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EDITORIAL

Optimal Anti-ischemic Therapy: Newer Data from the HOPE, EUROPA and PEACE Trials

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ABSTRACT

Several trials have proposed ACE-inhibitors as the foundation of anti-ischemic secondary preventive therapy for both short and long-term benefit in systolic heart failure, and an important anti-ischemic therapy in ischemic heart disease, diabetic and renal disease patients. The results of the HOPE trial indicated that ramipril, with "tissue" ACE-inhibition features, would benefit a broad range of patients for both primary and secondary prevention of both ischemic and vascular disease, and was beneficial in all subgroups of atherosclerotic coronary disease, cerebrovascular disease, peripheral vascular disease, or diabetes with one cardiovascular risk factor. Subsequently, the EUROPA trial complemented the findings of the HOPE trial in indicating the unique ability of tissue ACE-inhibition, this time with use of perindopril, in preventing cardiovascular events. On the other hand, the findings of a third trial (PEACE) using trandolapril did not confirm these favorable effects, albeit in a lower risk group of patients with ischemic heart disease. Nevertheless, combined analysis of the results of all three trials indicated that there seems to be a significant reduction of cardiovascular events in all patients with ischemic heart disease treated with an ACE inhibitor even in the absence of systolic left ventricular dysfunction or evidence of heart failure. These unique findings of these landmark trials are herein discussed.

KEY WORDS: *ACE inhibitors; ischemic heart disease; secondary prevention; cardiovascular events*

ABBREVIATIONS
ACE = angiotensin converting enzyme
IHD = ischemic heart disease

INTRODUCTION

Although the medical treatment of ischemic heart disease (IHD) over the past 25 years has evolved based on randomized clinical trials to include aspirin, nitrates, beta-blockers, angiotensin II-receptor blockers, aldosterone-blockers and revascularization therapies; a very significant addition to this regimen for both primary and secondary prevention of IHD has been the understanding of angiotensin-converting enzyme (ACE) inhibitors. Introduced in the 1980s as an anti-hypertensive therapy,[1] the benefit of ACE-inhibitors in heart failure, acute myocardial infarction, remodeling of left ventricular mass, reno-protection independent of blood pressure lowering, reduction of lipids, and reducing the risk of myocardial infarction, stroke, sudden death, cardiovascular death and new onset diabetes has been established by numerous randomized, double-blind, placebo-controlled clinical trials. This brief report focuses

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on the unique aspects realized from the Heart Outcomes Prevention Evaluation (HOPE),[2] the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA),[3] and the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE)[4] Trials and their combined analysis.[5]

PREVIOUS ACE-INHIBITOR TRIALS

When originally introduced clinically, ACE-inhibitors were considered as adjunctive therapy to treat hypertensive patients suspected of high angiotensin levels.[1] In the most recent application of ACE-inhibitors to a hypertensive population of 10,985 patients in the Captopril Prevention Project (CAPPP),[6] captopril failed to demonstrate superiority over a conventional beta-blocker/diuretic regimen in reducing cardiovascular events. Notwithstanding that outcome, the realization that some ACE-inhibitors possess tissue effects that are beneficial on left ventricular structure and function even in patients with controlled blood pressure and preserved ejection fraction, argues for primary and secondary preventive benefit in a wide range of hypertensive patients.[7] Following introduction clinically, the application of ACE-inhibitors in patients with symptomatic heart failure in the Veterans Administration Cooperative Vasodilator-Heart Failure Trial (V-HeFT I),[8] the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[9] the Study of Left Ventricular Dysfunction (SOLVD),[10] and V-HeFT II[11] clearly established ACE-inhibitors as a cornerstone of therapy in patients with systolic heart failure. During these trials other important observations were appreciated. ACE-inhibitors were demonstrated both experimentally and during clinical trials to improve renal insufficiency, retard the progression of renal disease, and improve nephropathies in both diabetics and non-diabetics.[12] Simultaneously, both experimental and clinical data demonstrated that ACE-inhibitors attenuated the adverse remodeling that accompanied acute myocardial infarction,[13,14] and provided the original stimulus to employ ACE-inhibitors in acute myocardial infarction. Subsequently, ACE-inhibitors were employed early in the course of acute myocardial infarction in SAVE,[14] the Acute Infarction Ramipril Efficacy (AIRE),[15] the Gruppo Italianao per la Studio della Sopravvivienza nell'Infarcto Miocardico (GISSI)-3[16] and the Fourth International Study of Infarct Survival (ISIS-4)[17] trials and clearly established their benefit in the secondary prevention of mortality, cardiovascular mortality, re-infarction and fatal myocardial infarction. Overall, there was a consistent reduction of mortality and cardiovascular mortality during the acute and chronic phases of myocardial infarction and chronic ischemic heart disease. The most impressive results were demonstrated in high-risk patients who maintained ACE-inhibitor therapy chronically. These factors unequivocally made ACE-inhibitors the foundation of anti-ischemic secondary preventive therapy for both short and long-term benefit in systolic heart failure,[18] and an important anti-ischemic therapy in ischemic heart disease, diabetic and renal disease patients.

