Evidence for Benefits of Perindopril in Hypertension and Its Complications

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Structural and functional changes in large and small arteries in hypertension, even at early stages, may affect one or several end organs such as the brain, heart, and kidneys, contributing to cardiovascular morbidity and mortality. Therefore, modern treatment strategies should not only target blood pressure (BP) reduction but also normalize vascular structure and function. The purpose of this article is to review the large body of evidence, from randomized double-blind clinical trials, that has been gathered in regard to the angiotensin-converting enzyme (ACE) inhibitor perindopril, demonstrating its efficacy in reducing BP, reversing abnormalities of vascular structure and function in patients with essential hypertension, and ultimately preventing cardiovascular events. At the site of small resistance arteries, long-term treatment with perindopril, but not atenolol, reduced arterial wall hypertrophy for a given BP reduction. The improvement in small artery function in response to structural changes is exemplified at the site of the coronary circulation. Perindopril increased coronary blood flow and coronary reserve, in parallel with the regression of periarteriolar and interstitial collagen of coronary arterioles. At the site of large arteries, long-term treatment with perindopril reduced carotid and radial artery wall hypertrophy, and reduced carotid artery internal diameter. In response to these structural changes, large artery function improved at the site of the carotid and brachial arteries, showing a higher arterial distensibility, and at the site of the coronary circulation, showing a normalized arterial dilation in response to a cold pressor test or an increase in blood flow. Moreover, in patients with end-stage renal disease, perindopril decreased pulse wave velocity independently of BP changes, resulting in a highly significant relative risk reduction in all-cause and cardiovascular mortality. The multifactorial antiatherosclerotic profile of perindopril suggests a beneficial effect not only in patients with uncomplicated hypertension but also in patients with established coronary heart disease or previous stroke, as exemplified by the EUropean trial on Reduction Of coronary events with Perindopril in stable coronary Artery disease (EU-ROPA) and the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS). Am J Hypertens 2005;18:155S–162S © 2005 American Journal of Hypertension, Ltd.

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Hypertension is a common and often progressive disorder that poses a major risk for cardiovascular and renal disease.1,2 Recent data have revealed that the global burden of hypertension is an important and increasing public health problem worldwide and that the level of awareness, treatment, and control of hypertension varies considerably among countries.3 In 2000, 26.4% (972 million) of the worldwide adult population ≥18 years of age was affected by hypertension, and this number is predicted to increase by 60% to a total of 1.56 billion individuals by 2025.3 In economically developed countries, the level of blood pressure (BP) control (<140/ <90 mm Hg) among patients receiving antihypertensive treatment ranges from approximately 30% to 50%.4 (Table 1).

From a meta-analysis of individual data in 61 prospective studies,5 it is estimated that each increment of 20 mm Hg usual systolic BP (SBP) or 10 mm Hg usual diastolic BP (DBP) is associated with at least a twofold increase in the risk of death from stroke, ischemic heart disease, or other vascular cause. Similarly, a meta-regression analysis across 27 clinical trials of antihypertensive drugs has demonstrated that reduction in high BP reduced the risk of death and morbidity from stroke and coronary heart disease, and that the level of protection achieved against cardiovascular disease was related to the degree to which BP was reduced.6

However, it is estimated that only one half of the risk for cardiovascular disease is explained by conventional risk factors, including BP.7 Indeed, newly individualized risk factors are not taken into account, particularly markers of small and large artery damage, including small artery remodeling, carotid intima-media thickening, endothelial...
dysfunction, and arterial stiffening. All of these parameters have demonstrated their predictive value for cardiovascular events.8–15

From a pathophysiologic viewpoint, it is important to note that hypertensive disease involves changes in at least one of three hemodynamic variables (cardiac output, arterial stiffness, or peripheral resistance) that determine the measurable BP. Each of these variables is a potential therapeutic target, and it is likely that changes in these variables also contribute to the heterogeneity in the pharmacologic response of patients with hypertension. Vascular remodeling of large and small arteries in hypertension, even at early stages, may affect arterial stiffness and peripheral resistance, respectively, and thus one or several end organs such as the brain, heart, and kidney, contributing to cardiovascular morbidity and mortality. Therefore, modern treatment strategies should not only target BP reduction but also normalize vascular structure and function. Pharmacologic studies in animals and human beings have shown that, despite similar effects on BP, antihypertensive treatments have unequal efficacy in reversing vascular damage.

