP in hypertensive patients; however only perindopril caused normalization of small artery morphology.[35]

Combining different classes of antihypertensive drugs with the aim of maximizing efficacy and minimizing adverse events is now standard clinical practice, as reflected in numerous guideline recommendations. Increasingly, the protocols of clinical studies in hypertension allow the addition of other classes to ACE inhibition therapy. In such studies, there was no difference between perindopril and other antihypertensive therapies in the proportion of patients who received adjunctive therapy (15% to 50%).[24,25,65,66] Combinations of perindopril and a diuretic have been extensively studied, and the additive effect is well established.

Guidelines recommend the use of long-acting formulations to provide 24-h antihypertensive cover.[3,68] The 2004 British Hypertension Society guidelines (BHS-IV) emphasize that any drug taken as a single daily dose should ideally be effective for 24 hours.[69] A measure of sustained BP control is provided by the trough:peak ratio (TPR). Among tested ACE inhibitors, perindopril has been listed as having the highest TPR (75% to 100%),[70] making it suitable for once-daily dosing[59,62,64,71] and furthermore reducing the adverse consequences of a missed dose.[72] This has also been reinforced by studies comparing the TPR of perindopril with that of other ACE inhibitors such as enalapril or captopril.[60,62,73]

Congestive Heart Failure

In the management of CHF, the two aims are to improve quality of life and, in the longer term, to reduce morbidity and mortality. Therapy with ACE inhibitors has beneficial effects on both counts.

Currently, ACE inhibition, either with or without diuretics, is the cornerstone of CHF treatment and, notably, in all grades of symptomatic heart failure and in asymp-

tomatic left ventricular dysfunction (level of evidence A).[74,75] The effects of perindopril on symptoms were shown in a long-term study; however this study was primarily designed to assess tolerability.

The 320 patients with CHF (New York Heart Association class III or IV) were treated for 6 months (208 patients), 12 months (105 patients), or 30 months (30 patients) with 2 mg perindopril, which was increased, in the majority of cases, to 4 mg at 2 weeks. Improvements were seen in exercise tolerance, New York Heart Association class, and overall symptom severity score.[76] Direct evidence comes from two short-term blind trials that showed benefits of perindopril on symptom severity score and exercise capacity.[77,78]

It is well known that first-dose hypotension may occur with initiation of ACE-inhibitor therapy in patients with cardiac failure. However, there are clinically relevant differences among the various ACE inhibitors in this regard, with perindopril comparing favorably with other members in moderate-to-severe heart failure.[79,80] Thus, the mean maximal BP fall induced by 2 mg perindopril (−5.2 mm Hg) after initiation of therapy was not significantly different from baseline BP and was smaller than that seen with 6.25 mg captopril (−16.8 mm Hg), 2.5 mg enalapril (−13.3 mm Hg), or 2.5 mg lisinopril (−15.0 mm Hg).[81] The incidence rate with perindopril was also lower than that of either enalapril or captopril (15% *v* 50% and 42%, respectively).[82,83]

In the longer term, perindopril has a minimal effect, or no effect, on BP (8 and 12 weeks)[77,78] and renal function.[76,77,84] A sustained improvement is seen in indices of cardiac function. Perindopril may also improve peripheral vascular function.[85]

In terms of dose, European prescribing information recommends a starting dose of 2 mg for patients with mild-to-moderate CHF, and up to 4 mg for the maintenance dose. Guidelines emphasize the need for the dose to take into account long-term morbidity and mortality data rather than symptomatic improvement.[75]

Little is known about the effect of ACE inhibitors in elderly patients with CHF or in patients with CHF caused by diastolic dysfunction. A meta-analysis of trials with several antihypertensive drugs suggests that ACE inhibitors are the most effective agents in reducing LVH, one of the causes of diastolic dysfunction.[86] The Perindopril and Remodeling in the Elderly with Acute Myocardial Infarction (PREAMI) trial is exploring the effects of perindopril in elderly patients with acute MI and moderate or no LV dysfunction.[87] A series of trials have provided information on the role of ACE inhibition after acute myocardial infarction (AMI). There is a consensus that ACE inhibitors should be used early after AMI in all patients, particularly those at high risk.[75,88] For instance, in patients with AMI, perindopril showed better short-term tolerance than treatment with captopril, with significantly fewer acute hemodynamic changes and withdrawals.[89]

However, two key questions remained: 1) for how long should treatment be administered? and 2) what should the criteria be for withdrawal or maintenance of ACE inhibitor treatment?

These questions were resolved by the Heart Outcomes Prevention Evaluation (HOPE) and particularly in the EUROPA studies, showing that ACE inhibition is indicated for secondary prevention of CAD and that the longer the treatment, the better the results.[31,90]

Cerebrovascular Disease

There is a continuous and direct association between BP and risk of first stroke event in hypertensive and normotensive individuals.[91] Persons with cerebrovascular disease have a very high risk of stroke and also a high risk of cardiac events and left ventricular dysfunction.[92–94]

The structural and functional changes that occur in the cerebral vasculature in response to high BP, effectively shifting the autoregulatory curve to the right, play a large part in predisposing patients to stroke. Reducing BP reverses these changes, at least to some extent.[52] Hypertension is the single most important modifiable risk factor for stroke.

Although the value of BP lowering in primary prevention is unequivocal, the benefits in terms of secondary prevention were less obvious. With this in mind, a study was designed to resolve what was, and remains, an issue of high clinical relevance. The randomized, placebo-controlled Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) assessed the effects of routine BP-lowering therapy based on perindopril in persons who had experienced a stroke or a transient ischemic attack.[95]

There was no BP entry criterion and patients continued with their existing antihypertensive therapy. After a run-in period of 4 weeks, patients were assigned to receive active therapy or placebo. The active therapy consisted of 4 mg perindopril alone or in combination with indapamide (2.0 or 2.5 mg daily); the choice of monotherapy or combination therapy was at the investigators' discretion. The primary end point was fatal or nonfatal stroke.

A total of 6105 individuals were randomized, 3051 in the active treatment total stroke group (58% combination and 42% perindopril alone) and 3054 in the placebo group. At a mean follow-up period of 3.9 years, BP was reduced by an average of 9.0/4.0 mm Hg in the active treatment group, compared with placebo: an effect that, as expected, was substantially greater in the combination group than in the perindopril group (12.3/5.0 *v* 4.9/2.8 mm Hg).

