The thiazolidinediones (TZDs) were introduced to the US market in 1997 as therapies to control hyperglycemia in patients with diabetes mellitus. This class of drugs (agonists of peroxisome proliferator-activated receptor γ) has a wide range of biochemical effects, including lowering blood sugar by increasing insulin sensitivity. The TZDs were adopted relatively rapidly and achieved sales of nearly $3 billion in the United States in 2009.

Rapid increases in TZD use occurred despite accumulating safety concerns about the drugs. The first in the class troglitazone was withdrawn from the US market in 2000 because of evidence that it could cause hepatotoxicity that was in some cases lethal. Subsequently, reports emerged that the 2 remaining TZDs available in the United States (pioglitazone and rosiglitazone, both approved in 1999) were associated with substantially higher risks of fluid retention and heart failure, complications of particularly serious consequence in patients with diabetes.1 However, TZD use remained robust, including among patients with important contraindications.2

Further, the 2 currently available TZDs have varied metabolic effects beyond lowering blood glucose, raising questions about their effects on important cardiovascular outcomes. Both agents modestly lower blood pressure but also cause weight gain and raise low-density lipoprotein cholesterol levels. Further, rosiglitazone significantly raises triglyceride and low-density lipoprotein cholesterol more than pioglitazone.3 Hypotheses about the impact of these metabolic effects on health outcomes were merely speculation until larger clinical studies became available. The cardiovascular effects of pioglitazone were studied in the Prospective Pioglitazone Clinical Trial in Macrovascular Events, a placebo-controlled clinical trial. Although the study had negative findings with respect to the primary composite cardiovascular outcome, a principal secondary end point of death and selected cardiovascular outcomes was significantly improved in patients receiving pioglitazone.4 Although this study was considered by many as inadequate evidence of cardiovascular protection by pioglitazone, the findings were reassuring that pioglitazone was not likely to substantially increase cardiovascular risk. With respect to rosiglitazone, other studies generated important concerns about its cardiovascular effects. A metaanalysis published in 2007 of 42 rosiglitazone trials, many conducted by the manufacturer but not published, found higher rates of myocardial infarction and cardiovascular death.5 A number of subsequent studies, including a very large observational study in a Medicare population by Graham and colleagues6 and an expanded version of the original rosiglitazone metaanalysis,7 only amplified the concerns, finding that rosiglitazone was associated with adverse cardiovascular effects compared with pioglitazone,6 other antihyperglycemic comparators, or placebo.7

These studies motivated the Food and Drug Administration (FDA) to reassess rosiglitazone on 2 occasions. The first FDA panel assessment after the publication of the metaanalysis in 2007 (8 years after FDA initial approval of rosiglitazone) resulted in a black box warning that rosiglitazone may increase ischemic cardiac events. The second FDA panel convened in July 2010 after the conduct of the manufacturer of rosiglitazone regarding the release of comprehensive trial results was called into question by a US Senate subcommittee.8 The FDA panelists were presented with hundreds of pages of documents describing the existing studies regarding the safety of rosiglitazone, including the Graham et al study and a detailed reanalysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes trial, a controversial, open-label, active-comparator, manufacturer-sponsored study ostensibly designed to assess the cardiovascular safety of rosiglitazone.9 After 2 days of presentations and discussion, the advisory panel delivered a split verdict, with the majority recommending that rosiglitazone remain available but with strong precautions to physicians and patients regarding its use.

In this issue of Circulation: Cardiovascular Quality and Outcomes, Wertz and colleagues10 provide another perspective with an observational study of more than 36 000 patients in a commercial insurance plan initiating TZD therapy. After applying propensity methods to adjust for potential confounders, the investigators found that patients with prescriptions for rosiglitazone were no more likely than those receiving pioglitazone to experience a composite end point of death, myocardial infarction, or acute heart failure as ascertained from administrative records supplemented by the National Death Index for mortal events. These results were uniform across subgroups of patients, including those aged >65 years, and after excluding patients once therapy was terminated.
A number of factors should be considered in the interpretation of this study. On the one hand, it is relatively large, includes a patient population with a wide age range, and uses rigorous statistical methods to account for measured confounders. On the other hand, clinical events were ascertained using administrative sources rather than clinical records, and because the design was not randomized, the possibility that unmeasured confounders may exert an important influence on the results cannot be excluded.

What might explain the differences between the results of this study and those described previously that suggest important adverse consequences of rosiglitazone therapy? The differences between this study and the metaanalysis of randomized trials are substantial; perhaps the most relevant comparison is with the most recent observational study by Graham and colleagues, which found higher rates of adverse cardiovascular outcomes with rosiglitazone compared with pioglitazone in >200,000 Medicare patients initiating TZD therapy. First, the duration of follow-up differed from a mean of 105 days in the Graham et al study to 1.6 years in the Wertz et al study, but this would explain the differences in the findings if the risks of rosiglitazone diverged and then converged within these time frames, a seemingly unlikely explanation. Second, the time frame of the 2 studies differs. Wertz and colleagues studied patients starting TZD therapy between 2001 and 2005, whereas Graham and colleagues included those initiating therapy between 2006 and 2009. Perhaps the biggest difference between these 2 time frames is the availability of the results of the metaanalysis in the latter. It is conceivable that after the publication of the metaanalysis, only those physicians who were unaware of the safety concerns (and thus potentially less aware of other important developments in medicine) would continue prescribing rosiglitazone, thus confounding the Graham et al findings. To the extent that formularies determine drug choices, this explanation becomes less plausible, but it cannot be entirely excluded. Third, although both studies used a composite end point that incorporated death, myocardial infarction, and heart failure, the composite outcome of Graham et al also included stroke. Because subsequent strokes were not assessed by Wertz et al, direct comparisons are limited.

