Perindopril in diabetes: perspective from the EUROPA substudy, PERSUADE

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PERSUADE,1 the diabetic substudy of the EUROPA trial, examined the role of the angiotensin-converting enzyme-inhibitor (ACE-I) perindopril 8 mg vs. placebo in patients with coronary artery disease and concomitant diabetes mellitus. The main results of EUROPA indicated a clinically and statistically significant reduction in the primary endpoint of death, non-fatal myocardial infarction (MI), and resuscitated cardiac arrest in patients with coronary artery disease treated with perindopril. Given the relatively small subgroup of patients in PERSUADE (n = 1502), the results of this subgroup analysis did not reach statistical significance, although there was no heterogeneity observed between the PERSUADE and the EUROPA cohorts, indicating that the benefit of perindopril in diabetic patients was similar to that observed in the entire EUROPA cohort. Let us examine how the results of PERSUADE may impact on the use of ACE-I in people with diabetes.

The European Society of Cardiology, in a recent expert consensus document on ACE-I in cardiovascular disease,2 suggests that all patients with diabetes mellitus associated with one other risk factor receive an ACE-I. To a large extent this recommendation was based on the results of the MICRO-HOPE trial,3 a substudy of the HOPE trial, which examined the impact of ramipril in 3577 diabetic patients over the age of 55 with one additional cardiovascular risk factor. Although the patient demographics in the MICRO-HOPE and PERSUADE studies were quite similar, the Kaplan–Meier curves for the cumulative incidence of the primary endpoint at 1 year, with a blood pressure reduction of only 3/2 mmHg and a 26% RRR by year 2.

Patient demographics are unlikely to account for the delay in the onset of the benefit in PERSUADE, as the placebo event rates in both trials were similar (20 MICRO-HOPE vs. 16% PERSUADE). It is also unlikely that intrinsic characteristics of ramipril vs. perindopril can explain the aforementioned differences. What perhaps is more likely is the fact that PERSUADE reflected a population of diabetic patients with much greater background risk reduction therapy compared with MICRO-HOPE, with a reported 92% use of aspirin, 62% use of beta blockers, and 67% use of statins.

The fact that 67% of PERSUADE patients received a statin, compared with 23% in MICRO-HOPE, is very foretelling, especially when viewed in the context of the recently published Collaborative Atorvastatin Diabetes Study (CARDS).4 CARDS randomized 2838 diabetic patients with essentially normal lipid parameters and no evidence of vascular disease to atorvastatin 10 mg or placebo. The trial was stopped 2 years prematurely as there was a 37% reduction in the primary cardiac endpoint of time to first occurrence of acute coronary heart disease, coronary revascularization, or stroke (P = 0.001) with atorvastatin. More importantly, the absolute risk reduction in CARDS was 6% with a number needed to treat (NNT) of only 17 to prevent a cardiac event. This truly profound benefit of atorvastatin was in a cohort of patients who would not be deemed to be dyslipidaemic per se.

When multiple risk factor interventions are undertaken in patients with diabetics, the results are even more compelling. STENO-25 compared the effect of a targeted, intensified multifactorial intervention with that of conventional treatment on modifiable risk factors in type 2 diabetic patients with microalbuminuria. The intensive group included aggressive management of blood pressure, blood glucose, lipids, and lifestyle, and resulted in a 50% reduction in cardiac events (44 vs. 24%) with an NNT of 5 (P = 0.008). It is noteworthy that all patients in STENO-2 ultimately received an ACE-I as standard therapy in the study protocol as per the guidelines of the Danish Medical Association, independent of the presence or absence of hypertension. Although the evidence for the routine use of ACE-I therapy in patients with diabetes is well established, and is now