Compared with placebo, the active treatment significantly reduced the risk of stroke by 28% (RRR, $P < .0001$). Active treatment also reduced the risk of a major coronary event (nonfatal MI or death caused by coronary heart disease) by 26%, the risk of nonfatal MI by 38%, and the risk of CHF by 26%.[96] The effects were maintained regardless of the presence of hypertension or history of coronary heart disease. The effect of the therapy on different coronary outcomes is shown in Fig. 4.

The PROGRESS data were also subjected to several

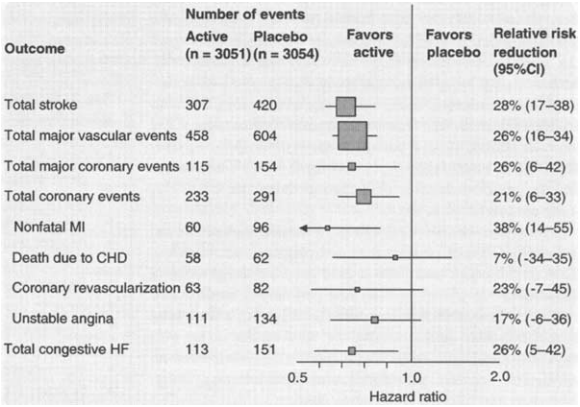

FIG. 4 Impact of perindopril-based treatment regimen on the risk of stroke recurrence and incidence of cardiovascular disease events in 6105 patients with a history of stroke or transient ischemic attack. CHD = coronary heart disease; CI = confidence interval; HF = heart failure; MI = myocardial infarction.

predefined analyses that helped to answer other clinically pertinent questions and that will also enrich possible future meta-analyses in this field.[97] Thus it was shown that the therapy was protective against all stroke subtypes, including fatal or disabling stroke (RRR, 33%), ischemic stroke (RRR, 24%), and hemorrhagic stroke (RRR, 50%), and that this benefit was independent of medical history.[98] A separate analysis found that active treatment reduced the relative risk of recurrent stroke by 38% in diabetic patients and by 28% in nondiabetic patients.[99] The beneficial effect on the incidence of stroke and major vascular events was maintained across subgroups defined by age, sex, and geographic area.[100] Patient outcome in terms of dementia and cognitive decline was also improved by 34% and 45%, respectively, and this was shown to be a corollary of reduced incidence of recurrent stroke.[101] Similarly, active therapy had a beneficial effect on the risk of long-term disability and dependency, which were reduced by 24% and 16%, respectively, and also primarily mediated through the reduction in recurrent strokes.[102]

The primary findings may be reformulated: active treatment was associated with one less stroke, coronary event, or heart failure case per 17 patients treated for 5 years. Use of the combination treatment would improve this outcome further, to 10 patients. These findings are the strongest argument yet for the routine use of a perindopril-based treatment regimen in the secondary prevention of stroke, as advocated by the investigators.[95]

The issue of administration of BP-lowering agents in the acute stage after a stroke has yet to be satisfactorily resolved. Evidence obtained with ACE inhibitors is encouraging, suggesting that they do not lead to clinically relevant changes in cerebral perfusion.

Administration of perindopril to stroke patients has been studied in normotensive and hypertensive patients. Thus in 24 hypertensive patients who received perindopril at days 2 to 7 after a stroke, BP fell by 19/11 mm Hg, but cerebral perfusion was unchanged (although local changes could not be assessed).[103] A similar study in 25 normotensive patients showed no change in either local or general blood flow.[104]

The presence of carotid stenosis in stroke patients could theoretically make them more vulnerable to BP-lowering agents. Early data with perindopril in this high-risk group are encouraging: BP in nonacute patients was lowered, whereas global and regional cerebral perfusion remained unchanged.[105] Further studies are warranted.

Stable Coronary Artery Disease

The ACE inhibitors have proven effects in reducing morbidity and mortality in high-risk CAD patients—namely, those with heart failure, LV dysfunction, or previous MI.[106–110]

The HOPE study[90] was the first to demonstrate the positive effects of ACE inhibitors in patients at high risk of developing cardiovascular events (≥55 years of age with a history of CAD, stroke, obstructive peripheral vascular disease, or diabetes mellitus with at least one other cardiovascular risk factor). The trial was terminated early after an analysis showed a reduction in the primary combined end point of cardiovascular mortality, MI, and stroke, as well as all-cause mortality, in patients receiving ACE-inhibitor therapy.

Subsequently, another study was designed to assess whether these positive effects of ACE inhibition would be seen in the general population with stable coronary disease, comprising all risk levels. The resulting EUROPA study was a randomized, double-blind, placebo-controlled study that involved 424 centers in 24 countries.[31] Inclusion criteria were stable CAD with no heart failure or LV systolic dysfunction. After a run-in period, a total of 12,218 patients were randomized to perindopril 8 mg once daily or placebo for 3 years. The reasons that led to the selection of perindopril for the EUROPA study are presented in Table 2.

Table 2. Properties of the angiotensin-converting enzyme (ACE) inhibitor perindopril that led to its selection in the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)

Once-daily dosing and long-acting 24-h blood pressure control
High affinity for tissue ACE
Anti-ischemic effects in coronary artery disease
Reduces serum ACE and increases plasma bradykinin concentrations
Reduces neointimal proliferation in coronary arteries
Prevents progression of atherosclerosis
Enhances expression of nitric oxide synthase in coronary arteries
Improves endothelial function
Improves fibrinolytic balance

Adapted from Ref. 1.

