Benefits of First-Line Combination of Perindopril and Indapamide in Clinical Practice for Patients With Hypertension and Diabetes

Faiez Zannad

Because of the importance of attaining rapid and tight blood-pressure (BP) control, those guidelines that base treatment recommendations on a risk-stratification approach include combination therapies as first-line pharmacologic treatment options. Monotherapies were shown to be ineffective in many patients, and delays in BP control significantly increase the risk of cardiac events, stroke, and death. In diabetic patients in whom BP control is particularly hard to achieve, the use of angiotensin-converting enzyme (ACE) inhibitors, which inhibit the renin-angiotensin system, has been recommended. Consistent with these guidelines, comparative clinical trials confirmed the value of the ACE inhibitor-and-diuretic combination treatment, perindopril/indapamide, in hypertensive diabetic patients and in patients with uncomplicated essential hypertension, multiple risk factors, and associated clinical conditions. Perindopril/indapamide was shown to have an early and sustained effect on systolic BP, and a specific and positive effect on hemodynamics. Treatment attenuates carotid-wave reflections and pulse-wave velocity, both of which are components of pulse pressure and are determinants of left-ventricular afterload, myocardial hypertrophy, and myocardial oxygen consumption. In diabetic patients with albuminuria, perindopril/indapamide treatment significantly reduces BP, the albumin excretion rate, and the urinary albumin:creatinine ratio. The nephroprotective effects of perindopril/indapamide remain significant after adjustment for changes in BP. Together, these data suggest that a combination of perindopril and indapamide, through its effect on BP-lowering and target-organ protection, is suited to the medical needs of a wide range of hypertensive patients, including those with diabetes. Am J Hypertens 2007; 20:9S–14S © 2007 American Journal of Hypertension, Ltd.

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As the understanding of hypertension evolves, criteria for treatment also evolve. According to European and United States guidelines, the assessment of a patient's risk category should be a composite of a blood-pressure measurement and of an evaluation of risk factors such as dyslipidemia and age, target-organ damage (eg, left-ventricular hypertrophy [LVH] and microalbuminuria), associated clinical conditions (eg, heart disease and renal disease), and diabetes (Table 1).[1,2] For example, a patient with Grade 2 hypertension and no risk factors will be in a lower risk category than a patient with high normal hypertension and an associated clinical condition such as diabetic nephropathy.

As a patient progresses through higher risk categories, the relative risk of cardiovascular disease increases. Low risk is associated with an absolute 10-year risk of cardiovascular disease of $<15\%$, whereas very high risk is associated with an absolute 10-year risk of $>30\%$. Not surprisingly, suggested treatment strategies, aimed at the long-term reduction of cardiovascular morbidity and mortality, reflect this risk-stratification approach and vary from lifestyle changes, to glucose control in diabetic patients, to blood pressure-lowering through pharmacological treatment, to appropriate management of associated clinical diseases.[1,2]

Combination therapies, such as an angiotensin-converting enzyme (ACE) inhibitor and a diuretic, eg, perindopril/indapamide, have been included in guidelines as first-line options. This change in approach reflects that monotherapies are often ineffective, that combination therapies are often needed to reach blood-pressure goals, and that delays in blood-pressure control of as little as 6 months significantly increase the risk of cardiac events, stroke, and death.[3,4]

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From the Department of Cardiovascular Disease, Clinical Investigation Center, Institute National de la Santé et de la Recherche Médicale, Centre Hospitalier Universitaire (CHU), Université Henri Poincaré, Nancy, France.

Address correspondence and reprint requests to Dr. Faiez Zannad, Department of Cardiovascular Disease, Clinical Investigation Center, Institute National de la Santé et de la Recherche Médicale, CHU, Université Henri Poincaré, Nancy, France; e-mail: f.zannad@chu-nancy.fr

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Table 1. Stratification of risk to quantify prognosis*

Other risk factors and disease history	Blood pressure (mm Hg)				
	Normal (SBP 120–129, or DBP 80–84)	High normal (SBP 130–139, or DBP 85–89)	Grade 1 (SBP 140–159, or DBP 90–99)	Grade 2 (SBP 160–179, or DBP 100–109)	Grade 3 (SBP ≥180, or DBP ≥110)
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
≥3 risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