The purpose of this article is to review the large body of evidence from randomized double-blind clinical trials, that has been gathered with the angiotensin-converting enzyme (ACE) inhibitor perindopril, demonstrating its efficacy in reducing BP, reversing abnormalities of vascular structure and function in patients with essential hypertension, and ultimately preventing cardiovascular events.

### Effects of Perindopril on Small Artery Structure and Function

In a double-blind, randomized trial, the effects of treatment with perindopril and a β-blocker (atenolol) on small artery structure were compared in previously untreated patients with essential hypertension.16 Subjects were randomly assigned to treatment for 12 months with either perindopril (n = 13, 4 to 8 mg/day) or atenolol (n = 12, 50 to 100 mg/day). Before and at the end of treatment, gluteal biopsy samples were taken under local anesthetic; from these samples, two small arteries were dissected and mounted on a myograph for morphometry. Even though the absolute reduction in BP with atenolol (drop in mean BP 28.4 ± 1.8 mm Hg) was greater than with perindopril (20.6 ± 1.8 mm Hg), both treatment regimens achieved significant reductions compared with baseline values (P < .05). However, although perindopril treatment caused a significant 19% increase in small artery diameter (P < .02) and a 25% reduction in the ratio of media thickness to lumen diameter (P < .01), atenolol did not show such an effect. As compared with values in control subjects, the mean values achieved with perindopril indicate a complete normalization of the lumen diameter of small arteries. The change in small artery morphology caused by perindopril was not accompanied by any change in media cross-sectional area, suggesting that the change was caused by remodeling.

In line with the above study, Buus et al more recently reported the effect of long-term treatment with ACE inhibition and β-blockade on myocardial perfusion in previously untreated patients with essential hypertension.17 Patients were randomized in a double-blind design to receive either perindopril 4 to 8 mg once daily (n = 15) or atenolol 50 to 100 mg once daily (n = 15) for 1 year and were compared with a healthy normotensive control group (n = 15). Despite a similar and significant reduction in BP in both treatment arms (P < .01), only perindopril significantly reduced left ventricular mass by 14% ± 4% (P < .01), peripheral vascular resistance by 12 ± 6% (P < .01), and media thickness-to-lumen diameter ratio of resistance arteries by 16% ± 4% (P < .05), whereas these parameters remained unchanged with atenolol (Fig 1). Myocardial perfusion assessed by positron emission tomography at rest was significantly reduced in both treatment arms. However, hyperemic myocardial perfusion was significantly decreased by atenolol (−32% ± 5%, P < .01) and

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Adapted from Ref. 4.
remained unaltered on perindopril (2% ± 6%, P = NS). These changes in myocardial perfusion resulted in a significant difference in coronary reserve (P < .05) between perindopril and atenolol. Although an increase of 11% was observed in patients receiving perindopril, coronary reserve was reduced by 10% in those receiving atenolol. Cardiac output measured by echocardiography improved slightly with perindopril by 5% ± 5%, but was significantly reduced with atenolol by 15% ± 3% (P < .01). With perindopril, left ventricular mass and media-to-lumen ratio in resistance arteries were improved and peripheral vascular resistance, hyperemic myocardial perfusion, and coronary reserve were normalized compared with control values (Table 2).

Thus, despite similar reductions in BP, these studies support the possibility that treatment with perindopril causes a greater normalization of the structure of the resistance vasculature in patients with essential hypertension than treatment with atenolol.

