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Diabetes and CVD: impact of antidiabetic agents on morbidity and mortality

Conflicting evidence currently exists on how best to achieve glycemic control in diabetic patients at risk of developing cardiovascular complications or in those with coexisting cardiovascular disease. This is illustrated by three recently published papers, one of which reviewed the outcomes with different antidiabetic agents in patients with diabetes and heart failure, whereas the other two evaluated the risk of cardiovascular morbidity and mortality in diabetic patients treated with thiazolidinediones.

The objective of a review and meta-analysis of eight clinical trials (five cohort studies, one randomized controlled trial and two post-hoc subgroup analyses from randomized trials) published by Eurich *et al.* was to evaluate the association between different antidiabetic agents (insulin, thiazolidinediones, sulfonylureas and metformin) and morbidity and mortality in patients ($n = 24{,}758$) known to have both diabetes and heart failure. Three out of four trials evaluating the effects of insulin suggested an increased risk of mortality compared with other antidiabetic treatments and one of those trials also found a significantly increased risk of cardiovascular morbidity and mortality in patients treated with insulin. Thiazolidinediones were compared with placebo in one trial and with other antidiabetic agents in three trials. The pooled effect of the four studies evaluating thiazolidinediones suggests that these drugs are associated with reduced all-cause mortality, but with an increased risk of hospital admission for heart failure. One of two studies evaluating sulfonylureas showed that sulfonylurea monotherapy is associated with an increased risk of mortality compared with metformin, whereas the second study showed no increased risk of mortality with sulfonylureas compared with other antidiabetic agents. Metformin was the only antidiabetic agent in this review not associated with measurable harm in patients with diabetes and heart failure. The risk of hospital admission or mortality was not increased for patients on metformin (compared with patients not receiving insulin sensitizers) in the three trials evaluating this drug, mortality being significantly reduced in patients receiving metformin in two of the studies.

The study by Lincoff *et al.* reviewed the data from clinical trials of pioglitazone. A total of 19 trials (16,390 patients) were included and these were all randomized, double-blinded and controlled with a placebo or with an active comparator. Death from any cause, nonfatal myocardial infarction and nonfatal stroke were defined as primary outcomes in this meta-analysis and occurred in 375 of 8,554 patients on pioglitazone and in 450 of 7,836 patients receiving control therapy ($P = 0.005$). Serious heart failure was specified as a secondary end point, and this occurred in 200 of the patients on pioglitazone and in 139 of the patients on control therapy ($P = 0.002$). The authors conclude that pioglitazone has a favorable effect on ischemic vascular complications and that this effect is distinct from the efficacy in reducing blood glucose levels. Serious heart failure is increased in patients on pioglitazone, although there is no associated increase in mortality.

The cardiovascular risk associated with rosiglitazone was evaluated in a meta-analysis published by Singh *et al.* The data from four randomized controlled trials (14,291 patients with impaired glucose tolerance or type 2 diabetes) were analyzed and relative risks of myocardial infarction, heart failure and cardiovascular mortality were estimated. Pooled data from the four trials showed that rosiglitazone significantly increased the risk of myocardial infarction (RR = 1.42) and of heart failure (RR = 2.09) compared with controls. Rosiglitazone did not significantly increase the risk of cardiovascular mortality (RR = 0.90). The authors suggest that rosiglitazone should be re-evaluated by regulatory agencies and that, in the meantime, this drug should be avoided in patients with diabetes who are at risk of cardiovascular events.

In conclusion, it appears that further research is still required to determine the optimal approach for glycemic control in patients with diabetes who are at risk of developing cardiovascular events and in those with cardiovascular comorbidity.

Original articles Eurich DT *et al.* (2007) Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *BMJ* **335:** 497
Lincoff AM *et al.* (2007) Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* **298:** 1180–1188
Singh S *et al.* (2007) Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* **298:** 1189–1195