Have the risks of rosiglitazone been exaggerated?

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'Meta-analyses ... are best utilized as exploratory tools for generating hypotheses, not validating them.'

Nissen and Wolski recently reported a meta-analysis of 42 clinical trials of 27,847 subjects that ignited a firestorm of controversy by claiming that treatment with rosiglitazone (Avandia, GlaxoSmithKline [GSK]), a widely prescribed PPAR- γ agonist, was associated with a "...worrisome..." 43% greater risk of myocardial infarction (MI; $p = 0.03$) and a 64% greater risk of cardiovascular death (CVD; $p = 0.06$) [1]. A number of criticisms have been raised against this analysis with many pointing to the initial conclusions as premature, indefinite or even alarmist [2–10,101]. We herein attempt to further explicate these issues, and offer suggestions for potential solutions.

Limitations of the index meta-analysis

A careful scrutiny of the meta-analysis reveals several flaws that undermine the reliability of the investigator's conclusions.

First, the meta-analysis was not based on a comprehensive search for all studies that might yield evidence about rosiglitazone's cardiovascular effects. In addition, despite having first identified 48 trials by their predefined inclusion criteria (having a randomized comparator group plus at least 24 weeks of drug exposure), six trials were excluded from the analysis because they did not report any cardiovascular events. Peeking at the outcome data first before choosing studies to include in a meta-analysis would not generally be considered acceptable.

Second, even though the authors justified the pooling of the studies based on a lack of any statistical heterogeneity across the trials, there was sufficient clinical heterogeneity in patient populations (nondiabetics, prediabetics and diabetics; with or without congestive heart failure [CHF]), design protocols (different trial sizes and durations, 38 double-blind and four open-label trials) and treatment regimens (seven different comparator groups with two different doses, some

placebo-controlled, others active-controlled, some add-on comparisons, others background therapy comparisons) to preclude pooling. Indeed, one trial that enrolled patients with CHF, already a contraindication for rosiglitazone, reported the highest number of adverse cardiovascular events (five MIs and three CVDs in the treatment arm compared with two MIs and two CVDs in the control). Exclusion of this trial would fail to yield a statistically significant odds ratio (OR) for MI using the Peto method (OR: 1.39; 95% confidence interval [CI]: 0.99–1.94).

Third, the quality of the data was not particularly robust. The majority of these trials were not designed to address cardiovascular end points; the adverse events were not collected or adjudicated in a standardized manner, thus, being unverifiable and likely vulnerable to ascertainment errors and potential misclassification. This could have had a material impact on the results, especially given the small number of events. Furthermore, patient-level data for the more robust time-to-event analysis were unavailable. Other relevant events such as stroke or noncardiovascular death were not reported (making assessment of all-cause mortality difficult), and it was not possible to determine if the outcomes were uniformly defined or mutually exclusive, or if the same patient was counted in more than one trial.

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Fourth, the quantity of the data was sparse, partly owing to the relatively short-term follow-up (mostly 24–52 weeks) and partly owing to the enrollment of a relatively low-risk population. Four trials did not report any MI and 19 trials did not report any CVD in both the treatment and the control arms (zero total event trials). In addition, a large number of trials exhibited zero events in either the treatment or the control arm (zero event trials) – 20 in the control and six in the treatment arm for MI, and 15 in the control and two in the treatment arm

for CVD. Thus, there were only 12 trials that reported MI and six trials that reported CVD in both comparator groups.

