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Editorial Commentaries

ACE Inhibition and Cardiovascular Mortality and Morbidity in Essential Hypertension: The End of the Search or a Need for Further Investigations?

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Scientific evidence currently available supports the concept that renin-angiotensin blockade with angiotensin converting enzyme inhibitors as a first-line treatment exhibits in arterial hypertension beneficial effects in the prevention of mortality and morbidity comparable to those achieved with diuretics and β-blockers. In addition, the renin-angiotensin blockade has also proved to be beneficial in the secondary prevention of several complications of hypertensive disease such as after myocardial infarction and congestive heart failure, as well as in the prevention of the incidence of type 2 diabetes, and the progression of diabetic and nondiabetic nephropathy. In this later regard, recent evidence with angiotensin II receptor antagonists in reducing the progression of nephropathy in type 2 diabetes strongly confirms that antagonism of the renin-angiotensin system is an effective approach to cardiovascular and renal disease. Finally, the renin-angiotensin blockade in high-risk patients may reduce cardiovascular mortality independently of the effect on blood pressure (BP). The effect of other antihypertensive drugs on cardiovascular risk in patients with high-normal BP should be investigated to establish whether they exhibit a comparable effect or whether there is a class-related benefit of drugs blocking the renin-angiotensin system. Such a strategy could also be encouraged to design future interventional studies with the newer classes of compounds (angiotensin II AT_1-receptor antagonists, vasopeptidase inhibitors, endothelin antagonists), which would have the additional potential advantage of providing information more easily transferable to large-scale clinical practice. Am J Hypertens 2002;15:367–371 © 2002 American Journal of Hypertension, Ltd.

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The goal of antihypertensive treatment is to reduce cardiovascular mortality and morbidity associated with arterial hypertension by using a strategy focused both on lowering blood pressure (BP) and minimizing the impact of other associated cardiovascular risk factors. This strategy has the aim of avoiding or delaying fatal and nonfatal cardiovascular events and prolonging life in hypertensive patients.[1,2] Prospective randomized intervention trials, in which active therapy was compared to placebo, have demonstrated that even modest reductions of 5 to 6 mm Hg in diastolic BP and of 10 to 12 mm Hg in systolic BP over a 5-year period are associated with a 35% to 42% decreased risk of stroke and a 12% to 16% decreased risk of coronary heart disease.[3–5] In those trials a high proportion of patients received combination therapy with two or more drugs rather than a single diuretic or a β-blocker agent. Thus, the conclusion to be drawn from those initial studies was that the reduction of cardiovascular events and death observed in hypertensive patients was related to the magnitude of the BP decrease attained by treatment, and not to the specific properties of a particular class of antihypertensive agents.[6]

Angiotensin Converting Enzyme Inhibition: Good Expectations

The work of John Laragh's group, recently reviewed by this journal,[7–9] introduced the concept of blockade of the

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renin-angiotensin system for the control of BP. About 70% of the hypertensive population (those with normal and elevated values of plasma renin) would respond to the administration of a drug capable of blocking the effects of angiotensin II. Further investigation by the same group advanced the possibility that global cardiovascular risk was associated in an independent manner with renin profile in hypertension.[10] This theory was also valid in different animal models.[11–13] Blockade of the system was obtained initially through the administration of propranolol, which decreased renin secretion by the kidney. Angiotensin converting enzyme (ACE) inhibitors came to fill the need of blockade of the system in daily clinical practice, and angiotensin receptor blockers have been recently added to the armamentarium at our disposal to counteract the effects of angiotensin II.