In hypertensive heart disease, peripheral artery remodeling parallels coronary artery remodeling. To demonstrate the repair of coronary resistance vessels after long-term ACE inhibitor treatment, Schwartzkopf et al18 studied coronary flow reserve in 14 patients with essential hypertension and performed a transvenous endomyocardial biopsy before and after 12 months of antihypertensive treatment with perindopril (4 to 8 mg/day). Left ventricular muscle mass index significantly decreased by 11% (P = .04). Maximal coronary blood flow was increased by 54% (P = .001), and minimal coronary vascular resistance was diminished by 35% (P = .001); consequently, coronary reserve increased by 67% (P = .001). Structural analysis revealed a regression of both periarteriolar collagen area by 54% (P = .04) and of total interstitial collagen volume density by 22% (P = .04), whereas arteriolar wall area was slightly but not significantly reduced. Thus long-term therapy with perindopril, 4 to 8 mg once daily, induced structural repair of coronary arterioles that was mainly characterized by the regression of periarteriolar fibrosis and that was associated with a marked improvement in coronary reserve. These findings indicate the beneficial reparative effects of ACE inhibition on coronary microcirculation in hypertensive heart disease.

In summary, at the site of small resistance arteries, long-term treatment with perindopril reduced arterial wall hypertrophy. Perindopril increased coronary blood flow and coronary reserve, in parallel with the regression of periarteriolar and interstitial collagen of coronary arterioles. Considering these findings, perindopril has thus been shown to significantly improve all three hemodynamic variables that are involved in hypertensive disease: specifically, cardiac output, arterial stiffness, and peripheral resistance.

### Effects of Perindopril on Large Artery Structure and Function

#### Pressure-Dependent Increase in Arterial Distensibility

Asmar et al19 were the first to demonstrate, in a single-blind study, that 3 months’ treatment with perindopril significantly increased brachial artery compliance and reduced pulse wave velocity in patients with sustained essential hypertension. More recently, Kool et al,20 using echo-tracking techniques, showed that chronic treatment with perindopril increased femoral artery compliance and, to a lesser extent, carotid artery compliance. The PERIndropil and hydrochlorothiazide + amiloride for the Control at Long term of wall thickness in ESsential hypertension (PERICLES) study was conducted to determine the effect of perindopril on large artery thickness and stiffness.21 A total of 77 elderly hypertensive patients between 60 and 80 years of age were randomized to 9 months of double-blind treatment with perindopril (2 to 8 mg once daily) or the diuretic combination hydrochlorothiazide (HCTZ) + amiloride (HCTZ 12.5 mg + amiloride 1.25 mg to HCTZ 50 mg + amiloride 5 mg once daily), after a 1-month placebo wash-out period. Arterial parameters including radial artery mass and common ca-
rotid artery compliance were calculated from noninvasive measurements of internal diameter and wall thickness using high-resolution echo-tracking systems at baseline and after 5 and 9 months. During treatment, BP and arterial parameters changed to the same extent in both groups. After 9 months of treatment, SBP, DBP, and pulse pressure, and radial artery wall thickness, mass, and thickness/radius ratio decreased significantly ($P < .01$), whereas carotid compliance increased ($P < .001$). Thus, the PERICLES study indicates that in elderly hypertensive patients, both the ACE inhibitor perindopril and a diuretic combination-based treatment can reduce radial artery wall hypertrophy and improve carotid artery compliance.

To determine the effects of perindopril on arterial wave reflections, a prospective, randomized, 12-week study was performed in previously treated hypertensive subjects, in 67 of whom usual treatment was replaced with perindopril therapy.

Large artery properties were assessed as central arterial pressure augmentation, determined by applanation tonometry of the radial artery and a transfer function. After 12 weeks of treatment, the augmentation index (AI, %) decreased significantly (152 ± 2% to 145 ± 3%) in patients treated with perindopril. Perindopril treatment produced a greater decrease in AI than did continuation of previous therapy, but this could be largely explained by hemodynamic changes rather than by direct arterial effects.

