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Rosiglitazone: to be or not to be?

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Abbreviations:

ADA American Diabetes Association
ADOPT A Diabetes Outcome Progression Trial

To the Editor: The American Diabetes Association (ADA) and the EASD recently recommended an update [1] to their algorithm for the initiation and adjustment of therapy for the management of hyperglycaemia in type 2 diabetes, which was originally published in 2006 [2] and specifically revised in early 2008 regarding the use of thiazolidinediones [3]. The recent consensus statement update may cause some controversy concerning the recommendations on the use of glitazones: 'Although the meta-analyses [...] are not conclusive regarding the potential cardiovascular risk associated with rosiglitazone, given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone.' [1] Pioglitazone remains an option among the so-called less well-validated therapies, more specifically, when hypoglycaemia is particularly undesirable, but rosiglitazone is not recommended anymore in the algorithm. Such a strongly negative statement is astonishing given that the same experts concluded in a specific update regarding thiazolidinediones 1 year previously: 'At this time, we do not view as definitive the clinical trial data regarding increased or decreased risk of myocardial infarctions with rosiglitazone or pioglitazone, respectively' [3] The same group also recommended 'greater caution in using the thiazolidine-diones, especially in patients at risk of, or with, CHF [congestive heart failure]', without distinguishing between rosiglitazone and pioglitazone [3].

Such a sudden change of position between the 2008 publication [3] and the 2009 update [1] is surprising as no new trials which provided any evidence against rosiglitazone were published in this period. In the last meta-analysis to compare the cardiovascular safety of rosiglitazone and pioglitazone with that of placebo or other glucose-lowering agents, published in late 2007, Lago et al. reported no significant increase in the risk of cardiovascular mortality owing to either rosiglitazone or pioglitazone as compared with the comparators, and there was no apparent difference between the two thiazolidinediones (RR 0.91 for rosiglitazone vs placebo and other oral glucose-lowering agents combined and RR 1.01 for pioglitazone vs placebo and other comparators), although no head-to-head trials comparing the two glitazones were available [4]. A recent paper showed that alternative reasonable methodological approaches to the rosiglitazone meta-analysis can yield increased or decreased risks that are either statistically significant or non-significant for both myocardial infarction and cardiovascular death [5], A meta-analysis of randomised controlled trials more specifically assessing the effect of thiazolidinediones on instent restenosis in patients after coronary stenting concluded that thiazolidinediones are an effective strategy for the prevention of instent restenosis [6]. Although the number of trials conducted on rosiglitazone was lower than the number on pioglitazone, the results were consistent between the two compounds. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, an increased risk of mortality (HR 1.35, p=0.02), contrasting with a reduced risk of non-fatal myocardial infarctions (HR 0.76, p=0.004), was described among those in the intensive-therapy group; these patients received multiple glucose-lowering therapies, including insulin (77% of patients) and thiazolidinediones (92% of patients, mostly rosiglitazone). However, preliminary non-prespecified exploratory analyses of differences in the use of drugs (including rosiglitazone) did not identify an explanation for the mortality finding [7]. Similarly, in the Veterans Affairs Diabetes Trial [8], the use of rosiglitazone (72% of patients in the intensified group) was not associated with increased cardiovascular risk in a post hoc analysis presented at the 2008 ADA meeting [9]. A Diabetes Outcome Progression Trial (ADOPT)—a key study published in 2006 [10]—directly compared rosiglitazone with metformin or glibenclamide (known as glyburide in the USA and Canada), and reported better durability of the glucose-lowering effect with rosiglitazone than with the other compounds in patients with newly diagnosed type 2 diabetes. Although ADOPT was not a cardiovascular outcome trial, glibenclamide appeared to be superior to metformin in terms of cardiovascular safety, and rosiglitazone was equivalent to metformin (now recognised as the gold standard) [10]. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study is the only trial to date to be specifically designed to assess the cardiovascular efficacy and safety of rosiglitazone [11]. It compared the effects of the addition of rosiglitazone (vs the addition of metformin or sulfonylurea in the control group) to the treatment regimen of patients with type 2 diabetes with inadequate glycaemic control while receiving metformin or sulfonylurea as monotherapy. An interim analysis

conducted after 3.75 years of follow-up produced inconclusive results regarding the effect of rosiglitazone on the overall risk of hospitalisation or death from cardiovascular causes (primary endpoint). There were no statistically significant differences between the rosiglitazone group and the control group in terms of myocardial infarction and death from cardiovascular causes [11]. It must be noted that this interim analysis had limited statistical power to detect treatment differences in this trial; however, this limitation was as apparent in 2008 (at the time of the so-called update regarding the thiazolidinediones) [3] as it is now in 2009 [1].

Together, the sudden change between 2008 [3] and 2009 [1] in the ADA-EASD consensus statements regarding rosiglitazone does not appear to be supported by objective data (it is stated in the consensus itself that the data are less than conclusive) and evidence-based medicine, but, rather, driven by the caution principle. As discussed recently many glucose-lowering drugs were withdrawn, or almost retired, from the market because of safety concerns [12].

Even sulfonylureas raised concerns because of a higher risk of myocardial infarction observed in the University Group Diabetes Program in the early 1970s [13]; similarly, there were concerns surrounding the use of biguanides (including metformin) in the early 1980s following a reported association with a higher incidence of lactic acidosis vs other glucose-lowering strategies [14]. Interestingly, both are now considered to be well-validated core therapies by the authors of the consensus statement [1] and are leaders in the diabetes market. Even if data obtained on completion of ongoing trials may help to produce accurate estimates of the effect of rosiglitazone on cardiovascular outcomes [5], given the negative recommendation stated in the recent ADA-EASD consensus statement, the use of rosiglitazone may greatly decline prior to the generation of these data. Be careful not throw the baby out with the bath water in the absence of clear-cut, evidence-based data.

Duality of interest

A. J. Scheen is a consultant for AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline and sanofi-aventis, and has received lecture fees from these companies. He was a member of the International Steering Committee in the PROactive study supported by Takeda

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