Death in diabetes: Where next?

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Cardiovascular events are the leading cause of death in type 2 diabetes, being responsible for over 80% of mortality. People with type 2 diabetes are at 3–5 times greater risk of death by myocardial infarction than those without diabetes. We are perhaps all familiar with these figures, but are we confident that our current practice will improve upon these patient outcomes in the future?

There is now irrefutable evidence from large outcomes studies conducted in patients with type 2 diabetes that aggressive lowering of LDL-cholesterol can significantly reduce cardiovascular morbidity and mortality (e.g. HPS [Heart Protection Study], CARDS [Collaborative AtoRvastatin in Diabetes Study]). All our at-risk patients will undoubtedly be treated with a statin. Similarly, aggressive treatment of hypertension produces major benefits in terms of reduced cardiovascular events (e.g. as shown in HOT [Hypertension Optimal Treatment], UKPDS [UK Prospective Diabetes Study], CAPPP [CAPtopril Prevention Project], LIFE [Losartan Intervention For Endpoint reduction], ALLHAT [Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial]). There is increasing support for the use of agents that interfere with the renin–angiotensin system as first-line antihypertensive drugs, given the strength of evidence for the impact of their blood pressure lowering effect *per se*, their renoprotective actions and the recent data from large-scale studies and meta-analyses (BENEDICT [BErgamo NEphrologic DIabetes Complications Trial], RENAAL [Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan], IRMA-2 [IRbesartan MicroAlbuminuria type 2 diabetes], IDNT [Irbesartan in Diabetic Nephropathy Trial]).

But what about glucose-lowering agents, the backbone of our practice? Once the core of a glucocentric view of the disease, have we now moved to multifactorial intervention and neglected our former *raison d'etre*? Back in 1998 the UKPDS showed that neither sulphonylureas nor insulin had any impact on cardiovascular outcomes, while metformin treatment showed some benefit in a selected cohort of overweight patients. Up until now this evidence has driven our practice in placing metformin at the centre of therapy. However, single agents are not enough either in terms of treating to glycaemic target or for other risk factors that impact on cardiovascular outcomes. We now have the opportunity, with the results of the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study (Dormandy et al, 2005), to decide whether glucose lowering alone or other properties, perhaps related to insulin sensitisation or PPARγ-agonist actions, can take us another step closer to reducing the toll of cardiovascular death in type 2 diabetes with pharmacotherapy.

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PROactive is the first prospective outcome study for the insulin-sensitising agents, the glitazones. People with type 2 diabetes randomised to either placebo or pioglitazone, in addition to best-practice treatment, had already experienced macrovascular events: nearly half had experienced a myocardial infarction, one-third a previous coronary revascularisation and one-fifth a stroke. Therefore, patients were those that we see frequently in practice at around 10–15 years after diagnosis. Like all outcome studies, especially the first for a class of agents, initial interpretation has been the subject of wide debate in the weeks following publication of the results. The primary endpoint combining hard cardiovascular endpoints with procedure-dependent peripheral vascular endpoints did not reach statistical significance (a 10% reduction in seven combined vascular events was observed). However, arguably the more clinically pertinent secondary endpoint of death, non-fatal myocardial infarction and stroke showed a relative risk reduction of 16% (*P*=0.027; Dormandy et al, 2005). A further analysis, recently presented at the *American Heart Association Scientific Sessions* (see page 273), showed that in people who had already suffered a myocardial infarction, pioglitazone reduced the risk of a further heart attack by 28% (*P*=0.045) and the risk of acute coronary syndrome by 37% (*P*=0.035). It is of note that this reduction in death and major cardiovascular events occurred on top of best-practice multifactorial intervention including statins, renin–angiotensin blocking agents and anti-platelet therapy in a high-risk patient group. In addition, pioglitazone halved the progression of patients towards permanent insulin therapy, reduced HbA_{1c} by 0.5%, improved HDL-cholesterol and triglyceride profile and reduced systolic blood pressure by 3mmHg (Dormandy et al, 2005). This raises the question as to whether this study marks a turning point in our definition of an anti-diabetic agent that addresses the cluster of risk factors associated with type 2 diabetes compared with glucose-lowering alone. Ongoing analysis of the PROactive data over the next year will provide more information on the use of the glitazones alongside statins and a greater understanding of the management of oedema and factors associated with a diagnosis of heart failure with these agents.

Can these findings be extrapolated to the class of glitazones or are they distinct to pioglitazone alone? Cardiovascular outcomes associated with rosiglitazone are being explored in the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) study where patients are assigned to rosiglitazone earlier in treatment (after 6–7 years diabetes duration) and for a longer (6-year) study period than PROactive. RECORD is expected to report in 2008. At the very least, pioglitazone appears to adhere to its core glucose-lowering values of offering an incremental reduction in hyperglycaemia on top of other glucose-lowering agents and reduces the need for insulin. In the meantime, while we await detailed sub-group analyses and answers to questions relating to heart failure, can we act on the evidence from the PROactive study in the belief that we are reducing death in diabetes by adding in pioglitazone?

For more analysis of the PROactive study results, see *Digest Debate* on pages 252–3

Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK et al (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**:1279–89