THE HOPE TRIAL

As a result of the SAVE[14] and SOLVD[10] trials, the benefit of ACE-inhibitors in preventing reinfarction and ischemia stimulated new investigations into mechanisms of how the renin-angiotensin-aldosterone system could be interacting in the emerging discoveries of endothelial dysfunction associated with atherosclerosis. Although hypertension and heart failure had become major therapeutic targets for ACE-inhibitors, by the 1990s it had become eminently clear that ACE-inhibitors were affecting vascular tissue in a beneficial way in many disease populations.

Thus the HOPE[2] trial explored this possibility by testing the hypothesis that ACE-inhibitors could favorably prevent atherosclerotic cardiovascular events. The HOPE trial selected 9297 men and women older than 55 years of age at increased risk of cardiovascular disease, defined as a history of a cardiovascular event or evidence of vascular disease (angina, peripheral vascular disease or stroke). Persons with diabetes mellitus but no indication of heart disease were included but had to have an additional risk factor. Important exclusions were heart failure, a decreased ejection fraction <0.40, prior use of an ACE-inhibitor and renal insufficiency.[2] The study enrolled patients from 19 countries in a two-by-two factorial design for randomization to either the ACE-inhibitor *ramipril* 10 mg daily, vitamin E 400 IU daily or placebo and were followed for a mean of 5 years. Whereas no beneficial effects of vitamin E on cardiovascular outcomes were disclosed,[17] there was a marked effect of ramipril on the primary endpoint, a 22% reduction in a composite measure of myocardial infarction, stroke and death from cardiovascular causes and significant reductions on each individual endpoint.[2] Significantly decreased mortality or morbidity was also observed for all-cause mortality (16%), revascularization (15%), heart failure (23%), cardiac arrest (37%), worsening angina (11%) and complications related to diabetes (16%).[2] These findings established that ramipril would benefit a broad range of patients for both primary and secondary prevention of both ischemic and vascular disease, and was beneficial in all subgroups of atherosclerotic coronary disease, cerebrovascular disease, peripheral vascular disease, or diabetes with one cardiovascular risk factor.[2] Benefits were observed whether or not patients were also taking aspirin, other antiplatelet agents, beta-blockers, lipid-lowering agents, or other antihypertensive drugs at randomization. Treating 1000 patients with ramipril for four years prevented ~150 events in 70 patients.[2]

