Special Lecture†

Reduction of coronary events in CAD with ACE inhibition: latest clinical evidence

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The mortality and morbidity attributed to cardiovascular disease is a major public health problem. In fact, of an estimated 50 million deaths worldwide in 1990, approximately 28%, were due to cardiovascular disease[1]. The commonest manifestation of cardiovascular disease is coronary artery disease (CAD), which is responsible for half the cases of incident heart failure in the general population under 75 years[2].

Over the past three decades, risk-factor modification for primary and secondary prevention has resulted in significant reductions in coronary end points. However, despite lifestyle modifications, use of aspirins, statins, β-blockers and coronary revascularization techniques, CAD is one of the principal causes of death worldwide[1]. In fact, one in every two men and one in every three women aged 40 years are at risk of developing CAD[3]. As the substantial global burden of CAD continues to escalate, projections estimate that cardiovascular disease will account for 37% of all deaths by 2020[4]. New strategies for secondary prevention are therefore urgently needed.

Angiotensin-converting-enzyme (ACE) inhibitors may play an important role in the secondary prevention of Coronary Artery disease. ACE inhibitors effectively reduce mortality and morbidity among patients with heart failure, left ventricular dysfunction after myocardial infarction, with hypertension, and among other high risk patients[5,6].

Previous ACE inhibitor studies have suggested a reduction in the rate of myocardial infarction and the need for revascularization in patients with heart failure and left ventricular dysfunction[7,8]. Further, the benefits of ACE inhibition in patients aged 55 years and above at high risk of cardiovascular complications, characterised by a high prevalence of diabetes, hypertension, stroke and obstructive peripheral vascular disease has been recently established[5].

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The recently completed EURopean trial On reduction of cardiac events with perindopril in stable coronary artery disease[9] aimed to evaluate the efficacy of perindopril to reduce cardiovascular death, myocardial infarction, and cardiac arrest in a broad spectrum of patients with stable coronary heart disease without heart failure or substantial hypertension.

EUROPA reported an impressive 20% relative risk reduction in the primary end point (Cardiovascular Mortality, non fatal MI, and resuscitated Cardiac arrest P = 0.0003). These results are likely to have a significant impact in the treatment strategy of Coronary Artery disease patients since the results for perindopril were in addition to other preventive therapies such as aspirin, statins, beta blockers and calcium antagonists and so forth. This paper reviews the rationale to the EUROPA trial as well as for the use of the ACE inhibitor perindopril in the trial. In this review we also discuss the main results of EUROPA and their clinical implications.

1. Potential effects of ACE inhibitors have in cardiovascular disease

ACE inhibitors, in addition to their well-established role as antihypertensives, are extensively used in the management of a variety of other cardiovascular disorders. They are a treatment of choice for patients with heart failure, with proven benefits both in terms of clinical improvement and reducing mortality[10,11] and are also used in patients with acute myocardial infarction (MI).

Because hypertension is a major atherosclerotic risk factor[12] and atherosclerosis has been shown to be clearly associated with abnormalities of the renin-angiotensin-aldosterone system (RAAS), an exceptionally promising lead in the fight against CAD is the use of angiotensin-converting enzyme (ACE) inhibition, preventing the generation of angiotensin II and at the same time increasing bradykinin levels.

2. Mechanism(s) of action of ACE inhinhibitors in CAD

Several possible mechanisms have been proposed to explain the beneficial effects of ACE inhibition on morbidity and mortality. These mechanisms include:

Cardioprotective effects

ACE inhibitors may have cardioprotective effects related to a reduction in inappropriate cardiac hypertrophy and a decrease in cardiac enlargement. ACE inhibition may counteract cardiac remodelling following long-term overloading of the heart following an infarct.

Vasculoprotective effects

In addition, ACE inhibitors may have vasculoprotective effects related to increased bradykinin production, which has been shown to improve endothelial dysfunction.

Antiatherogenic effects

ACE inhibitors also have antiproliferative and possible antiatherogenic properties. The expression of ACE and angiotensinogen increases following angioplasty in small animal models and precedes neointima proliferation. ACE inhibition diminishes intimal hyperplasia in these models, an effect that is linked to its effects on bradykinin degradation.

Anti-thrombotic effects

ACE inhibitors may improve fibrinolytic function by inducing antiplatelet effects through bradykinin and possibly improving the balance between plasminogen activator inhibitor-1(PAI-1) and tissue type plasminogen activator (t-PA).

Neurohormonal effects

Myocardial ischemia can induce activation of the sympathetic system and the renin-angiotensin system, thereby raising the levels of vasoconstrictive neurohormones. ACE inhibition limits this neurohormonal activation and vasoconstriction during ischemia. Furthermore, angiotensin II is a potent systemic and coronary vasoconstrictor and bradykinin has direct vasodilator effects and suppresses platelet adhesion and aggregation. Therefore, there may be direct effects of ACE inhibitor action from its effect on angiotensin II and bradykinin.

