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Moving forward with glitazones?

Three major clinical studies have recently yielded data on glitazone use in type 2 diabetes. But what new information do these studies reveal about the CV risk : benefit profile of these agents and their place in therapy?

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), the effect of adding pioglitazone to best-practice treatment of people with type 2 diabetes at high CV risk was investigated (Dormandy et al, 2005). Pioglitazone significantly reduced the secondary combination endpoint of death, stroke or myocardial infarction (MI) by 16 % compared with placebo ($P=0.027$). The study also showed a 28 % ($P=0.045$) risk reduction in recurrent MI, a 37 % ($P=0.035$) risk reduction in acute coronary syndrome and a 47 % ($P=0.0085$) risk reduction in recurrent stroke associated pioglitazone (Erdmann, 2005; Wilcox et al, 2006; Wilcox and Kupfer, 2006). Although the incidence of heart failure (HF) was higher with pioglitazone (5.5 %) than placebo (4.2 %), the mortality due to HF was the same in both groups (0.6 %; Thrainsdottir et al, 2006).

The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study investigated whether rosiglitazone could prevent type 2 diabetes in individuals with impaired fasting glucose or impaired glucose tolerance (The DREAM Trial Investigators, 2006). After 3 years of treatment rosiglitazone reduced the primary outcome of incident type 2 diabetes or death by 60 % compared with placebo ($P<0.001$) and significantly increased normoglycaemia ($P<0.0001$). In this group, rosiglitazone had no effect on the secondary composite outcome of CV events compared with placebo. Of those participants receiving rosiglitazone, 14 (0.5 %) developed HF compared with two individuals (0.1 %) in the placebo group ($P=0.01$).

A Diabetes Outcome Progression Trial (ADOPT) assessed the durability of glucose control with different classes of oral glucose-lowering medications in people recently diagnosed with type 2 diabetes (Kahn et al, 2006). The incidence of monotherapy failure at 5 years was 15 % with rosiglitazone, 21 % with metformin and 34 % with glyburide. While there were no CV outcome endpoints in ADOPT, congestive HF occurred in 1.5 % of people with diabetes taking rosiglitazone compared with 1.3 % receiving metformin and 0.6 % taking glyburide.

These large-scale studies have delivered much information about the influence of glitazones on the progression of diabetes, however the findings of DREAM may solely be explained by the glucose-lowering effects of rosiglitazone rather than an agent-specific effect, as exemplified by the post-trial washout period data demonstrating equivalent progression to diabetes in both groups. Therefore, can we really justify the use of glitazones versus cost-effective lifestyle intervention in diabetes prevention? We must also consider with the increased CV risk associated with diabetes the small elevated risk of HF observed in the DREAM study in people with diabetes taking glitazones without overt CV disease.

PROactive was conducted in patients at the other end of the diabetes spectrum: those with established CV disease taking several glucose-lowering agents. The evidence for improved outcomes in recurrent MI and stroke cannot be ignored, but it will not be until the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) study reports in 2009 that we will be able to elucidate whether these observations are a response to the glitazone class.

Evidence from this swathe of studies does suggest some benefits of earlier intervention with glitazones to slow the relentless progression of the condition. While metformin remains the unequivocal first-line agent of choice, ADOPT provides evidence that glitazones produce durable glucose-control over the long-term, potentially endorsing glitazones as appropriate second-line agents.

Particularly in overweight people with diabetes licences now support triple oral therapy as metformin, a sulphonylurea, plus a glitazone and a recommendation for use of a pioglitazone in combination with insulin when metformin is inappropriate (European Medicines Agency, 2006).

The overriding caution is for a pragmatic approach to the potential for HF exacerbation with these agents. Each study has delivered a warning signal, but with appropriate use in patients without existing HF and management of fluid retention and oedema the benefits of these agents will outweigh the risks.

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