Following publication of the HOPE trial there emerged several substudies indicating that ramipril reduced progression on atherosclerosis and improved myocardial remodeling. Although an early debate emerged that the benefits of ramipril

might have resulted from its modest blood pressure lowering (3/2 mmHg) effects,[2] the emergence of these data made it clear that the effects on the vasculature, heart, and kidneys went far beyond these small effects. One of the early reports[20] from the HOPE study of 3577 diabetics showed the primary endpoint to be lowered by 25%, myocardial infarction by 22%, stroke by 33% and cardiovascular death by 37%. The Microalbuminuria, Cardiovascular and Renal Outcomes in HOPE (MICRO-HOPE) study[20] showed that ramipril lowered the risk of overt nephropathy in participants who did and did not have baseline microalbuminuria, and led to a lower albumin/creatinine ratio than placebo at 1 year and at the end of the study. There was a 34% reduction in new diagnoses of diabetes.[2] When the substudy data of 2480 high-risk women ≤55 years of age in HOPE were examined, the beneficial effects of ramipril were found to be similar to those detected in the larger cohort of men.[21] Further examination of the effects of ramipril disclosed that while the relative risk of any stroke was reduced by 32% (ramipril 156 vs placebo 226), the relative risk of fatal stroke was reduced by 61% (ramipril 17 vs placebo 44).[22] Significantly fewer patients on ramipril had cognitive or functional impairment.[22] Echocardiographic measurements of a HOPE subgroup that received two doses of ramipril (10 mg/d vs 2.5 mg/d) versus placebo in 506 patients with vascular disease on measurements of left ventricular mass and left ventricular function, showed beneficial remodeling in the ramipril treated patients.[23] The greatest benefit was found in the patients receiving ramipril 10 mg/d.[23] More recently HOPE substudy data have defined that there were trends over the median follow-up of 4.5 years that showed reduction in fatal primary outcome events (unexpected death or documented arrhythmic death; relative risk-RR 0.81, P=0.072) and nonfatal primary outcome events (resuscitated cardiac arrest; RR 0.65, P=0.127).[24] These observations are more germane when it is realized that these arrhythmic benefits were rendered in the absence of clinical heart failure or left ventricular systolic dysfunction. Similarly, another recent substudy[23] of HOPE in 3099 patients with a subnormal (≤0.9) ankle-brachial index (ABI) showed the ABI to be a strong predictor of mortality and morbidity during the follow-up even in patients with no clinical symptoms of peripheral arterial disease. Ramipril reduced the primary outcome of the study and all-cause mortality.[25] Whereas the HOPE trial measured the ABI employing digital palpation of ankle pulse as a relatively crude index, the data show that this simple measurement identified a high-risk subgroup that ramipril prevented events even in the absence of clinical symptoms of peripheral arterial disease.

These factors would be expected to influence all physicians to cast a wider perspective of the benefits of the ACE-inhibitor ramipril, and to prescribe it on a wider basis. In a study[26] of prescriptions filled in Ontario, Canada, from 1993 to 2001 there was an observed striking increase of 400% in ramipril prescription to elderly Ontario residents, including those not eligible for the trial. Whereas the fact that HOPE was a Canadian-led trial which undoubtedly had some influence on those observations, nevertheless is a dramatic testament to physician's acceptance of the HOPE data.

THE EUROPA TRIAL

Following the publication of the HOPE trial, previous and evolving studies of ACE-inhibitors suggested that there were distinct properties associated with ramipril. Quantitative differences exist between ACE-inhibitors, and because of the highly lipophilic and strong enzyme-binding capability associated with ramipril, this "tissue" ACE-inhibition feature drew attention. *Perindopril* is an ACE-inhibitor that also has these properties. Accordingly the EUROPA investigators sought to test whether perindopril could prevent atherosclerotic events in a low-risk population with stable coronary heart disease and no apparent heart failure.[3] Patients recruited had to be at least 18 years of age, and have evidence of coronary heart disease without clinical evidence of heart failure. Exclusion criteria included evidence of heart failure, uncontrolled hypertension, hypotension, renal insufficiency and recent use of ACE-inhibitors.[3] A total of 13,655 patients were recruited with either previous myocardial infarction (64%), angiographic evidence of coronary artery disease (61%), coronary revascularisation (55%), or a positive stress test only (5%). After a run-in period of 4 weeks, in which all patients received perindopril, 12218 patients were randomly assigned perindopril 8 mg once daily (n=6110) or matching placebo (n=6108). The mean follow-up was 4.2 years, and the primary endpoint was cardiovascular death, myocardial infarction, or cardiac arrest. Benefit was observed approximately after 1.5 years of treatment, and the event curves continued to separate being significant at 3 years and thereafter. This benefit showed a 20% relative risk reduction with perindopril over 4.2 years, and was consistently present in all predefined subgroups and secondary endpoints.[3] Approximately 50 patients needed to be treated for 4 years to prevent one major cardiovascular event.

