Cardiovascular event reduction in high-risk patients

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People with type 2 diabetes have a 2- to 4-fold increased risk of experiencing a cardiovascular event compared with the general population. Furthermore, the prognosis for those who have already experienced a major event such as stroke or myocardial infarction is poor owing to an increased likelihood of further events and complications such as congestive cardiac failure.

While there has been some debate regarding the PROactive study, which did not achieve statistical significance between pioglitazone and placebo in the primary composite end point, significant differences have been reported between the two treatment arms in pre-specified secondary end points. Two pre-specified analyses have recently been published from the PROactive study that looked at the effect of the addition of pioglitazone to best practice antidiabetic treatment specifically in people with type 2 diabetes who had already experienced either a stroke or a myocardial infarction (Wilcox et al, 2007; Erdman et al, 2007). In those individuals who had already experienced a stroke >6 months before randomisation (n=984), pioglitazone reduced the risk of recurrent stroke by 47 % (*P*=0.0085). This represented an event rate in those with a previous stroke of 5.6 % (Kaplan–Meier estimate) in the pioglitazone group versus 10.2 % in the placebo group. The studies did not show any effect of the glitazone on the incidence of first stroke. In the subgroup of participants who had experienced a previous myocardial infarction (n=2445) there was a 28 % (*P*=0.045) risk reduction in fatal and nonfatal myocardial infarction and a 37 % (*P*=0.035) risk reduction in acute coronary syndrome in people who were taking pioglitazone versus those taking placebo.

Treatment with glitazone has been shown to significantly reduce recurrence of coronary syndrome and stroke. The magnitude of the risk reductions shown here is comparable to that reported in stroke or myocardial infarction in landmark studies of statins or tight blood pressure control in type 2 diabetes (Colhoun et al, 2004; Dahlof et al, 2005; Collins et al, 2003; UK Prospective Diabetes Study Group, 1998). While further long-term studies are currently ongoing, the above and other trial data may assist in placing treatment with glitazones in current therapeutic algorithms. Regardless of the fact that the primary composite end point did not demonstrate significance between pioglitazone and placebo, these pre-specified analyses are worthy of note for treatment of type 2 individuals with pre-existing cardiovascular disease.

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Colhoun HM, Betteridge DJ, Durrington PN et al (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* **364**: 685–96

Collins R, Armitage J, Parish S (2003) MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* **361**: 2005–16

Dahlof B, Sever PS, Poulter NR et al (2005) Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* **366**: 895–906

Erdmann E, Dormandy JA, Charbonnel B (2007) The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *Journal of the American College of Cardiology* **49**: 1772–80

UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**: 703–13

Wilcox R, Bousser M-G, Betteridge DJ et al (2007) Effects of Pioglitazone in Patients With Type 2 Diabetes With or Without Previous Stroke Results From PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04) *Stroke* **38**: 865–73