

Do thiazolidinediones increase the risk of congestive heart failure and cardiovascular death?

Commentary

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The meta-analysis by Lago *et al.* has brought further valuable information to a highly controversial topic. Indeed, several meta-analyses (listed in Lago's paper) have already called into question the safety of rosiglitazone with regard to possible risks of myocardial infarction and cardiovascular mortality. None of the clinical trials included in these meta-analyses was designed to specifically evaluate the cardiovascular safety (or efficacy) of rosiglitazone, however, and the interim analysis of the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial did not report any increased cardiovascular mortality.¹ Similarly, Lago *et al.* found no increased risk of cardiovascular mortality associated with either rosiglitazone or pioglitazone when compared with placebo or a reference oral antidiabetic compound. In addition, there was no apparent difference between the two thiazolidinediones (RR = 0.91 for rosiglitazone and 1.01 for pioglitazone), although no head-to-head comparative trials were available.

The risk of CHF is a well-recognized complication reported in both RECORD with rosiglitazone¹ and PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) with pioglitazone.² In the meta-analysis of Lago *et al.*, patients given

thiazolidinediones had an increased RR of CHF across a wide background of cardiovascular risk (overall = 1.74, pioglitazone = 1.32, and rosiglitazone = 2.41). These findings have led to a stronger ‘black box’ warning in the prescribing information for the thiazolidinediones.

Nevertheless, the absence of higher cardiovascular mortality suggested that CHF in patients given thiazolidinediones might not carry the same high risk as is usually associated with CHF caused by progressive dysfunction of the left ventricle. A *post-hoc* analysis of the PROactive study confirmed that although the incidence of serious CHF was increased with pioglitazone versus placebo, subsequent mortality or morbidity were not increased in pioglitazone-treated patients with serious CHF.² However, because of the limited duration of observation after onset of CHF, longer term studies are needed to confirm that cardiovascular mortality is not an issue.

The controversy about thiazolidinediones should lead us to reconsider the place of these drugs in the management of type 2 diabetes mellitus. However, in an updated algorithm that followed the recent thiazolidinedione controversy, experts decided not to change the guidelines in the absence of definitive or compelling new data: thiazolidinediones still remain as one of three possible choices (sulfonylurea and insulin are the other two) that should be added to metformin and lifestyle intervention if target HbA_{1c} levels are not achieved.³ Nevertheless, greater caution should be recommended in the use of thiazolidinediones, especially for patients at risk of CHF or with pre-existing CHF. For diabetic patients in whom the absolute risk of CHF is estimated to be low, the use of thiazolidinediones should be weighed against the risks and benefits of other antidiabetic medications. Caution is also advised in patients with prediabetes.⁴

As highlighted by Lago *et al.*, the true risk–benefit profile of a thiazolidinedione as compared with another treatment for diabetes mellitus should be assessed when all other cardiovascular

risk factors (including glycemia) are similar in the two treatment groups. Large, long-term, head-to-head studies are, therefore, urgently needed to determine the comparative effects of the various pharmacological strategies on robust clinical end points in patients with type 2 diabetes mellitus.⁵

References

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Competing interests

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Practice Point

Greater caution is required in the use of thiazolidinediones for the management of type 2 diabetes mellitus, especially in patients with a history of congestive heart failure or in those at high-risk of this disorder.