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further strengthened by the results of PERSUADE, the role of ACE-I in contemporary managed vascular patients has recently been questioned with the results of the PEACE trial. PEACE was a placebo-controlled trial of trandolapril 4 mg in 8290 patients with coronary artery disease with a normal ejection fraction. For the combined endpoint of MI, death, and coronary revascularization, trandolapril demonstrated no apparent benefit. We share the opinion of many experts, that the PEACE conclusions of a neutral trial may not be valid as the trial was vastly underpowered to detect a benefit for the original cardiovascular endpoints, namely, death and MI. To compensate for both a low event rate and a less than optimal enrolment, revascularization was added as the third endpoint, which in fact became the main driving force of the primary outcome. By the end of the trial, upwards of 91% of patients may have had some form of revascularization. The high revascularization rate in PEACE may simply reflect the contemporary management of coronary artery disease, even in low risk patients, rather than a failure of trandolapril to prevent it. Trandolapril did, however, reduce new onset of congestive heart failure requiring admissions or resulting in death by 24%, a new diagnosis of diabetes mellitus by 14%, and stroke by 22% (P = 0.08), with an NNT of 33 to prevent one of these important clinical events. When the combined results of HOPE, EUROPA, and PEACE are evaluated with respect to cardiovascular death, there appears to be no inconsistency, reaffirming the routine use of ACE-I in patients with atherosclerosis.

The authors of PERSUADE suggest that benefits of perindopril were greater than those predicted by blood pressure lowering alone, a phenomenon perhaps best referred to as ‘vascular protection’. Although it is difficult to dissect out the blood pressure-dependent and independent effects on vascular protection, it is widely held that ACE-I are disease-modifying agents, and their anti-atherosclerotic benefits are distinct from their blood pressure lowering properties. The Australian National Blood Pressure trial (ANBP2) offers some insight into this exact issue, specifically whether ACE-I have blood pressure-independent vascular protection. ANBP2 randomized 6083 hypertensive patients (age > 65), the majority having neither cardiac disease nor diabetes, to an initial treatment with either a diuretic or an ACE-I. At the end of the trial, both treatment arms had exactly equal reductions in blood pressure (26/12 mmHg). Despite similar blood pressure reduction, the ACE-I arm in ANBP2 exhibited a 11% reduction in the time to first cardiovascular event or death (P < 0.05) when compared with the diuretic, lending credence to a vascular protective effect of ACE-I. A number of mechanisms have been suggested to account for an anti-atherosclerotic effect of ACE-I, including improving endothelial function, augmenting fibrinolysis, promoting ischaemic preconditioning, and direct effects to stabilize vulnerable plaques. Recent evidence presented at the American Heart Association (2004) and American College of Cardiology (2005) indicate that perindopril therapy in EUROPA was associated with improvements in endothelial function (PERTI-NENT and PERFECT).

Most national and international cardiology societies and associations would agree that diabetic patients with an additional risk factor be treated with an ACE-I, even in the absence of documented vascular disease. However, the Endocrinology Guidelines appear to be quite variable in this regard. The International Diabetes Federation (1999) recommends ACE-I as the drug of choice in diabetics with nephropathy. The American Diabetes Association’s (ADA) guidelines were revised in October 2004. Recommendations included either an ACE-I or an angiotensin receptor blocker (ARB) for diabetic patients with hypertension, or nephropathy, with no preference for either therapy. The most recent Canadian Diabetes Association (www.CDA.ca) guidelines, however, recognizes the unique role of ACE-I in macrovascular disease, and recommended ACE-I therapy as a component of a vascular protective strategy as a first priority in patients with diabetes, irrespective of the presence or absence of hypertension or nephropathy.

Diabetic nephropathy is a harbinger of vascular complications. Inhibition of the renin–angiotensin system (RAS) plays a central role in the management of nephropathy. The results of the Lewis 1 trial were an important advancement in the management of type 1 diabetic subjects with nephropathy. Despite a small difference in blood pressure, ACE-inhibition with captopril offered a 48% reduction in the combined endpoint of death, dialysis, and transplantation. The results were even more impressive in that the event curves continued to diverge throughout the ~3 year follow-up. The NNT to prevent one death was only 33, and for the combined endpoint of death, dialysis, and renal transplantation, the NNT was only eight patients. Few would disagree that the Lewis 1 trial supported the critical role of ACE-inhibition at modest doses to powerfully modify the biology of diabetic nephropathy, with rigorous attenuation of both renal and cardiovascular endpoints. The unfortunate and malignant nature of vascular disease in the Lewis trial is apparent when one evaluates that the placebo event rate for death plus MI was 9.9% in relatively young patients with type 1 diabetes (average age 35 years). More recent trials have focused on whether inhibition of the RAS with ARB would exert similar benefits in type 2 diabetes in terms of both renal and cardiovascular protection.