Altogether, these studies show that the increase in large artery compliance and distensibility in response to perindopril, in parallel with the reduction in aortic stiffness and wave reflection, leading to the lowering of AI and central pulse pressure, could be caused by the BP-lowering effect, unloading the stiff component of the arterial wall. Hypertension and diabetes are associated with increased carotid thickness and stiffness. The ACE inhibitors could theoretically reduce both, either through a BP-lowering effect or direct BP-independent pharmacologic blockade of the renin-angiotensin system, although the latter has never been demonstrated. A pressure-independent decrease in arterial stiffness implies a pharmacologic remodeling of the arterial wall. Various changes have been described in response to long-term antihypertensive treatment in animals. They include a reduction in collagen content and density, an increase in the elastin/collagen density ratio, a decrease in intima-media thickness, and changes in the connections of smooth muscle cells to extracellular matrix through fibronectin-integrin relationships. Thus a major issue, which was raised by the above clinical trials, is to what extent the reduction in arterial wall thickness and stiffness is BP independent.

**Pressure-Independent Increase in Arterial Distensibility**

The objective of the Diabetes Artery Perindopril Hypertension Normalization Excess Thickness (DAPHNET) study was to demonstrate a BP-independent effect of an ACE inhibitor on carotid structure and function. To detect this effect better, this study combined several features: 1) the high precision of echo-tracking systems for measuring carotid parameters; 2) multivariate analyses; and 3) an experimental design in which patient responders to perindopril (4 mg once daily for 1 month, leading to a fall in SBP of >10 mm Hg) were randomized in a double-blind manner either to perindopril 4 mg once daily or perindopril 8 mg once daily for 6 months. Internal diameter, carotid change in diameter, and intima-media thickness were measured with an echo-tracking system at the site of the common carotid artery at baseline and after the 6-month treatment period, in 57 patients with essential hypertension with type 2 diabetes (mean age 63 ± 7 years). The reduction in office and ambulatory BP was significantly higher with perindopril 8 mg than with perindopril 4 mg. Carotid intima-media thickness significantly decreased after perindopril, with no difference between doses. Carotid internal diameter, wall stress, and elastic modulus were significantly lower after perindopril 8 mg than perindopril 4 mg and distensibility was higher after perindopril 8 mg than after perindopril 4 mg, independently of BP reduction. The reduction in mean BP explained only 27% of the difference in inward carotid remodeling whereas dose (8 mg $\times$ 4 mg) explained 73%. The dose of perindopril explained most of the difference in the reduction in elastic modulus and the increase in distensibility, whereas the reduction in BP was not significantly associated with these changes. These results indicate a BP-independent improvement in geometrical and functional properties of the common carotid artery on chronic treatment with the ACE inhibitor perindopril. They suggest that distensibility was improved through inward remodeling, leading to a reduction in wall stress and thus elastic modulus. They also suggest that higher doses of perindopril (8 mg) have a more pronounced effect on the improvement in carotid properties in patients with essential hypertension with type 2 diabetes.

**Reversal of Endothelial Dysfunction**

Beside arterial stiffening, endothelial dysfunction is a common feature of large artery alterations with hypertension. Epicardial coronary arteries are major targets for treatment, as cold pressor test (CPT)–induced and flow-dependent dilations are impaired in patients with hypertension. Use of ACE inhibitors can attenuate sympathetic coronary constriction and potentiate or restore endothelium-dependent relaxations. To determine whether the active metabolite of the ACE inhibitor perindopril, perindoprilat, can restore normal coronary dilatory responses in hypertensive patients, the coronary vasomotor responses to CPT and to maximal increase in blood flow induced by papaverine were studied in 10 previously untreated patients with essential hypertension. Patients had no other risk factors and had angiographically normal coronary arteries before and after intravenous ACE inhib-
bition by perindopril.25 Diameters of proximal and distal left anterior descending (LAD) and circumflex coronary arteries were measured by quantitative angiography. Estimates of coronary blood flow and resistance index were calculated with an intracoronary Doppler catheter in the distal LAD. Perindoprilat did not modify the hemodynamic responses to CPT and papaverine. In response to CPT, perindoprilat changed the epicardial coronary constriction (−8.4% ± 5.8%; P < .001) into a significant dilation (+12.0% ± 6.4%; P < .001). Perindoprilat significantly increased the coronary blood flow and enhanced the decrease in coronary resistance caused by CPT. Flow-dependent dilation of the proximal LAD was abolished in the control condition and was restored after perindoprilat. This study shows that ACE inhibition with the metabolite of perindopril restored CPT-induced and flow-mediated coronary artery dilations in patients with essential hypertension, and indicates that impaired coronary vasomotor responses may be reversible in hypertensive patients.