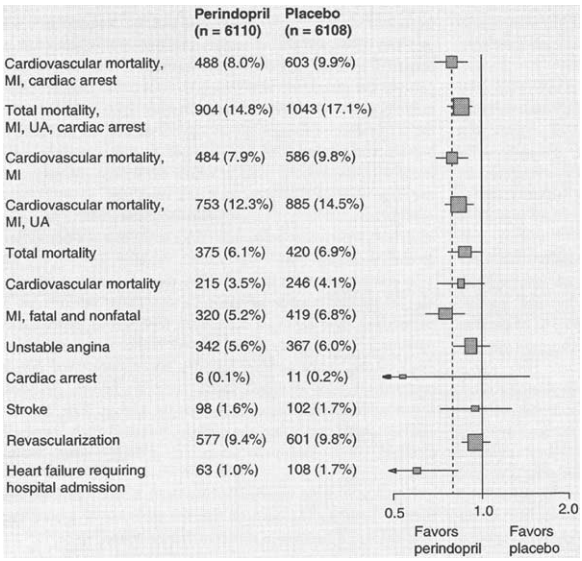

FIG. 5 Beneficial effect of treatment with perindopril on the primary end point and selected end points. Size of **squares** is proportional to the number of patients in that group. **Dotted line** indicates overall relative risk. MI = myocardial infarction; UA = unstable angina. Adapted from Ref. 5.

Existing treatments for secondary prevention were continued (at baseline, 92% of patients were receiving a platelet inhibitor, 62% a β-blocker, and 58% a lipid-lowering drug). After a mean follow-up period of 4.2 years, perindopril use resulted in a 20% RRR ($P = .0003$) in the primary end point, a composite of cardiovascular death, nonfatal MI, and cardiac arrest with successful resuscitation. Notably, a specific analysis showed no interaction between perindopril and lipid-lowering drugs, β-blockers, and calcium antagonists, confirming that the effect of perindopril was independent.

Reductions were also seen in the secondary end points, although they did not always reach statistical significance (Fig. 5).

The effect of perindopril was consistent among all of the subgroups studied. Outcome was improved in subgroups of all ages and in patients with and without hypertension, diabetes, or previous MI.

It was estimated that one major cardiovascular event would be prevented by treating 50 patients for 4 years. The weight of this evidence is enormous and the potential clinical impact huge. The latest American College Cardiology (ACC)/American Heart Association (AHA) guidelines on the management of chronic stable angina suggested that ACE inhibitors should be used as routine secondary prevention far patients with known CAD.[111] More recently, ACC/AHA guidelines on the management of patients with ST-elevation MI suggest that, unless contraindicated, an ACE inhibitor should be prescribed at discharge for all these patients (class 1, level of evidence A). With this evidence for perindopril, there is a strong case for adding CAD to the list of compelling indications for ACE inhibitors in the European guidelines.[112] The guidelines set forth in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommend that hypertensive patients with a compelling cardiovascular risk factor such as CAD should start initial therapy with an antihypertensive drug with proven efficacy in reducing that risk factor, for example, perindopril.[3]

Diabetes

The American Diabetes Association underlines that antihypertensive drugs, such as ACE inhibitors, are preferred as initial therapy in hypertensive diabetes patients because of their proven efficacy in reducing cardiovascular disease events.[113] In the prevention of microvascular and macrovascular complications of diabetes, control of BP is as important as glycemic control.[114] As a result of their nephroprotective properties, ACE inhibitors may be particularly useful for preventing the development and progression of the renal complications of diabetes.

A recent meta-analysis comparing the effects of ACE inhibitors and ARB demonstrated that ACE inhibitors, but not ARB, prevent early death in patients with diabetic nephropathy, which advocates the use of ACE inhibitors as first-line treatment.[115]

Perindopril effectively lowers BP in hypertensive diabetic patients, as shown in a survey of 23,460 patients in which the BP control target was reached in a similar proportion of diabetic and nondiabetic patients; however, significantly more diabetic patients required adjunctive therapy.[116]

The protection afforded by perindopril in normotensive normoalbuminuric patients was shown in a randomized, double-blind, placebo-controlled study involving 89 patients treated for 36 months. Both BP and glomerular filtration rate were the same in both groups; however, a durable improvement in albumin-creatinine ratio was observed in the perindopril group.[117]

The nephroprotective effect of ACE inhibition appears to prevent the progression of microalbuminuria to nephropathy in patients with type l or 2 diabetes. Long-term treatment with perindopril has been shown to be more effective than nifedipine or placebo in delaying the progression of diabetic nephropathy and reducing albumin excretion rate to normal levels of albumin (<20 μg/min) in normotensive type 1 diabetic patients with microalbuminuria.[118]

In terms of preventing the progression of diabetic nephropathy, RAS blockade is a well-established strategy.[113] Beneficial effects of perindopril on glomerular structure have been observed after 3 years in patients with established nephropathy with either type 1 or 2 diabetes.[119]

A continuous monitoring study demonstrated the 24-h BP-lowering effect of perindopril in hypertensive patients with diabetic nephropathy; the study also highlighted the activity of perindopril against raised nocturnal BP, a risk factor in this patient group.[49]

The benefits of perindopril extend to end-stage renal dis-

ease. Research efforts have focused on reducing LVH and arterial stiffness, the main cardiovascular complications associated with poor outcomes.[120–122] Sensitivity of PWV to BP lowering was shown to be a prognostic factor for survival in a trial examining the survival outcomes of different combinations of perindopril, nitrendipine, and a β-blocker. Use of perindopril was associated with improved survival (risk ratio 0.19 for all-cause mortality and 0.18 for cardiovascular mortality) compared with the other drugs or even with a number of drugs. Furthermore, the beneficial effect was independent of BP lowering or PWV.[39]

The diabetic substudy of PROGRESS showed that, independently of other risk factors, diabetic subjects had a significant 35% additional risk of stroke compared with nondiabetic subjects at baseline.[99] The perindopril-based treatment regimen significantly reduced the relative risk of recurrent stroke by 38% and 28% in patients with and without diabetes mellitus, respectively. Similarly, active treatment reduced the risk of major vascular events by 21% and 28%, respectively.

Finally, preliminary data of the PERindopril SUbstudy in coronary Artery disease and DiabEtes (PERSUADE) study, the diabetic substudy of EUROPA, have shown that the beneficial effects of perindopril in diabetics were of the relative magnitude similar to the effects observed in the overall EUROPA population; but because the event rate was higher in this population, the absolute treatment benefit was greater.

Tolerability

Over 15 years of clinical experience with perindopril, especially for hypertension and chronic heart failure, attest that perindopril is well tolerated.

As with other ACE inhibitors, the most commonly encountered adverse events are dry cough (believed to be mediated by bradykinin) and gastrointestinal symptoms. These are generally mild and reversible on discontinuation of treatment.

