

## Rosiglitazone: A Thunderstorm from Scarce and Fragile Data

The U.S. Food and Drug Administration (FDA) has approved many pharmacotherapies for treating diabetes on the basis of the drugs' ability to improve glycemic control. Although preventing adverse macrovascular outcomes, such as myocardial infarction, is a desirable goal for treatment of type 2 diabetes, there is no definitive evidence that any FDA-approved pharmacotherapy achieves such aims (1). Worse, recent meta-analyses suggest that rosiglitazone, a widely prescribed oral hypoglycemic agent, might increase the risk for ischemic heart disease by a small amount. We examine the fragile data underpinning that story and the challenges of summarizing trials with scarce events.

### EARLY STORM CLOUDS FOR THIAZOLIDINEDIONES

Rosiglitazone (Avandia, GlaxoSmithKline, Brentford, United Kingdom) is a thiazolidinedione (TZD)—a class of drugs that targets insulin resistance. Warning clouds about TZDs amassed quickly. Troglitazone, the first TZD, was withdrawn in early 2000—3 years after approval—because of severe cases of hepatotoxicity and death. The peroxisome proliferator-activated receptor- $\gamma$  agonists rosiglitazone and pioglitazone, approved in 1999, had less hepatotoxicity but were associated with hemodilution, anemia, weight gain, edema, and increased risk for heart failure.

### THUNDER RUMBLES

Prompted by a 2003 World Health Organization analysis of adverse event reports that suggested that TZDs might increase risk for cardiac disease, GlaxoSmithKline submitted preliminary pooled analyses to the FDA in 2005 that raised concerns about possible risk for ischemic cardiac events with rosiglitazone (2). The FDA's review of these and other data led to the first rosiglitazone label warnings about possible cardiac adverse effects other than heart failure, particularly in patients also receiving insulin (2). In August 2006, the FDA received GlaxoSmithKline's formal analysis of 42 randomized trials along with data from a large observational study. The meta-analysis suggested a possible "31% increase in cardiac ischemic events with rosiglitazone," whereas the observational study showed no such increased risk (2–4). Faced with confusing data, the FDA biometrics staff began their own analysis of the trials.

A September 2006 report of a placebo-controlled trial in prediabetic patients showed a small, not statistically significant increase in risk for myocardial infarction with rosiglitazone (5). A December report of a trial involving diabetic patients showed similar numbers of heart failure and ischemic events with rosiglitazone and metformin that were higher than those found with glyburide (6). In early spring, FDA staff called for prominent boxed warnings about the risk for heart failure and edema with peroxisome

proliferator-activated receptor- $\gamma$  agonists and requested a May meeting with GlaxoSmithKline to further discuss the "signal of cardiovascular ischemic events with rosiglitazone" (2). They planned to take the issue of heart failure and ischemic events for both rosiglitazone and pioglitazone to an Advisory Committee meeting in late summer or early fall.

### LIGHTNING STRIKES

In late May 2007, Nissen and Wolski (7) published a controversial meta-analysis that claimed that rosiglitazone increased the risk for myocardial infarction by about 43% and cardiovascular death by about 64%. The FDA moved the date for the Advisory Committee meeting to July 2007 and narrowed the focus of the meeting to the cardiovascular ischemic issue with rosiglitazone. Investigators of an ongoing trial evaluating add-on rosiglitazone to metformin or sulfonylurea performed an unplanned interim analysis that showed hazard ratios with rosiglitazone of 0.83 (95% CI, 0.50 to 1.36) for cardiovascular death and 1.17 (CI, 0.75 to 1.82) for myocardial infarction (8).