Since the introduction of ACE inhibitors for the treatment of hypertension at the beginning of the 1980s, these drugs have been widely used in clinical practice to treat all stages of essential hypertension. In many countries ACE inhibitors are the drugs most commonly used, either as monotherapy or in association with other antihypertensive drugs.[14,15] For many years their clinical use was based on their efficacy (not different from others classes), better tolerability, and easy combination, in particular with a diuretic. Beyond these properties, the demonstration of beneficial effects on intermediate end points such as the regression of left ventricular hypertrophy[16,17] or their capacity to diminish proteinuria[18] became available and contributed to the increase in prescriptions for ACE inhibitors for hypertension. It was inferred from these salutary effects and other observations on target organ damage that probably ACE inhibitors could be more effective than other antihypertensive drugs in the prevention of cardiovascular morbidity and mortality in arterial hypertension. To further support this potential positive effect, evidence emerged later convincingly demonstrating the beneficial effects of ACE inhibitors in the secondary prevention of mortality after acute myocardial infarction,[19–22] congestive heart failure,[23–25] as well as in diabetic and nondiabetic nephropathy.[26–28] The excellent results of these studies on secondary prevention seemed to herald that renin-angiotensin system blockade with ACE inhibitors would provide additional cardiovascular benefits beyond BP control in essential hypertensive patients. Therefore, one would expect ACE inhibitors to be superior to conventional therapy for primary prevention of cardiovascular events associated with elevated BP.

ACE Inhibitor Trials in Hypertension: Surprise and Disappointment?

However, the results of the first available studies addressing this hypothesis, which mostly compared ACE inhibitor-based strategies with diuretic-based or β-blocker-based strategies, such as the United Kingdom Prospective Diabetes Study (UKPDS),[29,30] Captopril Prevention Project (CAPPP),[31] and Swedish Trial in Old Patients with hypertension-2 (STOP-2)[32] studies have failed so far to demonstrate the postulated higher potential of ACE inhibitors for primary prevention of cardiovascular mortality and morbidity. In fact, these studies showed comparable efficacy of ACE inhibitors to conventional therapeutic strategies for most end points. With an optimistic attitude, one may conclude that treatment of hypertension with ACE inhibitors is at least as good as conventional therapy in the reduction of fatal and nonfatal cardiovascular events, while, at the same time, they display an overall better tolerability. Some data from these studies indicate that ACE inhibitors improve the prognosis in diabetics. In this direction are the trend for less myocardial infarctions in UKPDS,[29,30] and the positive effect of this therapy on the prevalence of this event and heart failure in the group of diabetic patients included in the CAPPP[31] study. However, one should pragmatically conclude, in agreement with the Blood Pressure-Lowering Treatment Trialist Collaboration,[33] that ACE inhibitors do not provide further benefit than that related to the BP lowering effect, as attained with diuretics or β-blockers.

However, important questions remain unanswered: have we thoroughly explored the capacity in ACE inhibitors for primary and secondary prevention of cardiovascular events and death in hypertension? For sure, these compounds are recommended as first-line drugs in hypertension, but shall we prefer them to the other first-line classes of antihypertensive drugs simply based on their beneficial effects in other cardiovascular and renal diseases and their better tolerability?

Limitations of Study Design Testing ACE Inhibitors

Cardiovascular disease is the most common cause of death in Western countries[34,35] and arterial hypertension is a major predisposing factor for this outcome. The risk attributable to BP is the highest in patients with severe hypertension (systolic BP $\geq$180 mm Hg or diastolic BP $\geq$110 mm Hg), but fortunately, only a minority of the hypertensive population falls in this category. The population with elevated BP may be represented as a risk pyramid, with the greatest number of people at the base (relative risk augmented but not high) and the smallest number at the top (where relative risk is high or very high). Therefore, the largest absolute number of complications and the highest excess of deaths attributable to high BP occurs at the base of the pyramid[34–36] in subjects with high-to-normal (systolic BP 130 to 139 mm Hg or diastolic BP 85 to 89 mm Hg) or mild hypertension (systolic BP 140 to 149 mm Hg or diastolic BP 90 to 99 mm Hg). These considerations highlight the necessity of reducing BP below these values to achieve substantial reductions in complications in the community as a whole.[1,2]