In a postmarketing surveillance study of 47,351 hypertensive patients who had received 2 to 8 mg perindopril once daily for 1 year, an adverse event was reported by 14.3% of patients. The most common adverse events were cough, gastrointestinal upset/dyspepsia, and asthenia. There were 14 serious adverse events (ie, serious allergic reactions including three cases of angioneurotic edema). The patient withdrawal rate was 8.5%; this withdrawal was mainly because of cough in 3.2% of cases.[54]

A large study with data on the safety of perindopril in CHF was an open study involving 208 patients treated with perindopril 4 mg once daily for at least 6 months and another 105 treated for at least 12 months. Overall, 30.3% of patients reported at least one adverse event; the most common was dry cough.[76]

More data for CHF are available from two double-blind, placebo-controlled studies in which patients received perindopril 4 mg daily for 3 months. In one of these studies, which involved 125 patients, the most common spontaneously reported adverse events were gastrointestinal problems (6%), fatigue (6%), and cough (3%). There were two withdrawals from the perindopril group compared with five from the placebo group.[77] In the other study, which involved 103 patients, the most common spontaneously reported adverse events were gastrointestinal problems (14%), asthenia (7%), and cough (2%). There were no withdrawals in the perindopril group because of adverse events.[77]

In EUROPA, perindopril at a dose of 8 mg once daily was well tolerated in more than 12,000 CAD patients. At 3 years, 81% of patients were still receiving blinded perindopril treatment, a percentage similar to that in the placebo group (84%). Cough was a reason for stopping treatment in only 2.7% of patients and hypotension in 1.0% (0.5 and 0.3%, respectively, in placebo patients). Kidney failure occurred in 0.3% of patients, a percentage identical to that in patients given placebo. More patients given placebo stopped treatment because of hypertension. Moreover, 93% of patients taking the target dose of 8 mg of perindopril were still at this dose at 3 years, whereas only 7% had dropped to 4 mg.[31] This contrasts with the HOPE trial, in which 62% of subjects were still receiving the target dose of 10 mg ramipril at 3 years.[90]

In patients with acute stroke, perindopril lowers BP, a favorable effect in this patient population, but not at the cost of a diminished cerebral perfusion.[103] In comparison with other ACE inhibitors, there is evidence favoring the tolerability profile of perindopril. Thus, advantages of perindopril over captopril have been reported in hypertensive patients.[24] One study found a lower rate of cough than with enalapril, whereas another found a lower withdrawal rate in comparison with enalapril.[59,61] In heart failure, first-dose hypotensive effects are not appreciably higher than placebo and are significantly fewer than those observed with captopril, enalapril, and lisinopril, even in elderly patients with heart failure.[81]

Together with the excellent tolerance in EUROPA, these data further support the assertion that perindopril is a safe and well-tolerated therapy in different disease states.

Conclusion

Because increased ACE is induced in virtually every model of cardiac injury—including volume overload, atherosclerotic plaque, infarction, postinfarction remodeling, heart failure, and aging—RAS blockade has become the universal first-line strategy for both cardiologists and, more importantly, their patients. The ACE inhibitors may be less specific in their blockade of angiotensin II than AT_1 receptor blockers, but they confer valuable cardiovascular protection by increasing the availability of bradykinin. If anything, the bradykinin effect compensates for the incomplete blockade of angiotensin II. Not only have their safety and efficacy been extensively documented, but they confer biological, structural, and neuroendocrine ben-

efits across disease conditions as clinically diverse as hypertension, CHF, ischemic heart and coronary artery disease, MI, secondary stroke prevention, and diabetic or nondiabetic nephropathy. Therefore, ACE inhibitors are currently recognized as having the broadest impact of any drug in cardiovascular medicine and thus remain the gold-standard RAS blocker. The outcomes from large morbidity-mortality trials, such as EUROPA and PROGRESS, found a similar treatment effect among patients with and without hypertension. Moreover the reduction in cardiovascular events was higher than could have been expected from the observed reduction in BP achieved with perindopril. These findings suggest specific antiatherosclerotic and anti-inflammatory effects, as well as effects on endothelial dysfunction. These specific properties of the long-acting ACE inhibitor perindopril beyond BP reduction will probably soon be elucidated by ongoing studies and further reinforce its use as first-line treatment and prevention in patients with hypertension and cardiovascular disease.

Key Points

1. Angiotensin-converting enzyme (ACE) inhibitors have had the broadest impact of any drug in cardiovascular medicine, reducing mortality and morbidity from hypertension, myocardial infarction, coronary artery disease, heart failure, stroke, diabetes mellitus, and renal impairment.
2. Perindopril is an ACE inhibitor that is characterized by the unique combination of several properties, including a high tissue ACE affinity and long duration of action, which has a wide range of effects: vasodilatory, hemodynamic, cardiovascular remodeling, anti-ischemic, antiatherogenic, and antithrombotic actions; and improvement in endothelial function and fibrinolytic balance.
3. Perindopril is widely used in hypertension management, and its duration of action affords full 24-h coverage with once-daily administration.
4. The seminal study PROGRESS showed the therapeutic value of perindopril in the secondary prevention of stroke.
5. In chronic heart failure, perindopril is associated with clinical improvement and a lower incidence of, and less severe, first-dose hypotension than other ACE inhibitors.
6. Perindopril reduces morbidity and mortality in coronary artery disease patients.
7. The results of the EUROPA study provide strong support for the routine use of perindopril in patients with stable coronary artery disease in addition to other preventive treatments and irrespective of cardiac function or risk factors.
8. Perindopril has beneficial effects in preventing the occurrence and progression of vascular complications of diabetes mellitus.
9. Perindopril is well tolerated, and is supported by more than 15 years of clinical experience.