At the Advisory Committee meeting, FDA staff presented various detailed analyses of the GlaxoSmithKline trial data (2). One of their analyses, based on exact methods that excluded trials with zero events, found that rosiglitazone was associated with a greater risk for myocardial ischemic events than was placebo, metformin, or sulfonylureas (odds ratio, 1.4 [CI, 1.1 to 1.8]) (2, 9). The magnitude and statistical significance of the risk varied across drug combinations and comparator and population subgroups. Some analyses suggested that the rosiglitazone-associated risk was either more likely or greater among patients taking insulin or metformin and among those taking nitrates for cardiovascular disease (2, 9). However, the Advisory Committee recommended, almost unanimously, against withdrawing rosiglitazone from the market and for enhancing the FDA's warnings about possible risk for ischemic heart disease.

### FOG REMAINS

In this issue, Diamond and colleagues (10) explicate some weaknesses of the evidence that rosiglitazone increases the risk for ischemic heart disease (10). They note that most of the studies were designed to assess end points other than cardiovascular disease; that patient inclusion criteria, drug dosing regimens, and comparators varied among studies; that trial durations were relatively short; and that overall event rates were low. They find that Nissen and Wolski's summary of trials compounded the problem of scarce events because that analysis dropped data from trials that reported no myocardial infarction events or deaths from cardiovascular events in any study group. Re-

analyzing the data with techniques that allow inclusion of trials with zero events, they find a smaller possible risk for ischemic cardiac events than that reported by Nissen and Wolski.

### PENETRATING THE FOG

The analyses by GlaxoSmithKline, Nissen and Wolski, Diamond and colleagues, and the FDA teach us that summarizing data about scarce adverse events is difficult. Summary estimates, confidence bounds, and statistical significance can vary depending on analysis techniques. Analytic challenges are most acute when 1 or more studies report zero events among the treatment group, comparison group, or both. One must decide whether to include or exclude the studies with zero events and select the appropriate statistical method to summarize the risks. Selection of appropriate methods requires careful consideration of the rarity of the outcomes, the relative numbers and sample sizes of trials with zero events versus trials with events, and the degree of balance of sample size in treatment and comparator groups. Investigators should also carefully consider the use of a correction in studies with 1 or more zero events through the addition of a fractional count, the size of this correction in relation to the overall risk for events, and the relative size of this correction across treatment groups. The optimum methods that minimize bias and accurately estimate confidence bounds vary depending on the answers to these questions.

Some general guides might include the following principles. If few trials have zero events or unbalanced numbers of participants assigned to the treatment and comparator groups, then common statistical methods, such as fixed-effects, stratified (Mantel–Haenszel) estimation, with or without correction for zero events, or the Peto method, might suffice (11, 12). If several trials report no events, consider whether the goal is a summary of ratios or differences in risk. Trials with zero events might not inform *relative measures of efficacy*, particularly if those trials have small sample sizes and short durations. Investigators might exclude them either explicitly or implicitly with the statistical method they use (for example, the Peto method) (13). Zero-event trials, however, do inform estimates of the *frequency of outcome* in both the treatment and comparator groups. Excluding them inflates estimates of event rates. One might choose absolute measures, such as risk differences, to incorporate the zero-event trials and help prevent inflated estimates of risks. Regardless of the measure used to estimate effects, the exclusion of large numbers of trials with zero events ignores the patients exposed in those studies, overstates the absolute risk associated with treatment and comparator exposures, and might introduce a positive bias in some estimates of relative outcomes.

Excluding zero-event trials is particularly concerning when adverse event rates are being investigated. Excluding many such studies can lead to false or inflated concerns

about safety because patients are deleted from the denominator of the calculations. In such instances, we encourage including the zero-event trials and using a continuity correction, such as the reciprocal of the sample size in the opposite treatment group (12). Because the size of the continuity correction can influence summary estimates, we suggest doing sensitivity analyses over a range of continuity corrections.

### EXPECT MORE THUNDERSTORMS

We have witnessed several (and expect to see many more) stormy stories about uncommon adverse events with common therapies. We must exercise caution when conducting and interpreting meta-analyses of trials that report these rare events. Careful consideration of the variation in treatments, study design and duration, event definitions, follow-up assessments, and patient populations should guide judgments about the fragility of the data and decisions about whether the data should be summarized quantitatively. These considerations apply to any meta-analysis, regardless of event rates. They are as or more important than the technique that one uses to combine data. Scarce events simply add another layer of complexity, particularly when several trials report zero events.