Recently, a prospective, randomized, parallel-group study reported the different effect of antihypertensive drugs on conduit artery endothelial function in a population of 168 patients with essential hypertension.26 Patients were randomly assigned to a 6-month period of treatment with nifedipine (n = 28), amlodipine (n = 28), atenolol (n = 29), nebivolol (n = 28), telmisartan (n = 29), and perindopril (n = 28), and results were compared with those in healthy control subjects (n = 40). The investigators evaluated brachial artery flow-mediated, endothelium-dependent dilation (measured by high-resolution ultrasonography) compared with the endothelium-independent response to glyceryl trinitrate (25 g/sec). All treatments equally and significantly reduced BP. However, compared with baseline values, flow-mediated dilation was only increased in the perindopril group to values (from 5.1% ± 2% to 6.4% ± 2.4%) no different from normotensive control subjects. In addition, the degree of improvement in flow-mediated dilation (+1.5% ± 2.1%) was significantly higher than that obtained with other treatments (P < .01), without modifying the response to glyceryl trinitrate. This study thus showed that perindopril 4 mg effectively not only reduces BP in patients with essential hypertension but that, compared with other antihypertensive treatments, it appears to be the only compound able to restore endothelial function to normal values (Fig. 2).

In summary, at the site of large arteries, long-term treatment with perindopril improved endothelial function, reduced radial and carotid artery wall hypertrophy, and reduced carotid artery internal diameter. In response to these structural changes, large artery function improved at the site of the aorta, and carotid, femoral and brachial arteries, showing a greater arterial distensibility. On perindopril, endothelial function was normalized at the site of the coronary circulation, with an arterial dilation in response to a CPT or an increase in blood flow.

**FIG. 2.** Effects of different classes of antihypertensive drugs on correction of arterial endothelial dysfunction. Although all antihypertensive agents reduced blood pressure, endothelial function expressed as flow-mediated dilation was only significantly improved and normalized on perindopril. *P < .01 vs baseline and other agents. Adapted from Ref. 25.

### Improvement in Survival in Clinical Trials

The ACE inhibitors have shown their ability to prevent cardiovascular complications in hypertensive patients. Among patients assigned ACE inhibitor therapy in various clinical trials, the meta-analysis of the Blood Pressure Lowering Treatment Trialists’ Collaboration,27 which included 12,124 patients, showed significant reductions in risk of total major cardiovascular events. Compared with placebo, ACE inhibitor therapy led to a risk reduction of 28% in stroke, 20% in coronary heart disease, 22% in major cardiovascular events, 18% in heart failure, 20% in cardiovascular death, and 12% risk reduction in total mortality.

The multifactorial antiatherosclerotic profile of perindopril, detailed above, suggests a beneficial effect not only in hypertensive patients corresponding to the populations of clinical trials included in the above meta-analysis but also in patients with established coronary heart disease or previous stroke.