References

1. Fox KM: Management of coronary artery disease: implications of the EUROPA trial. Br J Cardiol 2004;11:195–204.
2. White HD: Should all patients with coronary disease receive angiotensin-converting enzyme inhibitors? Lancet 2003;362:755–757.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, and the National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Hypertension 2003;42:1206–1252.
4. Brown NJ, Vaughan DE: Angiotensin-converting enzyme inhibitors. Circulation 1998;97:1411–1420.
5. Ferrari R: Preserving bradykinin or blocking angiotensin II: the cardiovascular dilemma. Dialog Cardiovasc Med 2004;9:71–89.
6. Vincent M, Marchand B, Remond G, Jaguelin-Guinamant S, Damien G, Portevin B, Baumal JY, Bouchet JP, Lambert PH: Synthesis and ACE inhibitory activity of the stereoisomers of perindopril (S-9490) and perindoprilate (S-9780). Drug Des Discov 1992;9:11–28.
7. Hurst M, Jarvis B. Perindopril: an updated review of its use in hypertension. Drugs 2001;61:867–896.
8. Zhuo J, Mendelsohn F, Ohishi M: Perindopril alters vascular angiotensin-converting enzyme, AT_1 receptor, and nitric oxide synthase expression in patients with coronary heart disease. Hypertension 2002;39:634–638.
9. Louis WJ, Conway EL, Krum H, Krum H, Workman B, Drummer OH, Lam W, Philips P, Howes LG, Jackson B. Comparison of the pharmacokinetics and pharmacodynamics of perindopril, cilazapril and enalapril. Clin Exp Pharmacol Physiol 1992;19(Suppl):55–60.
10. Johnston C, Fabris B, Yamada H, Mendelsohn FA, Cubela R, Sivell D, Jackson B. Comparative studies of tissue inhibition by angiotensin-converting enzyme inhibitors. J Hypertens 1989;7(Suppl 5): S11–S16.
11. Bussien JP, d'Amore TF, Perret L, Porchet M, Nussberger J, Waeber B, Brunner HR. Single and repeated dosing of the converting enzyme inhibitor perindopril to normal subjects. Clin Pharmacol Ther 1986;39:554–558.
12. Jackson B, Cubela RB, Johnston CI: Inhibition of tissue angiotensin-converting enzyme by perindopril: in vivo assessment in the rat using radioinhibitor binding displacement. J Pharmacol Exp Ther 1988;245:950–955.
13. Sakaguchi K, Jackson B, Chai SY, Mendelsohn FA, Johnson CI: Effects of perindopril on tissue angiotensin-converting enzyme activity demonstrated by quantitative *in vitro* autoradiography. J Cardiovasc Pharmacol 1988;12:710–717.
14. Sakaguchi K, Chai SY, Jackson B, Johnston CI, Mendelsohn FA: Differential angiotensin-converting enzyme inhibition in the brain after oral administration of perindopril demonstrated by quantitative in vitro autoradiography. Neuroendocrinology 1988;48:223–228.
15. Andreatta SH, Averill DB, Santos RA, Ferrario CM: The ventrolateral medulla. A new site of action of the renin-angiotensin system. Hypertension 1988;11:I163–I166.
16. Phillips MJ, Kimura B: Converting enzyme inhibitors and brain angiotensin. J Cardiovasc Pharmacol 1986;8:582–590.
17. Unger T, Genten D, Lang RE: Tissue-converting enzyme and cardiovascular actions of converting enzyme inhibitors. J Cardiovasc Pharmacol 1986;8(Suppl 10):S75–S581.
18. Lees KR, Reid JL: Effects of intravenous S-9780, an angiotensin-converting enzyme inhibitor, in normotensive subjects. J Cardiovasc Pharmacol 1987;10:129–135.
19. Lees KR, Reid JL. Hemodynamic and humoral effects of oral perindopril, an angiotensin-converting enzyme inhibitor, in man. Br J Clin Pharmacol 1987;23:159–164.