ACC = associated clinical conditions; DBP = diastolic blood pressure; SBP = systolic blood pressure; TOD = target-organ damage.
* Adapted with permission from Table 2 of the European Society of Hypertension-European Society of Cardiology guidelines.[1]

In diabetic patients, in whom blood-pressure control is particularly hard to achieve, the use of ACE inhibitors was recommended in the guidelines of diabetes associations.[5] Not only do ACE inhibitors reduce blood pressure, but they block the activation of the renin-angiotensin system, thereby reducing damage to the kidney. This renal outcome was shown to extend beyond simple antihypertensive effects.[6] Diuretics are also of interest because they counterbalance the propensity of diabetic patients to retain sodium. Consistent with this pharmacological understanding of the benefits of an ACE inhibitor/diuretic combination, head-to-head clinical trials confirmed the value of the perindopril/indapamide combination treatment in hypertensive, diabetic patients and in patients with uncomplicated essential hypertension, multiple risk factors, and associated clinical conditions.[7–11] Here, we review the evidence for the benefits of treatment with a first-line combination of perindopril and indapamide.

Systolic Blood-Pressure Reduction With Perindopril and Indapamide

Systolic blood pressure (SBP) has emerged in epidemiologic studies as an independent risk factor for cardiovascular disease mortality.[12] As a result, the effect of treatments on SBP is gaining in importance. In clinical trials, perindopril/indapamide has both an early and long-term effect on SBP in a wide range of patients.[7–11] Clinically significant decreases in SBP ranged from ≥22 mm Hg in elderly patients, patients with LVH, and patients with uncomplicated hypertension, to 15 mm Hg in patients with diabetes.

Perindopril/Indapamide May Offer an Effective Alternative to Current Strategies

The results of the randomized, controlled, double-blind, multicenter, French STRAtegies of Treatment in Hypertension Evaluation (STRATHE) Study are of particular note, because conventional strategies were compared with perindopril/indapamide combination treatment. Five hundred and thirty-three patients with uncomplicated hypertension were treated with perindopril/indapamide (2 mg/0.625 mg, titrated as needed to 3 mg/0.937 mg and then to 4 mg/1.25 mg), sequential monotherapies (atenolol 50 mg, changed as needed to losartan 50 mg, and then to amlodipine 5 mg), or a stepped-care approach (valsartan 40 mg, titrated as needed to 80 mg, and then to valsartan 80 mg plus hydrochlorothiazide 12.5 mg) for 9 months.[10] The SBP-lowering was more pronounced with perindopril/indapamide than with other strategies ($P = .047$ versus sequential strategy; $P = .088$ versus stepped care).

At the end of the study, a mean reduction in SBP of 27 mm Hg and a normalization rate (SBP/diastolic blood pressure [DBP] ≤140/90 mm Hg) of 62% were achieved.[10] In addition, in a subset of higher-risk patients

with Grade 2 hypertension, blood pressure was normalized in 64% of patients on perindopril/indapamide, compared with 48% to 50% for the other strategies.[13]

The normalization rates (62% to 64%) noted in the STRATHE Study vastly exceed those recorded in French epidemiologic studies (≤33%).[14,15] Interestingly, the rates of normalization observed in STRATHE were confirmed in the large real-life French interventional trial, OPTIMiser le tAuX de normalisation tensionnelle grâce à la plurithérapie de première intention (OPTIMAX), in which 69% of patients were normalized after 3 to 6 months of treatment with perindopril/indapamide.[16] Similarly, in the large interventional German PReterax® fIx koMbiniert Und niedrig doSiert bei hypertonie von Anfang an (PRIMUS) Trial, after perindopril/indapamide treatment (2 mg/0.625 mg, titrated as needed to 4 mg/1.25 mg), normalization rates of 50% were reached, whereas epidemiologic studies recorded a normalization success rate of 8% in Germany.[17,18]

Together, these data, which were collected in a wide range of patients (including newly diagnosed and treated but uncontrolled patients), suggest that perindopril/indapamide may offer an effective alternative to current strategies that appear in real-life practice to be insufficient. Greater efficacy may be attributable to the inhibition of multiple pathways and the blockade of compensatory feedback mechanisms, but also to greater patient compliance because of good tolerability and the need to take fewer pills.