In contrast to HOPE, EUROPA examined a relatively low-risk (placebo mortality 12% vs 7% over 4 years duration) group of patients of younger age (mean age 66 vs 60 years). The major annual event rates in HOPE were 40% to 80% higher than in EUROPA.[3] The frequency of clinical myocardial infarction and cardiovascular death was reduced by 21% in HOPE, and a similar 20% reduction was noted in EUROPA.[2,3] This is all the more surprising when it is realized that a higher usage of beneficial concomitant medications were taken in EUROPA, i.e. platelet inhibitors 92%, beta-blockers 62% and lipid-lowering therapy 58%. Thus, the benefit of perindopril was evident on top of current recommended secondary preventive therapies. Once again there was controversy over a lowering of blood pressure (5/2 mm Hg) as the mechanism for perindopril's benefit, nonetheless proponents of the study indicate this change did not account in EUROPA's low-risk group for

such an effect.[27] Therefore, the EUROPA trial complemented the findings of the HOPE trial in indicating the unique ability of tissue ACE-inhibition in preventing atherosclerotic cardiovascular events. These observations appear to be true for both low and high-risk individuals without evidence of heart failure or left ventricular dysfunction, and in the presence of concomitant secondary preventive therapies of platelet inhibition, beta-blocker therapy and lipid-lowering agents.

As of the present, substudies of EUROPA have not been published, and are awaited with regards to various subgroups of this low-risk population.

THE PEACE TRIAL

The PEACE trial is the latest randomized trial testing an ACE inhibitor in IHD patients with normal or near-normal systolic left ventricular function (mean ejection fraction 58±9%).[4] It comprised 8290 patients, randomly assigned to either *trandolapril* (4158 patients) or placebo (4132 patients). Patients received optimal therapy, with 72% having had coronary revascularization and 70% receiving lipid-lowering drugs. The incidence of the primary end point – death from cardiovascular causes, myocardial infarction, or coronary revascularization – was 21.9% in the trandolapril group, and 22.5% in the placebo group (P=0.43) over a median follow-up period of 4.8 years. Thus, trandolapril was not effective in the PEACE Trial, which apparently recruited patients with a lower cardiovascular risk compared with the prior two trials, as patients in PEACE received more intensive therapy, including coronary revascularization and lipid-lowering agents.

COMBINED ANALYSIS

A combined analysis of all three trials (HOPE, EUROPA, and PEACE trials including 29,805 patients)[5] indicated that ACE inhibitors significantly reduced all-cause mortality (7.8 vs 8.9%, p=0.0004), cardiovascular mortality (4.3 vs 5.2%, p=0.0002), non-fatal myocardial infarction (5.3 vs 6.4%, p=0.0001), all stroke (2.2 vs 2.8%, p=0.0004), heart failure (2.1 vs 2.7%, p=0.0007), and coronary-artery bypass surgery (6.0 vs 6.9%, p=0.0036). The composite end-point (cardiovascular mortality, non-fatal myocardial infarction, or stroke) occurred in 1599 (10.7%) of the patients receiving ACE inhibitor and in 1910 (12.8%) of those in the placebo group (odds ratio, 0.82; p<0.0001).

Thus, ACE inhibitors appear to reduce vascular events in patients with IHD even without known evidence of systolic dysfunction or heart failure and their use should at least be considered in all patients with IHD.

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