Fifth, the meta-analytical methodology used by the investigators was incomplete and arguably biased against rosiglitazone treatment. In performing their analysis, the investigators employed Peto's fixed-effects model for pooling the data, which necessitated the exclusion of four zero total event trials from the MI analysis and 19 zero total event trials from the CVD analysis. Zero events are a marker of safety, just as events are a marker of risk. The investigators justified their choice of the Peto method by the overall paucity of cardiovascular events, by the absence of statistical heterogeneity among the studies and by reference to simulation studies indicating that this method provided the most reliable estimates under such circumstances [1]. However, Peto's method performs less reliably when there is an imbalance between the number of subjects in the comparator groups (numbers of patients assigned rosiglitazone were two-to-three-times greater than the numbers of patients assigned the comparator in some of the trials) or when there is an imbalance in the number of zero event trials (imbalance favoring the control arm by 20:6 for MI and 15:2 for CVD) [5]. In such cases where the number of zero event trials favors the control arm, the Peto method tends to overestimate risk with the treatment arm. Alternative analytical strategies might mitigate this error and provide more consistent and reliable estimates of risk. Specifically, it is recommended to employ continuity corrections instead of excluding zero event trials and to perform sensitivity analyses to judge the fragility of the conclusions. Consequently, when Diamond *et al.* reanalyzed the rosiglitazone data according to these recommendations, the corrected analyses shifted the resultant ORs toward null [5]. Although the corrected ORs remained elevated (suggesting a signal for increased risk), the CIs were wide and overlapped unity, indicating greater uncertainty than was originally reported in the unadjusted analyses. Furthermore, subgroup analyses failed to identify any particular group of patients in which the cardiovascular risk was significantly increased [5]. Given the fragility of the risk estimates, the claim that rosiglitazone increases the risk of adverse cardiovascular events is not supported by the adjusted analyses. The exaggerated values observed in the index study are likely the result of these limitations.

Finally, all of the published studies of cardiovascular risk associated with rosiglitazone have been meta-analyses. Meta-analyses have important limitations in that they may not always provide an accurate and reliable estimate of treatment effects as measured in large clinical trials [11]. They are best utilized as exploratory tools for generating hypotheses, not validating them.

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Additional analyses

Several additional analyses have also assessed cardiovascular risk associated with rosiglitazone [12–16,102,103]. The Integrated Clinical Trial Analyses conducted by the sponsor, GSK [102], and the meta-analysis conducted by the US FDA [103], were based on 42 randomized trials (only 28 of these being identical to those included in the Nissen and Wolski meta-analysis). However, unlike in the latter meta-analysis, the pooled sample size was approximately 50% smaller (mean duration 6 months; 14,237 total patients, the larger long-term trials such as A Diabetes Outcomes Progression Trial [ADOPT] and Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication [DREAM] were excluded), all of the trials were double-blind and patient-level data were available for the GSK and FDA analyses. A proportional hazards model was used for pooling the data in the GSK analysis [102], and an Exact test stratified on homogenous subgroups (metagroup) in addition to a Mantel–Haenszel model with a continuity correction of 0.5 added to each cell of those studies with zero events in one arm or in both arms was used in the FDA analysis [103]. The results of these analyses summarized in Figure 1 yield interesting insights.

A statistically significant increase in risk with rosiglitazone was observed only with respect to ischemic heart disease (IHD) events (serious plus nonserious ones) in both the GSK and FDA meta-analyses [102,103]. Neither serious IHD events nor the clinically more relevant triple composite end point of CVD, MI or stroke, or its individual components, yielded a statistically significant increase in risk with rosiglitazone. Of note, the results of the FDA analysis using the Mantel–Haenszel approach (with continuity correction of 0.5 added) were more

Figure 1. Risk of adverse cardiovascular events associated with rosiglitazone.

Risk estimates are based on Peto's odds ratio (Nissen & Wolski), Mantel-Haenszel fixed-effect analysis with continuity correction (Diamond *et al.*, US FDA), proportional hazards (GSK ICT) and fixed-effects meta-analysis (Cochrane Review).

CVD: Cardiovascular death; ICT: Integrated Clinical Trial; IHD: Ischemic heart disease; GSK: GlaxoSmithKline; MI: Myocardial infarction.

closely aligned with Diamond *et al.* than with Nissen and Wolski (1.25 and 1.26 vs 1.43 for MI, and 1.04 and 1.17 vs 1.64 for CVD, respectively). Similar inconclusive observations were reported from the Cochrane Review of 18 studies amongst patients with Type 2 diabetes [12], an interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial (which had the highest number of MI events reported) [13] and three large observational studies – one commissioned by the sponsor, the Balanced Cohort Study [14], and two conducted independently by Tricare for the Department of Defense and by Well-Point [15]. An updated meta-analysis of four trials with a follow-up of greater than 12 months revealed a statistically significant 42% increase in the risk of MI associated with rosiglitazone [16]. Interestingly, the increase in MI was not associated with an increase in the risk of cardiovascular mortality (OR: 0.90; 95% CI: 0.63–1.26). Thus, none of these

analyses conclusively adjudicate the association between rosiglitazone and the risk for MI or CVD.