The EUROpean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA study) assessed whether perindopril reduced cardiovascular risk in a low-risk population with stable coronary heart disease and no apparent heart failure.28 A total of 13,655 patients were registered who had previous myocardial infarction (64%), angiographic evidence of coronary artery disease (61%), coronary revascularization (55%), or a positive stress test only (5%). After a run-in period of 4 weeks, in which all patients received perindopril, 12,218 patients were randomly assigned to receive perindopril 8 mg once daily (n = 6110), or matching placebo (n = 6108). In each arm of the study, 27% of patients were hypertensive. After a mean follow-up of 4.2 years, 603 (10%) placebo and 488 (8%) perindopril patients experienced the primary end point (cardiovascular
death, myocardial infarction, and cardiac arrest). This yielded a 20% relative risk reduction (95% confidence interval [CI], 9 to 29; \( P = 0.0003 \)) with perindopril. These benefits were achieved with standard recommended background therapy and were consistent in all predefined subgroups and secondary end points. In addition, the benefits were greater than could have been expected from the observed reduction in BP (mean, \(-5/-2 \) mm Hg), and similar benefits were observed regardless of whether patients were hypertensive (19% and 20% risk reduction, respectively) and irrespective of the degree of BP reduction. To explain these findings and considering that CAD progression correlates with an alteration of endothelial function, the PERindopril Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial (PERTINENT), a predefined substudy of EUROPA, assessed whether the benefits could be explained by an effect of perindopril on endothelial function and markers of inflammation and thrombosis. Compared with placebo, treatment with perindopril for 1 year resulted in a significant restoration of the angiotensin II/bradykinin balance (\(-27\% \) and \(+17\% \), respectively). Furthermore, perindopril led to a significant reduction in tumor necrosis factor–\( \alpha \), an index of low-grade chronic inflammation, and von Willebrand factor, an index of endothelial cell damage. Finally, perindopril induced an upregulation of endothelial cell nitric oxide synthase expression and activity by 19% and 27%, respectively, and a significant reduction in endothelial cell apoptosis (\(-37\% \)).

These data thus confirm that, apart from its BP-lowering effect, perindopril has specific vascular and antiatherosclerotic effects that may explain, at least in part, the observed benefits in the EUROPA trial.

The Perindopril rPRotection aGainst REcurrent Stroke Study (PROGRESS)\(^{29} \) was designed to determine the effects of a BP-lowering regimen in hypertensive (48%) and nonhypertensive patients with a history of stroke or transient ischemic attack. A total of 6105 individuals from 172 centers in Asia, Australasia, and Europe were randomly assigned active treatment (\( n = 3051 \)) or placebo (\( n = 3054 \)). Active treatment comprised a flexible regimen based on perindopril (4 mg daily) with the addition of the diuretic indapamide at the discretion of treating physicians. The primary outcome was total stroke (either fatal or nonfatal).

Over 4 years of follow-up, active treatment reduced blood pressure by 9/4 mm Hg; 307 (10%) individuals assigned to active treatment experienced stroke, compared with 420 (14%) assigned to placebo (relative risk reduction 28%; 95% CI, 17 to 38; \( P < .0001 \)). Active treatment also reduced the risk of total major vascular events (relative risk reduction, 26%; 95% CI, 16 to 34). There were similar reductions in the risk of stroke in both the hypertensive and nonhypertensive subgroups (all \( P < .01 \)). Single-drug therapy reduced BP by 5/3 mm Hg and produced (as could reasonably be expected) a smaller reduction in the risk of recurrent stroke than combination therapy with perindopril plus indapamide, which reduced BP by 12/5 mm Hg and stroke risk by 43% (95% CI, 30 to 54).

**Impact of Reduction in Target-Organ Damage on Survival**

Although media-to-lumen ratio of small arteries, endothelial dysfunction, and carotid intima-media thickness are now well accepted as intermediate end points for cardiovascular events (that is, a significant longitudinal relationship between these parameters and the occurrence of cardiovascular events has been demonstrated, independently of classic cardiovascular risk factors), their values as surrogate end points have not been demonstrated.