Myocardial and Vascular Protection

Perindopril/indapamide has a superior effect on blood pressure-lowering compared with conventional strategies, as noted in STRATHE,[10,19] and a specific effect on the arterial tree. Indeed, studies of perindopril/indapamide in patients with LVH, and studies that examined the effects of perindopril/indapamide on the macrocirculation and microcirculation, support the notion that perindopril/indapamide has a positive effect on stiffness of the large arteries and the microcirculation.

Improvements in coronary microcirculation, for example, were noted in a 6-month pilot study of patients with hypertension ($n = 6$).[20] Not only did perindopril/indapamide normalize blood pressure in all patients, but it also improved coronary vasodilator reserve. Left-ventricular mass (LVM) was also normalized after treatment of the one patient with LVH. These data suggest that perindopril/indapamide positively affects the structure of small vessels and reduces microvascular rarefaction.[20]

In the multicenter, randomized, controlled, double-blind pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd (REASON) Study, 12 months of treatment in 471 patients with uncomplicated hypertension with perindopril/indapamide (2 mg/0.625 mg, titrated as needed to 4 mg/1.25 mg) lowered brachial and carotid artery SBP and pulse pressure significantly more than did treatment with atenolol (50 mg, titrated as needed to 100 mg).[21] This lowering of SBP and pulse pressure suggests a specific effect of perindopril/indapamide on the arterial tree and on the macrocirculation. Indeed, in this study, perindopril/indapamide also attenuated large-vessel pulse-wave velocity and carotid-wave reflections, both of which are independent cardiovascular risk factors. Wave reflections are ultimately determinants of left-ventricular afterload, myocardial hypertrophy, and increased myocardial oxygen consumption. The effect of treatment on LVM was also measured directly in 214 patients participating in the REASON Study. Reduction in LVM was significantly greater with perindopril/indapamide compared with atenolol.[22]

The effects of perindopril/indapamide on LVH were further evaluated in 556 hypertensive patients with LVH, in the multicenter, randomized, controlled, double-blind Perindopril/Indapamide in a double-blind controlled study versus Enalapril in left ventricular hypertrophy (PICXEL) Trial.[9] After 1 year of treatment with either perindopril/indapamide (2 mg/0.625 mg, titrated as needed to 4 mg/1.25 mg and then to 8 mg/2.5 mg) or with enalapril alone (10 mg, titrated as needed to 20 mg and then to 40 mg), not only were SBP and DBP significantly decreased, but measures of ventricular hypertrophy, such as LVM index, were decreased significantly more with perindopril/indapamide than with enalapril treatment (Fig. 1).[9] Left-ventricular internal diameter and posterior-wall thickness were also decreased significantly more with perindopril/indapamide compared with enalapril.

These data are consistent with results of meta-analyses in which ACE inhibitors were effective in reversing wall hypertrophy and reducing LVM, and diuretics were effective in decreasing ventricular diameter.[23–25] Thus, an ACE inhibitor combined with a diuretic, such as perindopril/indapamide, may be more effective than an ACE inhibitor alone with respect to myocardial protection.

Renal Protection With Perindopril/Indapamide in Patients With Diabetes

An effect on vascular health suggests that treatment with perindopril/indapamide may be effective in controlling hypertension, as well as in controlling vascular and renal complications in diabetic patients. Indeed, diabetes is associated with macrovascular and microvascular complications, which result from and contribute to hypertension. The diabetic kidney, in particular, because of its sensitivity to alterations in the microcirculation and macrocirculation, is subject to tubular damage and renal disease, which in turn increase hypertension.