In the end, it is deplorable that all FDA-approved pharmacotherapies for type 2 diabetes have scarce data about important macrovascular clinical events. Better studies, not meta-analyses, are the answer to this problem. Society and our regulatory agencies must demand large comparative studies, designed and funded by parties representing the public interest, with well-defined and uniformly assessed clinical outcomes other than glycemic control. Otherwise, we will continue to have weak answers to important questions about the benefit and safety of widely used drugs.

*Cynthia D. Mulrow, MD, MSc*  
Deputy Editor

*John E. Cornell, PhD*  
Associate Editor

*A. Russell Localio, PhD*  
Associate Editor

**Potential Financial Conflicts of Interest:** None disclosed.

**Requests for Single Reprints:** Customer Service, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.

*Ann Intern Med.* 2007;147:585-587.

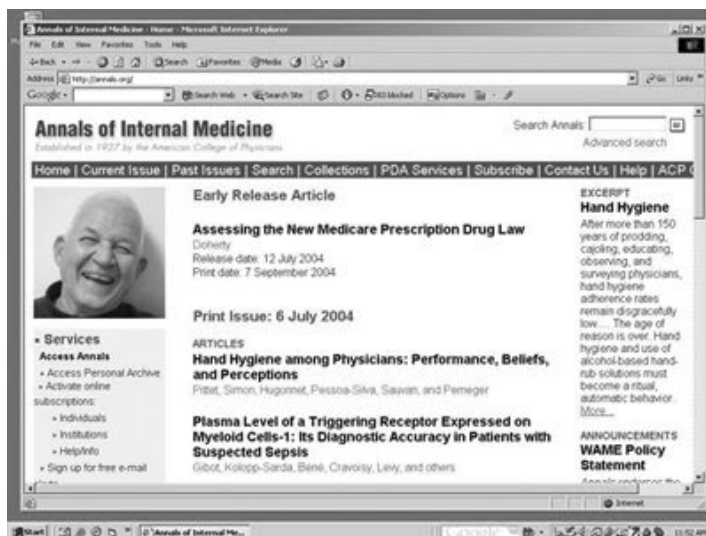
### References

1. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007;147:386-99.

2. FDA Briefing Document: Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. 30 July 2007. Philadelphia: GlaxoSmithKline; 2007. Accessed at [www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf](http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf) on 1 August 2007.
3. Advisory Committee Briefing Document: Cardiovascular Safety of Rosiglitazone. Philadelphia: GlaxoSmithKline; 2007. Accessed at [www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-01-sponsor-backgrounder.pdf](http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-01-sponsor-backgrounder.pdf) on 1 August 2007.
4. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. *Pharmacoepidemiol Drug Saf.* 2007;16:711-25. [PMID: 17551989]
5. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet.* 2006;368:1096-105. [PMID: 16997664]
6. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355:2427-43. [PMID: 17145742]
7. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356:2457-71. [PMID: 17517853]
8. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med.* 2007;357:28-38. [PMID: 17551159]
9. Rosen CJ. The Rosiglitazone story—lessons from an FDA Advisory Committee meeting. *N Engl J Med.* 2007. [PMID: 17687124]
10. Diamond GA, Bax L, Kaul S. Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. *Ann Intern Med.* 2007;147:578-81.
11. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med.* 2007;26:53-77. [PMID: 16596572]
12. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med.* 2004;23:1351-75. [PMID: 15116347]
13. Sankey SS, Weissfeld LA, Fine MJ, Kapoor W. An assessment of the use of continuity correction for sparse data in meta-analysis. *Communications in Statistics: Simulation and Computation.* 1996;25:1031-56.

# Where is that article I read in *Annals*?

Search archives  
of *Annals* – full texts  
of articles since 1993  
available for printing  
or online reading



IP4001aa

Interested? Go to [www.annals.org](http://www.annals.org)