Finally, and perhaps most importantly, it is possible that despite its size, the study by Wertz et al was simply underpowered. The point estimate and 95% CIs for the composite end point in the Wertz et al study (1.03; 95% CI, 0.91 to 1.15) overlap substantially with those in the Graham et al study (1.18; 95% CI, 1.12 to 1.23). Thus, the results could at least theoretically represent what one would expect to find in 2 studies of their respective sizes when a relatively modest, but still important increase in risk from rosiglitazone existed. Indeed, the Wertz et al study ultimately cannot exclude an adverse effect of the magnitude found by Graham and colleagues. Certainly, an increase in relative risk of 10% to 20% in a relatively high-risk population should be considered clinically significant. A risk of this magnitude seems even more important in light of the availability of numerous therapeutic alternatives to rosiglitazone.

Given the existing evidence, what is the value of the Wertz et al study, which identifies no clear evidence of harm with rosiglitazone? Publication bias (the tendency to publish positive studies), although not as insidious as the practice of willingly withholding important information about drug safety, may have a similar impact. In both cases, the public is misled because of its inability to access the full spectrum of existing data. Of course, not all negative studies should be published, especially those hampered by serious bias or confounding. Furthermore, negative studies often will be questioned for the lack of power, including the present case. Nevertheless, studies like those of Wertz and colleagues that are conducted with adequate statistical rigor must be available to provide a full picture and to inform the debate.

Perhaps the most troubling aspect of the rosiglitazone story is that the initial concerns about its effect on myocardial ischemic events did not emerge until the drug had been in wide use for almost a decade. Unfortunately, the documents compiled by the US Senate raise concerns that the manufacturer may have played an active role in delaying our understanding of rosiglitazone’s safety. This example, and that of rofecoxib, provide a strong basis for arguments that the regulations governing the timely release of safety information must be strengthened and that the penalties for violating these rules must be more severe.

Although more robust regulation and enforcement thereof may be necessary, we also need a more robust framework to assess drug safety in real-world populations. Certainly, randomized trials designed principally to determine safety would be ideal. If designed properly, randomized control trials eliminate concerns for confounding. However, they are extremely expensive and take a great deal of time to complete. Thus, although randomized control trials designed explicitly to assess drug safety have been conducted, they are relatively uncommon. It would be unrealistic to expect that much of our understanding of drug safety will derive from randomized studies.

Ultimately, our understanding of drug safety will necessarily depend predominantly upon observational data. Approaches relying on voluntary reports of possible safety events are simply inadequate. In such cases, the numerators of patients with events are biased, and the denominators of all patients who receive therapy are not available. Fortunately, large data sets with longitudinal follow-up such as those used by Wertz and colleagues are increasingly available. Sources of robust data to assess drug safety include national registries or large integrated health plans. For example, the Center for Drug Evaluation and Research, which is sponsored by the FDA through the HMO Research Network, has created the capacity to perform observational pharmacosurveillance in extraordinarily large populations. Such efforts have great potential for providing more timely information on the outcomes of drug use in the populations who receive treatment in clinical practice.

Naturally, concerns about confounding inevitably underlie the interpretation of observational data. Fortunately, the methodology used to account for confounding has evolved substantially beyond the use of simple multivariable adjustment alone. For example, Wertz and colleagues used propensity scores to correct for measured differences between patients treated with rosiglitazone and those treated with
pioglitazone. This method and others continue to evolve. The optimal approach is still debated, and different approaches to confounding may yield importantly different results. In addition, such methods can only reasonably account for variables that are measured, with resulting concerns about residual confounding by unmeasured factors. Even here, though, approaches have become substantially more advanced. For example, sensitivity analysis and external adjustment provides a quantitative approach to assessing the potential impact of unmeasured confounders. A holy grail—methods to eliminate confounding entirely from observational studies—does not exist. However, the evolution of statistical methods justifies increasing confidence in well-designed observational studies of drug safety.

Although a wealth of data around the safety of rosiglitazone is now available, this understanding only evolved after millions of patients were exposed to rosiglitazone over the decade since its approval. Some might consider the FDA actions a day late and a dollar short. On the other hand, this example and a few other prominent ones have shone a bright light on the importance of timely drug safety data. With growing sources of information and increasingly sophisticated methods to apply to these sources, there is good reason for hope that we will be able to have a more comprehensive and timely appreciation of the risks of the treatments we provide to patients.

Disclosures

None.

References


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