In the 12-month, randomized, controlled, double-blind Preterax in Albuminuria Regression (PREMIER) Trial, diabetic patients with albuminuria were treated with perindopril/indapamide (2 mg/0.625 mg, titrated as needed to

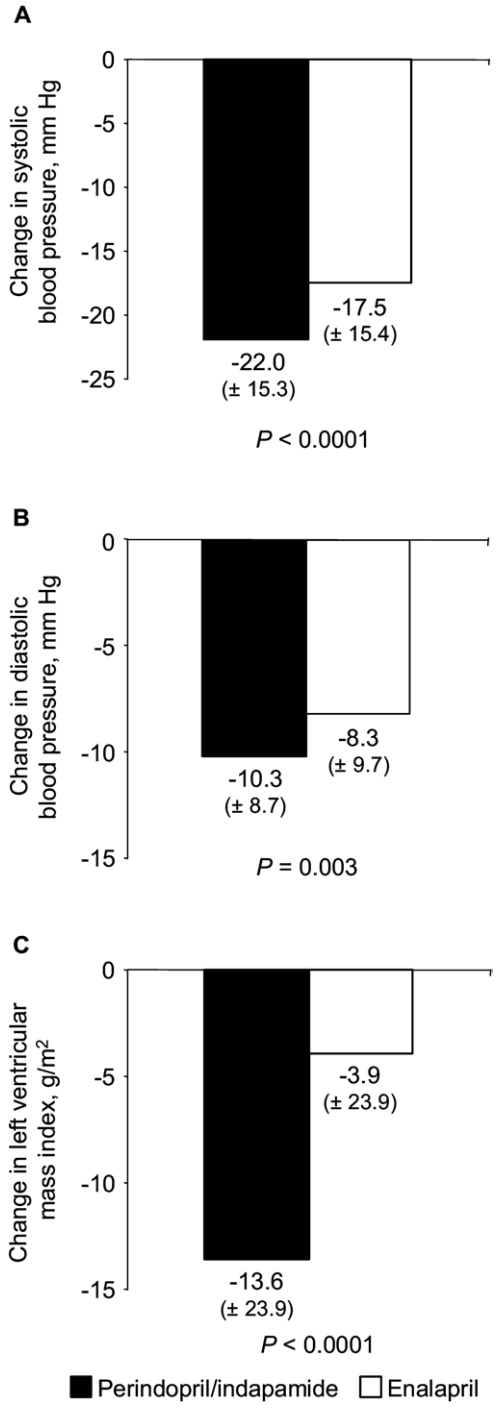

FIG. 1. Effect of perindopril/indapamide on blood pressure and left-ventricular mass index in patients with left-ventricular hypertrophy. In the Perindopril/Indapamide in a double-blind controlled study versus Enalapril in left ventricular hypertrophy (PICXEL) Study, a 12-month, randomized, double-blind, parallel-group, international trial, patients were treated with perindopril/indapamide or enalapril. Treatment with perindopril/indapamide had a significantly greater effect than treatment with enalapril on **(A)** mean systolic blood pressure (± SD); **(B)** mean diastolic blood pressure (± SD); and **(C)** mean left-ventricular mass index (± SD). Adapted with permission from Table 2 in Dahlof et al.[9]