20. Bidiville J, Porchet M, Bussien JP, Nussberger J, Waeber B, Brunner HR: Effect of 8-day converting enzyme inhibition on ambulatory blood-pressure recordings in normotensive volunteers. Arch Int Pharmacodyn Ther 1987;288:109–119.
21. Richer C, Thuillez C, Giudicelli JF: Perindopril, converting enzyme blockade, and peripheral arterial hemodynamics in the healthy volunteer. J Cardiovasc Pharmacol 1987;9:94–102.
22. Dollery CF, Causon RC, Brown MJ: Long-lasting inhibition of ACE and angiotensin I pressor responses by S9490 in healthy volunteers. Ricerca Sci Educ Perm 1985;34:181–186.
23. Hui Y, Dai Z, Chen X, Wang W: Effect of perindopril and metoprolol on left ventricular hypertrophy and performance in essential hypertension. Chin Med J (Engl) 1995;108:678–681.
24. Agabiti-Rosei E, Ambrosioni E, Finardi G, Folino P, Galbassi G, Malini P, Marchesi E, Muiesan ML, Semplicini A, Pessina AC: Perindopril versus captopril: efficacy and acceptability in an Italian multicenter trial. Am J Med 1992;92:S79–S83.
25. Grandi AM, Venco A, Barzizza F, Petrucci E, Scalise F, Perani G, Marchesi E, Folino P, Finardia G: Double-blind comparison of perindopril and captopril in hypertension effects on left ventricular morphology and function. Am J Hypertens 1991;4:516–520.
26. Agabiti-Rosei E, Cores L, Leonetti G: A double-blind assessment, perindopril vs. verapamil, of the effects on office BP and 24-h ambulatory BP on left ventricular morphology; Annual Meeting of the European Society of Hypertension 1995; Abstract 106.
27. Pellacani A, Brunner HR, Nussberger J. Plasma kinins increase after angiotensin-converting enzyme inhibition in human subjects. Clin Sci (Lond) 1994;87:567–574.
28. Campbell DJ, Kladis A, Duncan AM: Effects of converting enzyme inhibitors on angiotensin and bradykinin peptides. Hypertension 1994;23:439–449.
29. Squire IB, O'Kane KP, Anderson N, Reid JL: Bradykinin B_2 receptor antagonism attenuates BP response to acute angiotensin-converting enzyme inhibition in normal men. Hypertension 2000; 36:132–136.
30. Morishita T, Tsutsi M, Shimokawa H, Tasaki H, Suda O, Kobayashi K, Horiuchi M, Okuda H, Tsuda Y, Yanagihara N, Nakashima Y. Long-term treatment with perindopril ameliorated dobutamine-induced myocardial ischemia in patients with coronary artery disease. Jpn J Pharmacol 2002;88:100–107.
31. Fox KM, and the EUROPA investigators: Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicenter trial (the EUROPA study). Lancet 2003;362(9386):782–788.
32. Ferrari R: PERTINENT: PERindopril, Thrombosis, InflammatioN, Endothelial dysfunction and Neurohormonal activation Trial, a subanalysis of EUROPA European Society of Cardiology Annual Congress. Munich, Germany; 28 August–l September 2004 (Abstract 2585).
33. Safar ME, London GM, Plante GE: Arterial stiffness and kidney function. Hypertension 2004;43:163–168.
34. Asmar RG, Pannier B, Santoni JP, Laurent S, London GM, Levy BI, Safar ME: Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. Circulation 1988;78:941–950.
35. Thybo NK, Stephens N, Cooper A, Aalkjaer C, Heagerty AM, Mulvany MJ: Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension. Hypertension 1995;25:72–81.
36. Buus NH, Bottcher M, Jorgensen CG, Christensen KL, Thygesen K, Nielsen TT, Mulvany MJ: Myocardial perfusion during long-term angiotensin-converting enzyme inhibition or β-blockade in patients with essential hypertension. Hypertension 2004;44:465–470.
37. Kool MJ, Lustermans FA, Breed JG, Struijker Boudier HA, Hoeks AP, Reneman RS, Van Bortel LM: The influence of perindopril and the diuretic combination amiloride+hydrochlorothiazide on the vessel wall properties of large arteries in hypertensive patients. J Hypertens 1995;13:839–848.
38. Schwartzkopff B, Brehm M, Mundhenke M, Strauer BE: Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. Hypertension 2000;36:220–225.
39. Guérin AP, Blacher J, Pannier B, Marchais SI, Safar ME, London GM: Impact of aortic stiffness attenuation on survival of patients in end stage renal failure. Circulation 2001;103:987–992.
40. Grandi AM, Bignoni M, Gaudio G, Zanzi P, Guasti L, Venco A: Ambulatory blood pressure and left ventricular changes during antihypertensive treatment: perindopril versus isradipine. J Cardiovasc Pharmacol 1995;26:737–741.
41. Moroi M, Zhang L, Yasuda T, Virmani R, Gold HK, Fishman MC, Huang PL: Interaction of genetic deficiency of endothelial nitric oxide, gender and pregnancy in vascular response to injury in mice. J Clin Invest 1998;101:1225–1232.
42. Mancini GB, Henry GC, Macaya C, O'Neill BJ, Pucillo AL, Carere RG, Wargovich TJ, Mudra H, Luscher TF, Klibaner MI, Haber HE, Uprichard AC, Pepine CJ, Pitt B: Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. Circulation 1996;94: 258–265.
43. Diet F, Pratt RE, Berry GJ, Momose N, Gibbons GH, Dzau VJ: Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease. Circulation 1996;94:2756–27667.
44. Antony I, Lerebours G, Nitenberg A: Angiotensin-converting enzyme inhibition restores flow-dependent and cold pressor test-induced dilations in coronary arteries of hypertensive patients. Circulation 1996;94:3115–3122.
45. Fennessy P, Campbell J, Mendelsohn F, Campbell GR: Angiotensin-converting enzyme inhibitors and atherosclerosis: relevance of animal models to human disease. Clin Exp Pharmacol Physiol 1996;23(Suppl l):S30–S32.
46. Candido R, Jandeleit-Dahm KA, Cao Z, Nesteroff SP, Burns WC, Twigg SM, Dilley RJ, Copper ME, Allen TJ: Prevention of accelerated atherosclerosis by angiotensin-converting enzyme inhibition in diabetic apolipoprotein E-deficient mice. Circulation 2002;106: 246–253.
47. Fogari R, Mugellini A, Zoppi A, Corradi L, Preti P, Lazzari P, Derosa G: Losartan and perindopril effects on plasma plasminogen activator inhibitor-l and fibrinogen in hypertensive type 2 diabetic patients. Am J Hypertens 2002;15:316–320.
48. Erdem Y, Usalan C, Haznedaroglu IC, Altun B, Arici M, Yasavul U, Turgan C, Caglar S: Effects of angiotensin-converting enzyme and angiotensin II receptor inhibition on impaired fibrinolysis in systemic hypertension. Am J Hypertens 1999;12:1071–1076.
49. Yasuda G, Hasegawa K, Kuji T, Ogawa N, Shimura G, Umemura S, Tochikubo O: Perindopril effects on ambulatory blood pressure: relation to sympathetic nervous activity in subjects with diabetic nephropathy. Am J Hypertens 2004;17:14–20.
50. Heart Failure Society of America (HSFA): HFSA guidelines for the management of patients with heart failure due to left ventricular systolic dysfunction—pharmacological approaches. Congest Heart Fail 2000;6:11–40.
51. Bartels GL, van den Heuvel FM, van Veldhuisen DJ, van der Ent M, Remme WJ: Acute anti-ischemic effects of perindoprilat in men with coronary artery disease and their relation with left ventricular function. Am J Cardiol 1999;83:332–336.
52. Walters MR, Reid JL: Perindopril. J Drug Eval 2003;1:115–141.
53. Speirs C, Wagniart F, Poggi L: Perindopril postmarketing surveillance: a 12 month study in 47,351 hypertensive patients. Br J Clin Pharmacol 1998;46:63–70.
54. Julius S, Cohn JN, Neutel J, Weber M, Turlapaty P, Shen Y, Dong V, Batchelor A, Lagast H: Antihypertensive utility of perindopril in a large, general practice-based clinical trial. J Clin Hypertens 2004; 6:10–17.