Class effect or drug-specific effect

An important question is whether the risks and benefits associated with thiazolidinediones (TZDs) are class-specific or drug-specific. A large clinical trial designed to assess the effect of pioglitazone on cardiovascular outcomes, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, failed to yield statistically significant benefit in favor of pioglitazone with regards to the primary composite outcome [17]. However, pioglitazone treatment significantly reduced a secondary composite outcome of all-cause mortality, non-fatal acute MI or stroke. A recent meta-analysis of 19 trials (where nearly 80% of pooled events were contributed by the PROactive trial) reported a significant reduction in the composite end point of all-cause death, MI or stroke with pioglitazone compared with control [18],

providing indirect support for claims of its superior cardiovascular safety profile compared with rosiglitazone [16,18]. Because of substantial differences in the pioglitazone and rosiglitazone datasets – placebo-controlled versus active-controlled, patient demographics, treatment duration and so on, all of which can potentially have a material impact on outcomes – such indirect comparisons are often misleading and should, therefore, be avoided. Indeed, the all-cause mortality estimates for pioglitazone (OR: 0.92; 95% CI: 0.76–1.11) appear to be similar to those of rosiglitazone (OR: 0.90; 95% CI: 0.71–1.15) raising questions about the superior safety profile of the former.

The relationship between TZD use and CHF has been demonstrated in a number of studies [12,16,19–21], and TZDs are not recommended for use in individuals with class III or IV New York Heart Association (NYHA) CHF [104]. The association is felt to be the result of increased fluid retention and expansion of plasma volume by TZDs, however, the underlying mechanism for this volume expansion is not fully known [19]. A recent meta-analysis by Lago and colleagues suggested a 1.7-fold increased risk of CHF associated with TZDs with a slightly greater risk with rosiglitazone (2.18-fold) compared with pioglitazone (1.32-fold); however, the difference did not reach statistical significance [21]. Although TZDs have justifiably received black-box warnings for CHF exacerbation [104], it is noteworthy that the increase in CHF was not associated with an increase in risk of CVD in the Lago meta-analysis (relative risk: 0.93; 95% CI: 0.67–1.29) [21]. Dargie *et al.* recently reported that rosiglitazone did not adversely affect left ventricular systolic or diastolic function in patients with Type 2 diabetes mellitus and NYHA functional class I–II CHF despite edema and weight gain [20]. These observations lead to the question of whether the volume retention associated with TZDs is prognostically benign or harmful? Should these cases be classified as edema/volume retention or CHF exacerbation?

There are some minor differences with respect to changes in lipid profile. Less of an elevation in LDL and a greater elevation in HDL with pioglitazone, and an elevation in triglycerides with rosiglitazone compared with a drop with pioglitazone has been reported [1]. However, the clinical relevance of these differential changes in

lipid profile with these agents is not known. Only direct head-to-head comparisons in prospective randomized controlled trials can provide convincing conclusions about the comparability of these two agents.

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Conclusions & implications

The risk for adverse cardiovascular outcomes for diabetic patients taking rosiglitazone is uncertain: neither increased nor decreased risk is established. These uncertainties were reflected in the vote of the Advisory Panel who voted 20:3 in favor of a suggestion of increased risk for ischemic cardiac events, but voted 22:1 against pulling it off the market [105]. The FDA's recent decision to allow rosiglitazone to stay on the market with increased black-box warnings about the risk of IHD events also accurately reflects these uncertainties [106]. In our opinion, reasoned analysis of additional data, derived primarily from prospective clinical trials designed specifically for establishing the cardiovascular benefit or risk of rosiglitazone, will be required to adjudicate these inconclusive results and resolve the uncertainties regarding the safety of rosiglitazone. It is reassuring that GSK has agreed to conduct a new long-term study to evaluate the potential cardiovascular risk of rosiglitazone as requested by the FDA. Meanwhile, in the face of uncertainty, the best advice for the practicing clinician is a 'don't stop, don't start' strategy. No need to stop rosiglitazone in patients who have tolerated it long term without any adverse events and whose blood sugars are under good control. No need to start patients on rosiglitazone before exhausting alternative treatment options.

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