Studies in the past such as HOPE have demonstrated favourable effects of ACE inhibition. This trial studied high-risk patients of vascular disease who did not necessarily suffer from coronary artery disease. In contrast EUROPA demonstrated the long term benefits of ACE inhibition in patients at risk with proven coronary artery disease.

3. Rationale of choice of perinodopril in CAD

The long-acting ACE inhibitor perindopril is well-documented in cardiovascular disease, including the treatment of hypertension, heart failure and post-myocardial infarction. Perindopril has demonstrated antihypertensive efficacy over a 24-hour period[13] and is well tolerated[14] even in at-risk patients, such as the elderly[15], or in patients with recent ischaemic stroke, in whom it causes no changes in cerebral circulation[16]. Several possible mechanisms have been proposed to explain its beneficial effects on morbidity and mortality. These mechanisms include:

Cardioprotective and vasculoprotective effects

The results of the recent perindopril Protection Against Recurrent Stroke Study (PROGRESS)[17] support this hypothesis. This long-term trial demonstrated that a treatment based on the ACE inhibitor perindopril significantly prevents major coronary events, myocardial infarction and heart failure in patients with cerebrovascular disease. Importantly, these effects appear to be similar in both hypertensive and nonhypertensive individuals, suggesting that perindopril may have independent effects on cardiac outcomes above its role as an antihypertensive.

Moreover, perindopril has demonstrated beneficial effects on cardiovascular remodelling, which include improvement of arterial compliance in large arteries;[18] restoration of the structure of small resistance arteries;[19] restoration of flow-mediated coronary vasodilatation in hypertensive patients[20], and the reversal of endothelial dysfunction in patients with heart failure[21].

Antiatherogenic effects

Perindopril appears to exhibit antiproliferative and possible antiatherogenic properties and it diminishes intimal hyperplasia in small animal models, an effect that has been linked to its effects on bradykinin degradation[22]. Perindopril has also demonstrated antiatherogenic properties in other experimental models of atherosclerosis[23,24]. The ability to inhibit the development of atherosclerotic lesion size, making them more stable and less likely to rupture, was clearly linked with prevention of cellular and molecular mechanisms of atherosclerosis.

Antithrombotic effects

Perindopril has been specifically demonstrated to improve fibrinolytic function by altering beneficially the balance between plasminogen activator inhibitor-1 (PAI-1) and tissue type plasminogen activator (t-PA) in hypertensive patients[25,26].

4. The need for a large trial conducted specifically in coronary artery disease:

Some studies conducted in patients with heart failure, acute myocardial infarction, or high-risk patients with vascular disease (SOLVD[27], SAVE[28], HOPE[5]), including patients suffering from coronary artery disease, have suggested that ACE inhibitors could be beneficial, specifically in patients with coronary artery disease by preventing ischemic events. However, quinapril failed to reduce mortality, myocardial infarction, and revascularizations in 1750 patients with stable CAD (QUIET)[29]. Several hypotheses have been raised to explain this disappointing result. The most probable is that the dosage of quinapril to induce a sufficient blockade of RAAS in coronary artery disease was higher than the recommended thera-peutic regimen. Because of the disparity in clinical findings a large trial was necessary to explore specifically the potential of ACE inhibitors in patients who have stable CAD without heart failure.

The European trial on Reduction Of cardiac events with perindopril in stable coronary Artery disease (EUROPA) was designed to address[30]. It is a large, international, randomized, double-blind, placebo-controlled study conducted in 424 centers in 24 countries assessing the benefits of an (ACE) inhibitor, perindopril, on cardiovascular outcome in patients with stable coronary artery disease (CAD), and in addition to other preventive therapies. EUROPA is the largest study ever conducted in patients with stable coronary artery disease.

Methods

A total of 13 655 patients without clinical signs of heart failure were registered from October 1997 to June 2000: 64% had a history of previous myocardial infarction (MI) (>3 months before screening), 61% with angiographic evidence of CAD (70% narrowing of one or more major coronary arteries), 55% with coronary revascularization (>6 months before screening), or male with a positive stress test only (5%). During the run-in period, enrolled patients received in the morning and in addition to their usual medication 4 mg of perindopril once daily for 2 weeks, followed by 8 mg of perindopril once daily for the remaining 2 weeks. At the end of this 4-week period, 12 218 patients were randomly assigned to 8 mg of perindopril once daily, or placebo for an average follow-up of 4.2 years.

Results

The study population was very similar to everyday clinical practice: patients were relatively young (mean age 60; range, 24-90), 15% were female, 27% were hypertensive, and 12% were diabetic. In addition, all patients were treated according to modern standards of secondary prevention of CAD with 92% of patients taking platelet inhibitors, 62% β-blockers, and 58% lipid-lowering therapy.