55. Guo W, Turlapaty P, Shen Y, Dong V, Batchelor A, Barlow D, Lagast H: Clinical experience with perindopril in patients nonresponsive to previous antihypertensive therapy: a large US community trial. Am J Ther 2004;11:199–205.
56. Cohn JN, Julius S, Neutel J, Weber M, Turlapaty P, Shen Y, Dong V, Batchelor A, Guo W, Lagast H: Clinical experience with perindopril in African-American hypertensive patients: a large USA community trial. Am J Hypertens 2004;17:134–138.
57. Fenves A, Ram CV: Are angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers becoming the treatment of choice in African-Americans? Curr Hypertens Rep 2002;4:286–289.
58. Lees KR, Reid JL, Scort MG, Hosie J, Herpin D, Santoni JP: Captopril versus perindopril: a double-blind study in essential hypertension. J Hum Hypertens 1989;3:17–22.
59. Alcocer L, Campos C, Bahena JH, Nacaud A, Parra Carillo J, Calvo C, Weber C, Lerebours G, Mickalonis L, Villahermosa MT: Clinical acceptability of ACE inhibitor therapy in mild-to-moderate hypertension, a comparison between perindopril and enalapril. Cardiovasc Drugs Ther 1995;9:431–436.
60. Yusoff K, Razak TA, Yusof N, Rafee NM: Comparative efficacy of perindopril and enalapril once daily using 24-h ambulatory blood pressure monitoring. Int J Clin Pract 1999;53:277–280.
61. Yoshinaga K, Saruta T, Abe K: Clinical evaluation of monotherapy with perindopril in the treatment of hypertension: a double-blind parallel comparison with enalapril. Rinshu Fyaku 1997;13:4259–4297.
62. Polonia J, Pego M: A double-blind comparison of perindopril and enalapril on 24-h control of blood pressure. Am J Hypertens 1996; 9:162.
63. Zannad F, Bernaud CM, Fay R: Double-blind, randomized, multicenter comparison of the effects of amlodipine and perindopril on 24-h therapeutic coverage and beyond in patients with mild-to-moderate hypertension. General Physicians Investigators' Group. J Hypertens 1999;17:137–146.
64. Canadian Study Group on Perindopril: Once-daily perindopril versus slow release diltiazem in the treatment of mild-to-moderate essential hypertension. Can J Cardiol 1994;10(Suppl D):D8–D12.
65. Thurston H, Mimran A, Zanchetti A, Creytens G, Rorive G, Brown CL, Santoni JP: A double-blind comparison of perindopril and atenolol in essential hypertension. J Hum Hypertens 1990;4:547–552.
66. Morgan TO, Louis WJ, MacDonald GJ, Conway EL, Bartholomeusz LC, Anderson AI, Cameron DP, Donnelly T, Frewin DB, Hooper MJ: Antihypertensive efficacy and safety of perindopril in mild-to-moderate essential hypertension: results of a double-blind multicenter study versus atenolol. Am J Med 1992;92:S73–S78.
67. Kuperstein R, Sasson Z: Effects of antihypertensive therapy on glucose and insulin metabolism and on left ventricular mass: a randomized, double-blind, controlled study of 21 obese hypertensives. Circulation 2000;102:1802–1806.
68. Guidelines Sub-Committee: World Health Organization–International Society of Hypertension Guidelines for the management of hypertension. Blood Press 1999;8(Suppl):9–43.
69. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM, BHS guidelines working party, for the British Hypertension Society: British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. Br Med J 2004;328:634–640.
70. Physician's Desk Reference, 55th ed. 2001; Thompson Healthcare, Montvale, NJ.
71. Myers MG: A dose-response study of perindopril in hypertension: effects on blood pressure 6 and 24 h after dosing. Perindopril Multicenter Dose-Response Study Group. Can J Cardiol 1996;12: 1191–1196.
72. Tan KW, Leenen FHH: Persistence of antihypertensive effect after missed dose of perindopril. Br J Clin Pharmacol 1999;48:628–630.
73. Morgan T, Anderson A: Duration of antihypertensive effect of perindopril (P), enalapril (E), and captopril. Hypertension 1993;21: 568.
74. Davies MK, Gibbs CR, Lip GYH: ABC of heart failure. Management: diuretics, ACE inhibitors and nitrates. BMJ 2000;320:428–431.
75. Remme WJ, Swedberg K: Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–1560.
76. Desche P, Antony I, Lerebours G, Violet I, Robert S, Weber C: Acceptability of perindopril in mild-to-moderate chronic congestive heart failure. Results of a long-term open study in 320 patients. Am J Cardiol 1993;71:E61–E68.
77. Lechat P, Garnham SP, Desche P, Bounhoure JP: Efficacy and acceptability of perindopril in mild-to-moderate chronic congestive heart failure. Am Heart J 1993;126:798–806.
78. Bounhoure JP, Bottineau G, Lechat P, Garnham J, Lapeyre G: Value of perindopril in the treatment of chronic congestive heart failure. Multicenter double-blind placebo-controlled study. Clin Exp Hypertens 1989;11(Suppl 2):575–586.
79. Squire IB, MacFadyen RJ, Reid JL, Devlin A, Lees KR: Differing early blood pressure and renin-angiotensin system responses to the first dose of angiotensin-converting enzyme inhibitors in congestive heart failure. J Cardiovasc Pharmacol 1996;27:657–666.
80. Reid JL, MacFadyen RJ, Squire IB, Lees KR: Angiotensin-converting enzyme inhibitors in heart failure: blood pressure changes after the first dose. Am Heart J 1993;126:794–797.
81. Navookarasu NT, Rahman AR, Abdullah I: First-dose response to angiotensin-converting enzyme inhibition in congestive cardiac failure: a Malaysian experience. Int J Clin Pract 1999;53:25–30.
82. Anthopoulos L, Apostolou T, Bonoris P, Foussas S, Lefkos N, Zombolos S: Comparative hemodynamic responses to the first dose of short- and long-acting ACE inhibitors in patients with congestive heart failure. Curr Med Res Opin 2001;17:290–297.
83. Vitovec J, Spinar J: First-dose hypotension after angiotensin-converting enzyme (ACE) inhibitors in chronic heart failure: a comparison of enalapril and perindopril. Eur J Heart Fail 2000;2:299–304.
84. MacFadyen RJ, Barr CS, Sturrock NDC, Fenwick M, Struthers AD: Further evidence that chronic perindopril treatment maintains neurohormonal suppression but does not lower blood pressure in chronic cardiac failure. Br J Clin Pharmacol 1997;44:69–76.
85. Ghiadoni L, Magagna A. Versari D, Kardasz I, Huang Y, Taddei S, Salvetti A: Different effects of antihypertensive drugs on conduit artery endothelial function. Hypertension 2003;41:1281–1286.
86. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension. A meta-analysis of randomized double-blind studies. JAMA 1996;275:1507–1513.
87. Ferrari R, on behalf of the PREAMI Investigators: PREAMI: Perindopril and Remodeling in the Elderly with Acute Myocardial Infarction: study rationale and design. Cardiovasc Drugs Ther 2000; 14:671–679.
88. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E: Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000;355:1575–1581.
89. Lau CP, Tse HF, Ng W, Chan KK, Li SK, Keung KK, Lau YK, Chen WH, Tang YW, Leung SK: Comparison of perindopril versus captopril for treatment of acute myocardial infarction. Am J Cardiol 2002;89:150–154.
90. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: 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;342:145–153.
91. Eastern Stroke and Coronary Heart Disease Collaborative Research Group: Blood pressure, cholesterol and stroke in eastern Asia. Lancet 1998;352:1801–1807.