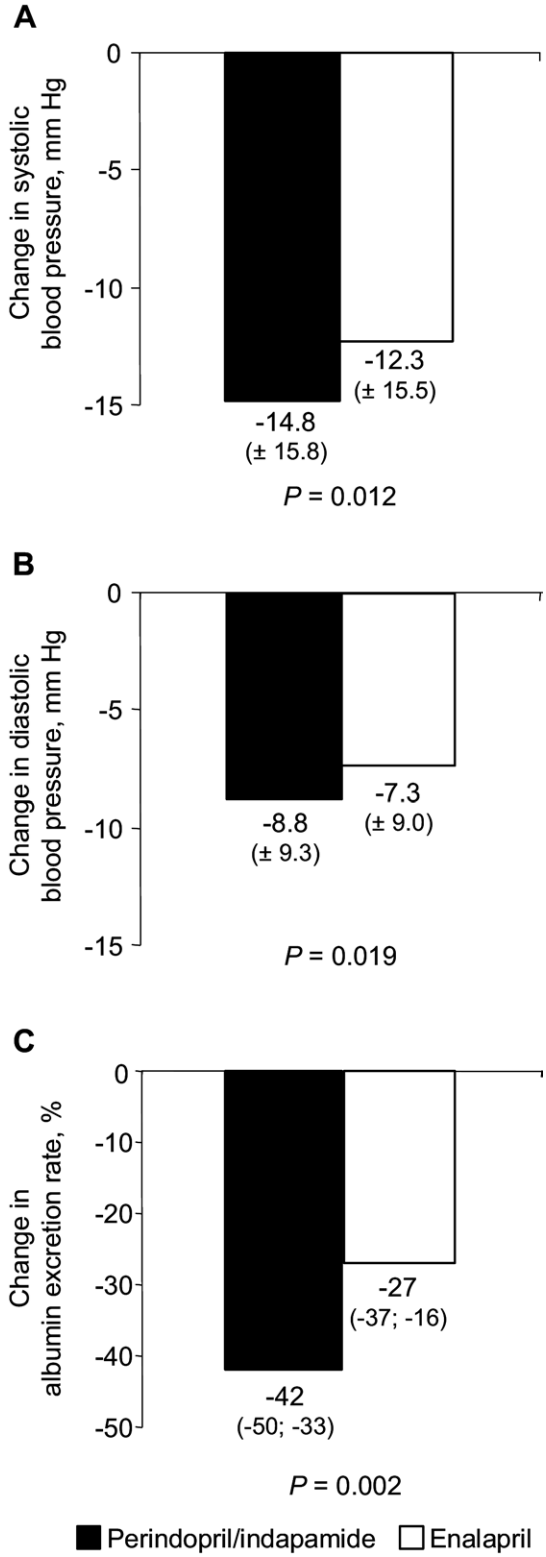

FIG. 2. Effect of perindopril/indapamide on blood pressure and albuminuria in patients with diabetes. In the Preterax in Albuminuria Regression (PREMIER) Study, a 12-month, randomized, double-blind, parallel-group, international trial, patients were treated with perindopril/indapamide or enalapril. Treatment with perindopril/indapamide had a significantly greater effect than treatment with enalapril on **(A)** mean systolic blood pressure (± SD); **(B)** mean diastolic blood pressure (± SD); and **(C)** percent albumin excretion rate (95% CI). Adapted with permission from Table 2 in Mogensen et al.[8]

4 mg/1.25 mg and then to 8 mg/2.5 mg) or enalapril (10 mg, titrated as needed to 20 mg and then to 40 mg).[8] At the end of the study, perindopril/indapamide was significantly more effective than enalapril in reducing blood pressure, the albumin excretion rate (Fig. 2), and the urinary albumin:creatinine ratio. This antiproteinuric effect remained significant after adjustment for changes in blood pressure, thereby suggesting a nephroprotective result that extends beyond blood-pressure control. These benefits on cardiovascular and renal health were accompanied by a significantly smaller rate of serious cardiovascular events compared with enalapril (2.5% *v* 6.3% for perindopril/indapamide and enalapril, respectively).

In the PREMIER Study, the initial dose was increased in two thirds of patients in each group.[8] These increases reflect that this study was performed in a high-risk population, and that with greater degrees of renal damage, blood-pressure control is increasingly difficult to attain. Thus, perindopril/indapamide 2 mg/0.625 mg can be used at early stages of renal disease, and titrated up to 4 mg/1.25 mg for more advanced stages of renal disease.

Hypertension increases cardiovascular risk and carries a worse prognosis for diabetic patients, with a significant increase in the rate of cardiovascular events, observed over a broad range of BP values.

Because high blood pressure, independent of high blood glucose, was shown to be the major determinant of diabetes-related cardiovascular complications,[26] the international randomized, multicenter, controlled Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release (MR) Controlled Evaluation (ADVANCE) Trial was undertaken to assess the combined effect of blood pressure-lowering through a perindopril/indapamide combination and intensive glucose control through a gliclazide-based regimen in patients with diabetes.[27] The study evaluates the effect of the two treatments on macrovascular and microvascular events, nephropathy, and retinopathy, both in a separate and a combined manner.

Conclusions

Together, these data suggest that a perindopril/indapamide combination, through its effect on blood pressure-lowering and target-organ protection, is well-suited for blood-pressure control and cardiovascular disease prevention in a wide range of hypertensive patients, including those with diabetes.

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