Perindopril at the dose of 4-8 mg once daily significantly reduced by 20% the primary end point, ie, cardiovascular death, MI, and resuscitated cardiac arrest (relative risk reduction 20%; 95% confidence interval, 9-29; P=0.0003)[9]. In the placebo group, 603 events (9.9%) were observed versus 488 (8%) in the perindopril group. The benefit began to appear at 1 year and progressively increased throughout the trial. The benefits of perindopril were consistent across all predefined subgroups and in addition to other preventive therapies. Secondary end points, such as the composite of total mortality, MI, unstable angina, and cardiac arrest (-14%, P=0.0009), fatal and nonfatal MI (-24% P=0.001), or hospitalization for heart failure (-39%, P=0.002) were significantly reduced, perindopril was well tolerated, and adherence to treatment was identical to the placebo group. Only 1% of the perindopril-treated patients withdrew during the follow-up period due to hypotension, compared with 0.3% in the placebo group, and 2.7% due to cough compared with 0.5% in the placebo group.

The benefits of perindopril were observed in addition to other recommended preventive treatments and were consistent for all patients. These data provide strong support for considering perindopril in addition to other preventive therapies, irrespective of cardiac function or risk factors for all patients with CAD. EUROPA results broaden these indications in that all patients with CAD, whatever their age, could significantly benefit from long-term treatment with perindopril irrespective of their risk profile. This includes patients with stable angina pectoris, patients with a history of revascularization procedures or documented coronary artery stenosis, and patients who have suffered a previous MI. Furthermore, treatment could benefit these patients regardless of the presence or absence of symptoms and regardless of their blood pressure levels. It is therefore possible that the EUROPA results could influence the development of future CAD guidelines.

As well as addressing the potential for perindopril in stable CAD, various substudies have been incorporated into the EUROPA trial to assess the effects of perindopril in patients with diabetes, as well as to provide data on the exact mechanism(s) by which this drug may reduce morbidity and mortality in CAD[30]. These substudies will provide further insight on the effect of ACE inhibition with perindopril on neurohormonal activation, thrombosis, endothelial dysfunction, inflammation, and coronary anatomy. They include:

PERSUADE (Perindopril SUbstudy in coronary Artery Disease and diabEtes): this substudy will provide information on the effects of perindopril administration in patients in the EUROPA study who also have diabetes (12% of the study population). In addition, this study will detect the progression of diabetic nephropathy in this patient population.

PERSPECTIVE (Perindopril'S Prospective Effect on Coronary aTherosclerosis by angiographical and IntraVascular ultrasound Evaluation): this substudy is investigating the effects of perindopril on the progression and regression of coronary atherosclerosis using qualitative coronary angiography (QCA) and intravascular ultrasound (IVUS).

PERFECT (Perindopril Function of the Endo-thelium in Coronary artery disease Trial): this substudy is examining the effect of perindopril on endothelial function by measuring forearm circulation and flow-mediated vasodilatation of the brachial artery in response to perindopril administration.

PERTINENT (Perindopril – Thrombosis, InflammatioN, Endothelial dysfunction and Neurohormonal activation Trial): this substudy is designed to evaluate the predictive value of several plasma and serum markers associated with atherosclerosis and the effects of perindopril on their levels.

PERGENE (Perindopril and GENEtic characterisation of coronary artery disease patients): this substudy is looking at the genetic characterization of all patients in the EUROPA study population.

These substudies will provide valuable scientific knowledge on the pathogenesis of CAD and, in particular, how perindopril acts to reduce mortality and morbidity.

Conclusions

The global burden of cardiovascular disease is immense. Despite the use of aspirin, β-blockers, and lipid-lowering agents, this burden is increasing and cardiovascular disease is expected to become the leading cause of premature death and overall mortality worldwide within the next two decades. New strategies for secondary prevention are therefore essential.

Evidence has revealed that the RAAS is critically involved in the pathogenesis of cardiovascular disease, and the blockade of this system using ACE inhibitors is consequently clinically beneficial. ACE inhibitors have an established role in hypertension and heart failure, but have also demonstrated beneficial effects in treating patients with all degrees of ischaemic heart failure, asymptomatic left ventricular dysfunction, and after acute MI.

The results of EUROPA appear to fulfil the need of a long term study in the management of stable coronary artery disease with ACE inhibition. In the EUROPA study, the ACE inhibitor, perindopril, was demonstrated to have a substantial role in preventing or delaying the progression of coronary artery disease in patients, irrespective of their blood pressure. These data provide strong support for considering perindopril in addition to other preventive therapies, irrespective of cardiac function or risk factors for all patients with CAD.

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