The expected differences among antihypertensive drug

Table 1. Initial, final, and BP decrease in recently published studies

Studies	Initial BP	Final BP	BP Decrease
UKPDS	159/94	144/82	15/12
HOT, DBP <90 mm Hg	170/105	144/85	26/20
HOT, DBP <80 mm Hg	170/105	140/81	30/24
STOP-2, DIU/BB	194/98	158/81	36/17
STOP-2, ACEI	194/98	159/81	35/17
STOP-2, CCB	194/98	159/80	35/18
INSIGHT, DIU	176/99	138/82	38/17
INSIGHT, CCB	176/99	138/82	38/17
NORDIL, DIU/BB	173/105	151/88	22/17
NORDIL, CCB	173/105	154/88	19/17

BP = blood pressure; UKPDS = United Kingdom Prospective Diabetes Study; HOT = Hypertension Optimal Treatment; DBP = diastolic blood pressure; STOP-2 = Swedish Trial in Old Patients with hypertension-2; DIU/BB = diuretic/beta-blocker; ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blockers; INSIGHT = International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment; NORDIL = NORdic DILtiazem study.

classes, provided they exist, are probably difficult to detect in studies performed on patients with baseline BP values in the highest range (where BP reduction per se is the most important factor lowering risk and mortality). Table 1 contains the data of initial and final BP levels in most of the recently published studies. As can be seen the decrease in BP was very high in most studies. On the contrary, if BP independent effects are relevant, it is mostly in studies including individuals with BP levels within the lower ranges (mild or high-to-normal BP), where the differences can be detected. In this respect, the average initial BP values in the group of 758 hypertensive patients with type 2 diabetes included in the UKPDS study[29,30] were 159/94 mm Hg for those randomized to captopril and 159/93 mm Hg for patients included in the atenolol group. After 9 years of follow-up, the final average BP values were 144/83 and 143/81 mm Hg, respectively, with average BP reductions of about 15 mm Hg for systolic BP and 10 mm Hg for diastolic BP. Despite the magnitude of the BP reduction, the majority of patients in this study remained in the initial grade or stage 1 (mild hypertension) due to the insufficient reduction of SBP achieved with either drug, and no differences between treatments were observed (RR = 1.10; P = not significant). However, a significant reduction of 32% (P = .019) in mortality was observed in patients with tight control (final BP 144/82 mm Hg) when compared to the group of patients with less tight control (final BP 154/87 mm Hg). The results were similar in the other two major studies in which ACE inhibitors were compared to conventional therapy, the CAPPP[31] and the STOP-2[32] studies. In these two studies final BP values, in particular those of the systolic component remained above the expected goal (<140 mm Hg) in more than 50% of patients. Could this fact have influenced the final results? It has to be considered here that the primary end point in most of these studies consist of a composite target including myocardial infarction, stroke, and cardiovascular death. Interestingly, recent reports have described that in treated hypertensives one-third of strokes can be ascribed to the insufficient control of BP,[37,38] and the accompanying elevated risk.[35] In fact, the different BP control was, according to the researchers the explanation for the higher prevalence of stroke in patients treated with captopril as compared to those receiving conventional therapy in the CAPPP study.[31] The possibility that differences in systolic BP control accounted for a different prevalence of stroke in several previously published studies has been recently confirmed in the recent analysis performed by Staessen et al.[39] The relevance of attaining a good BP, even in the presence of an ACE inhibitor, has been recently stressed by the results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).[40] This study has investigated the capacity of perindopril alone or in association with indapamide, as compared to placebo, in the secondary prevention of stroke. The prevention of a second stroke was significantly lower when both drugs were given together and BP decreased by mean 12/5 mm Hg for systolic and diastolic BP, respectively. Perindopril alone lowered BP by 5/3 mm Hg and no prevention of stroke was observed.

