Can ACE inhibitors reduce the burden of coronary artery disease? The impact of the EUROPA study

The mortality and morbidity attributed to cardiovascular disease is a major public health problem worldwide.[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] The prevalence of CAD in the kingdom is estimated at 5.5% between the age of 30 and 70 years. As the majority of the population in the country are below the age of 30 years, the prevalence is expected to rise with aging of the population and persistence of the current major risk factors.

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, ß-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.

The use of ACE-Is in cardiovascular disease: ACE-Is, 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[5,6] and are also used in patients with acute myocardial infarction (MI) and ejection fraction ≤40 % to prevent remodelling and progression to congestive heart failure.

Hypertension is a major atherosclerotic risk factor[7] and atherosclerosis has been shown to be clearly associated with abnormalities of the renin-angiotensin-aldosterone system (RAAS). A promising lead in the fight against CAD is the use of ACE-I, thus preventing the generation of angiotensin II and at the same time increasing bradykinin levels.

Mechanism(s) of action of ACE Is in CAD: Several possible mechanisms have been proffered to explain the beneficial effects of ACE inhibition on morbidity and mortality. These mechanisms include:

Cardioprotective effects: ACE-Is 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: ACE-Is may have vasculoprotective effects related to increased bradykinin production, which has been shown to improve endothelial dysfunction.

Antiatherogenic effects: ACE-Is 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-Is 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.

Rationale of choice of Perindopril in CAD: The long-acting ACE-I Perindopril is well-documented in cardiovascular disease, including the treatment of hypertension, heart failure and post-MI. Perindopril has demonstrated antihypertensive efficacy over a 24-hour period[8] and is well tolerated[9] even in at-high risk patients, such as the elderly,[10] or in patients with recent ischaemic stroke, in whom it causes no changes in cerebral circulation.[11] Several possible

mechanisms have been proffered to explain its beneficial effects on morbidity and mortality.

The results of the recent Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) [12] support this hypothesis. This long-term trial demonstrated that a treatment based on the ACE-I perindopril significantly prevents major coronary events, MI 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;[13] restoration of the structure of small resistance arteries;[14] restoration of flow-mediated coronary vasodilatation in hypertensive patients,[15] and the reversal of endothelial dysfunction in patients with heart failure.[16]

Concerning its antiproliferative and possible antiatherogenic properties, as an ACE-I, Perindopril diminishes intimal hyperplasia in small animal models, an effect that is linked to its effects on bradykinin degradation.[17]

Furthermore, Perindopril has demonstrated antiatherogenic properties in a different model of atherosclerosis.[18,19] 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.

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.[20,21]

The need for a large trial conducted specifically in coronary artery disease - the EUROPA trial:

Several studies conducted in patients with heart failure, acute MI, or high-risk patients with vascular disease (SOLVD,[22] SAVE,[23] HOPE[24]), including patients suffering from coronary artery disease, have suggested that ACE-Is could be beneficial, specifically in patients with coronary artery disease by preventing ischemic events. However, quinapril failed to reduce mortality, MI, and revascularizations in 1 750 patients with stable CAD (QUIET).[25] 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 that the recommended therapeutic regimen. As we are still awaiting the answer whether ACE-I are beneficial in coronary artery disease, a large trial is necessary to explore specifically the potential of ACE-Is in patients who have stable CAD without heart failure.

Addressing this unmet need is the ongoing EUropean trial on the Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) study,[26] the results of which are due to be presented at the European Society of Cardiology (ESC) meeting in September 2003. This important long-term trial is investigating the prevention of cardiovascular morbidity and mortality with Perindopril in a broad population with documented coronary heart disease, but without heart failure and irrespective of age, cardiovascular risk, and left ventricular function.

The EUROPA study has included 12 236 patients from 24 European countries to determine whether the addition of Perindopril 8 mg to standard therapy decreases the combined endpoint of cardiovascular death, nonfatal MI, and resuscitated cardiac arrest.[27]

To elucidate further the exact mechanism(s) by which Perindopril could reduce morbidity and mortality in coronary artery disease, numerous substudies have been incorporated into the EUROPA study. These are designed to provide further insights on the effects of Perindopril on neurohormonal activation, thrombosis, endothelial effects, inflammation, and coronary anatomy.

Conclusions: The global burden of cardiovascular disease is immense. Despite the use of aspirin, ß-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-Is is consequently clinically beneficial. ACE-Is 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.

Long-term trials with ACE-Is in patients with stable CAD are therefore clearly warranted, which is why the presentation of the EUROPA study results at ESC in August 2003 is so eagerly anticipated. ACE-Is, such as Perindopril, may have a substantial role to play in preventing or delaying the progression of coronary artery disease in patients, irrespective of their blood pressure. The results of the EUROPA study may therefore represent a major breakthrough in dealing with this serious and growing threat to world health.

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