The Irbesartan Diabetic Nephropathy Trial (IDNT), confirmed the extreme cardiovascular phenotype in type 2 diabetic patients with nephropathy. Indeed, patients with type 2 diabetes and nephropathy exhibited an even higher cardiovascular risk than patients with type 1 diabetes in the Lewis 1 trial, with a massive 30% of the patients having at least one cardiac event rate over 2.6 years (821 cardiovascular events in 1715 patients). The total rate of CV death and non-fatal MI in the three arms of this trial was as follows: placebo—CV death 8.1%, non-fatal MI 7.2%, for a total of 15.3%; irbesartan—CV death 9.0%, non-fatal MI 6.7%, for a total of 15.7%; and amlodipine—CV death rate 6.5%, non-fatal MI 4.4%, for a total of 10.9% [FDA Advisory Briefings NDA 20 757(5-021)]. When compared with placebo, irbesartan was an excellent ‘nephroprotective’ agent, but irbesartan did not reduce the combined endpoint of MI and CV death despite a further reduction of blood pressure of 4/3 mmHg.

A Cochrane group meta-analysis of ACE-I and ARB in diabetic kidney disease confirmed similar nephroprotection for both classes of drugs, and renal benefit was independent of whether the diabetes was type 1 or 2. The renal benefit of ACE-I in type 2 diabetes is supported further by the recent DETAIL and BENEDICT trials. The effects of ACE-I and ARB on mortality in the Cochrane meta-analysis, however,
were vastly different. ACE-I had a dramatic 20% reduction in mortality, whereasARB had a 0% reduction.

The Cochrane meta-analysis confirms that ARBs and ACE-I offer similar renal protection, but paradoxically, ARBs may not offer similar reduction in mortality despite the robust benefits seen with the ACE-I. These observations are surprising, and reinforce how two seemingly similar pharmacological agents can exhibit different clinical benefits. Some scientists have speculated that the renal and coronary vascular beds may be physiologically different in their biology and responses to ACE-I and ARB. One theory that remains to be proven relates to the preferential dependence of the coronary vasculature on bradykinin, vs. the renal and cerebral vasculature.

Renal disease is an important surrogate and prognostic marker for future cardiovascular events, especially in the diabetic population. ACE-I reduces both renal and cardiovascular endpoints, however ARBs appear to reduce renal outcomes (for example doubling of serum creatinine in diabetic nephropathy), without an effect on cardiovascular outcomes. This should not come as a surprise as there are countless examples where ‘reverse surrogate relationships’ may not hold true. For example, oxidized LDL and oxidative stress are strong surrogates of atherosclerosis progression, yet antioxidants that treat the surrogates do not reduce events. Treatment of blood pressure, a key surrogate for cardiovascular and cerebrovascular disease, does not always reduce event rates, nor does treatment of postmenopausal women with hormone replacement therapy lead to vascular protection despite improvement in the lipid profile. Likewise, a similar intervention may have different effects on MI in men and women, as was recently described for aspirin with a lack of vascular protection in the Women’s Health Study.

With the addition of PERSUADE to the well established MICRO-HOPE data, clinicians must recognize the important role of ACE-I for vascular protection in high-risk diabetic subjects. As echoed in the 2003 Canadian Diabetes Association guidelines, we believe the time has come to move away from a ‘glucocentric’ view of diabetes and PERSUADE physicians to protect the diabetic vasculature as the top priority.

References