It seems then reasonable to speculate that the excess of risk related to uncontrolled BP may substantially contribute to offset the possible different influence of the various classes of drugs on outcomes. All these parameters (BP values before intervention, magnitude of the BP reduction, final BP values achieved by antihypertensive treatment) may affect the reduction in morbidity and mortality observed and suggest that the results obtained with these different strategies and antihypertensive drugs is largely dependent on the BP reduction and independent of the specific drug treatment. This conclusion highlights the major problems inherent to these studies designed to dissect any possible additional and drug-related beneficial effect beyond BP lowering, and implies that different design strategies should be undertaken for this purpose. In favor of this possibility are also the recently published results of studies in which calcium channel blockers (CCB) were compared to conventional therapy. The INSIGHT[41] and the NORDIL[42] studies have in fact confirmed what had been observed in the STOP-2 study; on the basis of the levels of BP and risk at baseline, and the level of BP attained with therapy during a short follow-up (3 to 5 years), therapy with CCB does not seem to differ from conventional therapy.

Good News and HOPE

Recently the data of the Heart Outcomes Prevention Evaluation study (HOPE) and Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation (MICROHOPE) studies have been published.[43,44] In a sample of 9500 patients with high cardiovascular risk (53% normotensive, 39% diabetics)

Table 2. Suggested characteristics for future interventional comparative studies in hypertension

Initial BP levels: High normal
Risk profile: High or very high
BP reduction: Mild
Observational period: >5 years
Aim:
Data more transferable to the general hypertensive population
Evaluation of BP-unrelated effects of antihypertensive classes

Abbreviation as in Table 1.

treated with a high dose (10 mg) of the ACE inhibitor ramipril during 4 years, a 22% ($P < .01$) reduction in mortality and morbidity was obtained with the ACE inhibitor with respect to placebo. Initial average BP values were 139/79 mm Hg (high-to-normal BP) and thus it has been claimed that the results of this study cannot be extrapolated to hypertension. In fact, the investigators described that only 50% of patients presented a previous history of high BP.[39] However, the fact that three-quarters of patients were receiving, at baseline, one or several drugs capable of lowering BP and more importantly the new threshold BP (130/85 mm Hg) for patients in the conditions considered by entry criteria in these two studies confirm that nowadays most patients entering these studies require actually a strict (<130/85 mm Hg) BP control.[1,2] Patients randomized to placebo in the HOPE study did not modify systolic BP values, whereas a decrease of 2 mm Hg was observed in diastolic BP. Meanwhile, in patients receiving ramipril both systolic BP and diastolic BP were reduced by 3 mm Hg. This allows the consideration that within the range of high-to-normal BP patients with high cardiovascular risk, may benefit from treatment with ACE inhibitors even if this is associated with very small BP reductions. The clinical advantage of such a therapy was even more independent of BP changes in diabetics,[44] in whom the decrease was negligible. The HOPE and MICROHOPE studies support the guidelines of the JNC-VI and WHO-ISH guidelines,[1,2] which suggest that in high risk patients antihypertensive treatment must be started in the high-to-normal range of BP with the aim of achieving BP values ≤130/85 mm Hg, or even lower than 125/75 mm Hg in the presence of renal failure. However, a discrepancy exists among the data of HOPE[43] and PROGRESS.[40] In the last study and unlike a more marked decrease in BP, no prevention of stroke was seen when the ACE inhibitor was administered alone.

Another interesting finding observed both in CAPPP[31] and HOPE[43] studies was the potential capacity of ACE inhibitors to prevent the development of type 2 diabetes. In this regard, most recent evidence in patients with type 2 diabetes and nephropathy indicate that inhibition of the renin-angiotensin system by AT1 receptor antagonists markedly reduces development of overt diabetic nephropathy and retards the progression of renal failure once the nephropathy is present, and these effects are independent of changes in BP.[45–47] Altogether these observations emphasize the need for further studies in which the capacity of different classes of antihypertensive drugs to reduce cardiovascular events and death is analyzed looking at subjects with baseline BP lower than in previous trials. Table 2 summarizes the desirable characteristics of future studies. This may allow to dissect specific effects of drug classes on cardiovascular risk in the absence of the confounding effect of a relevant BP reduction that may offset the potential BP-independent benefits of specific drug classes.

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