The only exception, among biomarkers of vascular damage, is aortic stiffness, which has recently demonstrated its value as a surrogate end point in a population at high cardiovascular risk, namely, patients with end-stage renal disease.\(^{30} \) Indeed, a major issue is to determine the impact of aortic stiffness attenuation on survival, and particularly to demonstrate whether a reduction in pulse wave velocity (PWV) could predict a reduction in cardiovascular events, independently of the normalization of classic cardiovascular risk factors. Under these conditions, aortic stiffness may have a better predictive value than classic risk factors, as it integrates the damage of cardiovascular risk factors on the arterial wall over a certain period. Indeed, BP, glycemia, and lipids can be normalized in a few weeks by using antihypertensive, antidiabetic, and lipid-lowering drugs, leading to a marked reduction in cardiovascular risk scores, but still without any improvement in atherosclerotic lesions and aortic stiffness, which requires a long-lasting correction of biochemical abnormalities. A discrepancy is thus expected between the improvement in cardiovascular risk factors and a still-high aortic stiffness.

A direct response to the issue of the predictive value of aortic stiffness as a surrogate end point for cardiovascular events has not yet been afforded in the general population, but Guerin et al\(^{30} \) provided the first clear evidence in patients with end-stage renal failure (ESRF). These investigators, who have previously shown that aortic PWV was a predictor of mortality in ESRF patients,\(^{8} \) retained all-cause and cardiovascular mortality as a primary end point. Because PWV is partly dependent on BP, and a decrease in BP can attenuate the stiffness (reduction in PWV), they tested the hypothesis that the changes in PWV in response to decreases in BP could predict mortality in ESRF patients.

A total of 150 ESRF patients (mean age 52 years) were monitored for an average duration of 51 months. The changes in PWV in response to decreased BP were measured from entry until the end of follow-up. The BP was controlled by adjustment of “dry weight” and, when necessary, with the ACE inhibitor perindopril, the calcium antagonist nitrendipine, or the \( \beta \)-blocker atenolol, in combination if necessary. Patients were randomly assigned to
receive perindopril (4 to 8 mg every 48 h) or nitrendipine (10 to 20 mg/day). If the drug was not well tolerated (as evident by intradialytic hypotension, ankle edema, flush, or cough), the drugs were interchanged. If the target BP was still not achieved, the β-blocker atenolol was prescribed at a dose of 25 to 50 mg/day. Finally, if this combined dual therapy did not achieve the target BP, a combination of perindopril, nitrendipine, and atenolol was prescribed. Among patients receiving antihypertensive drugs, 46% took perindopril, 53% took atenolol, and 78% took nitrendipine.

A total of 59 deaths occurred, including 40 cardiovascular and 19 noncardiovascular events. Cox analyses demonstrated that independent of BP changes, the absence of a PWV decrease in response to a BP decrease was a significant predictor of all-cause and cardiovascular mortality. After adjustment for all confounding factors, the risk ratio for the absence of PWV decrease was 2.59 (95% CI, 1.51 to 4.43) for all-cause mortality and 2.35 (95% CI, 1.23 to 4.41) for cardiovascular mortality. These results indicate that in ESRF patients, the insensitivity of PWV to reduced BP is an independent predictor of mortality. Thus, in this population, aortic stiffness is a good surrogate end point, that is, its attenuation is predictive of a reduction in all-cause and cardiovascular mortality.

Survival was positively associated with perindopril use reducing the risk for all-cause mortality by 81% (95% CI, 0.14 to 0.43) and for cardiovascular mortality by 82% (95% CI, 0.06 to 0.55). Altogether, these results indicate that in ESRF patients, the insensitivity of PWV to decreased BP is an independent predictor of mortality, and that use of the ACE inhibitor perindopril has a favorable effect on survival that is independent of BP changes.

Conclusion

Several randomized, double-blind, parallel studies, performed according to good clinical practice, have demonstrated the efficacy of the ACE inhibitor perindopril in reducing BP, reversing abnormalities of vascular structure and function in patients with essential hypertension, and ultimately preventing cardiovascular events. The multifactorial antiatherosclerotic profile of perindopril suggests a beneficial effect not only in patients with uncomplicated hypertension but also in patients with established coronary heart disease or previous stroke, as exemplified by the EUROPA and the PROGRESS studies.

References


29. PROGRESS Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033–1041.