92. Hartmann A, Rundek T, Mast H, Paik MC, Boden-Albala B, Mohr JP, Sacco RL: Mortality and causes of death after first ischemic stroke: the Northern Manhattan Stroke Study. Neurology 2001;57: 2000–2005.
93. Bronnum-Hansen H, Davidsen M, Thorvaldsen P (Danish MONICA Study Group): Long-term survival and causes of death after stroke. Stroke 2001;32:2131–2136.
94. Kelly R, Staines A, MacWalter R, Stonebridge P, Tunstall-Pedoe H, Struthers AD: The prevalence of treatable left ventricular systolic dysfunction in patients who present with noncardiac vascular episodes: a case-control study. J Am Coll Cardiol 2002;39:219–224.
95. PROGRESS Collaborative Group: Randomized trial of a perindopril-based blood pressure-lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. Lancet 2001; 358:1033–1041.
96. PROGRESS Collaborative Group: Effects of a perindopril-based blood-pressure-lowering regimen on cardiac outcomes among patients with cerebrovascular disease. Eur Heart J 2003;24:475–484.
97. Lawes CM, Bennett DA, Feigin VL, Rodgers A: Blood pressure and stroke: an overview of published reviews. Stroke 2004;35:776–785.
98. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, Davis S, Donnan G, MacMahon S, Neal B, Warlow C, Woodward M; Writing Committee for the PROGRESS Collaborative Group: Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke 2004;35:116–121.
99. Berthet K, Neal BC, Chalmers JP, MacMahon SW, Bousser MG, Colman SA, Woodward M; Perindopril Protection Against Recurrent Stroke Study Collaborative Group: Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS Trial. Blood Press 2004;13:7–13.
100. Rodgers A, Chapman N, Woodward M, Liu LS, Colman S, Lee A, Chalmers J, MacMahon S; Perindopril Protection Against Recurrent Stroke Study Collaborative Group: Perindopril-based blood-pressure lowering in individuals with cerebrovascular disease: consistency of benefits by age, sex and region. J Hypertens 2004;22:653–659.
101. PROGRESS Collaborative Group: Effects of blood-pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163:1069–1075.
102. PROGRESS Collaborative Group: Effects of a perindopril-based blood-pressure lowering regimen on disability and dependency in 6105 patients with cerebrovascular disease. A randomized clinical trial. Stroke 2003;34:2333–2338.
103. Dyker AG, Grosset DG, Lees K: Perindopril reduces blood pressure but not cerebral blood flow in patients with recent cerebral ischemic stroke. Stroke 1997;28:580–583.
104. Nazir FS, Overell JR, Bolster A, Hilditch TE, Lees KR: Effect of perindopril on cerebral and renal perfusion on normotensives in mild early ischaemic stroke: a randomized controlled trial. Cerebrovasc Dis 2005;19:77–83.
105. Walters MR, Bolster A, Dyker AG, Lees KR: Effect of perindopril on cerebral and renal perfusion in stroke patients with carotid disease. Stroke 2001;32:473–478.
106. SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
107. SOLVD Investigators: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992;327:685–691.
108. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669–677.
109. AIRE Study Investigators: 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;342:821–828.
110. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Audert L, Pauly NC: A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. TRAndolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670–1676.
111. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV, Gibbons RJ, Alpert JS, Antman EM, Hiratzka LF, Fuster V, Faxon DP, Gregoratos G, Jacobs AK, Smith SC Jr, American College of Cardiology, American Heart Association Task Force on Practice Guidelines: ACC/AHA 2002 Guidelines Update for the Management of patients with chronic stable angina. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2003;107:149–158.
112. Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011–1053.
113. American Diabetes Association: Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26(Suppl 1):S80–S82.
114. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR: Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. Br Med J 2000;321:412–419.
115. Strippoli GF, Craig M, Deeks JJ, Schena FP, Craig JC: Effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: a systematic review. BMJ 2004;329:828.
116. Fressinaud P, Berrut G, Gallois H: Antihypertensive action, clinical and biological acceptability of perindopril: main results in 23,460 patients with mild to moderate hypertension treated for 6 months in general practice. Ann Cardiol Angiol (Paris) 1993;42:51–59.
117. Kvetny J, Gregersen G, Pedersen RS: Randomized placebo-controlled trial of perindopril in normotensive, normoalbuminuric patients with type 1 diabetes mellitus. Q J Med 2001;94:89–94.
118. Jerums G, Allen TJ, Campbell DJ, Cooper ME, Gilbert RE, Hammond JJ, Raffaele J, Tsalamandris C: Long-term comparison between perindopril and nifedipine in normotensive patients with type 1 diabetes and microalbuminuria. Am J Kidney Dis 2001;37:890–S99.
119. Nakervis A, NIcholls K, Kilmartin G, Allen P, Ratnaike S, Martin FI: Effects of perindopril on renal histomorphometry in diabetic subjects with microalbuminuria: a 3-year placebo-controlled biopsy study. Metabolism 1998;47(12 Suppl 1):12–15.
120. Silberberg JS, Barre PE, Prichard SS, Sniderman AD: Impact of left ventricular hypertrophy on survival in end stage renal disease. Kidney Int 1989;36:286–290.
121. Blacher J, Pannier B, Guerin AP, Marchais SI, Safar ME, London GM: Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end stage renal disease. Hypertension 1998; 32:570–574.
122. Blacher J, Guerin AP, Pannier B, Marchais SI, Safar ME, London GM: Impact of aortic stiffness on survival in end stage renal disease. Circulation 1999;99:2434–2439.