**Rosiglitazone and the Case for Safety Over Certainty**

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Approximately 10 years ago, the thiazolidinediones rosiglitazoneand pioglitazone were introduced for the treatment of type 2diabetes. Like their forerunner troglitazone, which was removedfrom the market following reports of hepatotoxicity, these drugsact on the gamma subtype of peroxisome proliferator-activatedreceptors (PPAR-) in the cell nucleus, resulting in heightenedinsulin sensitivity and improved glycemic control.[1](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-1) Becauseinsulin resistance is a common feature of type 2 diabetes, thebiological effects of thiazolidinediones made these drugs appealingto patients with diabetes and to their physicians who were lookingfor yet another way to avoid the need for insulin. Within afew years, both drugs became multibillion-dollar products despiteno direct evidence that they actually prevented the complicationsof diabetes.

As the popularity of rosiglitazone and pioglitazone increased,reports surfaced of peripheral edema and congestive heart failureduring treatment.[2](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-2) It quickly became apparent that these medicationscould cause both conditions, which are now thought to resultfrom activation of PPAR- in the distal nephron, leading to increasedreabsorption of sodium and water.[3](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-3) The lesson here is that pharmacologicaltinkering with a nuclear receptor is likely to have consequencesanywhere that receptor is expressed.

In May 2007, safety concerns regarding the thiazolidinedionesattracted widespread attention with the publication of a meta-analysissuggesting that, compared with other treatments for diabetes,rosiglitazone was associated with a 43% higher risk of myocardialinfarction (*P* = .03) and a 64% higher risk of cardiovasculardeath (*P* = .06).[4](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-4) Several other meta-analyses involvingrosiglitazone followed, and while their methods and conclusionsvaried, these reports provided a relatively consistent messagethat rosiglitazone might indeed increase the risk of myocardialischemic events, albeit with an inconsistent message regardingmortality.[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.954#REF-JED05041-5) In contrast, a meta-analysis of 19 trials involvingpioglitazone suggested that even though the drug appeared toincrease the risk of heart failure, it might reduce the riskof myocardial infarction, stroke, or death.[6](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-6)

Along with these meta-analyses, several large-scale pharmacoepidemiologicinvestigations have used health care databases to provide "real-world"data on the safety of the thiazolidinediones.[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.954#REF-JED05041-5) While some ofthese studies were more rigorous than others and several didnot specifically focus on the comparative safety of rosiglitazoneand pioglitazone, studies in which these drugs were comparedconsistently showed that rosiglitazone was associated with greaterrisk than pioglitazone, or at best, the risks associated withthese drugs were not statistically different.

In this issue of *JAMA,* Graham and colleagues[7](http://jama.ama-assn.org/cgi/content/full/jama.2010.954#REF-JED05041-7) report the resultsof a large cohort study examining the risk of cardiovascularevents in 227 571 patients 65 years or older who were treatedwith rosiglitazone or pioglitazone. The authors found that,compared with pioglitazone, rosiglitazone was associated withan increased risk of adverse cardiovascular events, includingheart failure and death. While the overall findings are notnovel, this study is large, rigorously conducted, and exceptionallytimely.

The report by Graham et al[7](http://jama.ama-assn.org/cgi/content/full/jama.2010.954#REF-JED05041-7) has limitations, as the authorsnote. Like all observational studies, because treatment assignment(in this instance, rosiglitazone or pioglitazone) was not randomized,the findings may reflect unrecognized biases or confounding—potentialthreats to validity that can be reliably mitigated only by randomization.However, a countervailing observation is that such studies can,when conducted carefully and with respect for their limitations,offer powerful insights into the real-world consequences ofdrug therapy. This is something conventional clinical trialscannot do.

With that background, several aspects of the report by Grahamet al merit emphasis. First, the results are supported by acertain measure of biological plausibility. Compared with pioglitazone,rosiglitazone exhibits less favorable effects on blood lipidlevels[8](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-8) and is also a more potent PPAR- agonist[9](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-9); consequently,the notion that rosiglitazone might impart a greater risk ofadverse events than pioglitazone is not far-fetched.

Second, the findings of an increased risk of heart failure anddeath among patients treated with rosiglitazone are consistentwith similar studies from other populations.[10](http://jama.ama-assn.org/cgi/content/full/jama.2010.954#REF-JED05041-10)-[11](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-11) Although someobservational studies have found no difference between the 2drugs, no study to date has suggested that rosiglitazone mightactually be safer than pioglitazone.

Third, rosiglitazone and pioglitazone did not differ with respectto risk of myocardial infarction, another observation made previously.[10](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-10)-[12](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-12) The significance of this seemingly unexpected findingis easy to miss. If patients treated with rosiglitazone weresystematically "sicker" than those treated with pioglitazone(the description of patients suggests otherwise), recipientsof poorer care, or destined for some other reason to have worseoutcomes than those treated with pioglitazone, they also shouldhave had an increased risk of myocardial infarction. However,that they did not (adjusted hazard ratio, 1.06 [95% confidenceinterval, 0.95-1.17]) provides considerable reassurance regardingconcerns of bias and confounding for the study en bloc. To beclear, this finding should not be construed to mean that rosiglitazonedoes not increase the risk of myocardial infarction—onlythat it is associated with no greater risk than pioglitazone.

Meta-analyses and observational studies are rarely definitive.Clinical trials sometimes are, but the only major trial examining"hard" outcomes with rosiglitazone failed to show a benefitover conventional treatment,[13](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-13) whereas the major trial of pioglitazoneshowed benefit only in a secondary analysis.[14](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-14) In an effortto definitively address some of the uncertainties surroundingthe safety of these thiazolidinediones, the US Food and DrugAdministration (FDA) compelled GlaxoSmithKline (GSK), the manufacturerof rosiglitazone (Avandia), to undertake a large, multicentercontrolled clinical trial. The Thiazolidinedione InterventionWith Vitamin D Evaluation (TIDE) trial commenced in May 2009,with an anticipated enrollment of 16 000 patients and completiontargeted for 2015. A major objective of this trial is to comparerosiglitazone and pioglitazone with regard to cardiovasculardeath, myocardial infarction, or stroke. The trial has beencriticized by some who perceive it to lack equipoise and viewit largely as a test of the dangers of one drug over another.[15](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-15)-[16](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-16) Moreover, negative media accounts regarding rosiglitazoneseem to have hampered recruitment.[17](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-17) The number of investigationalsites has nearly tripled in the past 3 months, now standingat 247 sites, with the bulk of the expansion occurring in SouthAmerica, India, Pakistan, and Eastern Europe.[18](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-18) Nearly halfof participating sites are not yet recruiting patients, in someinstances because investigators are awaiting the result of animpending review of rosiglitazone's safety by a panel convenedby the FDA.

The report by Graham et al[7](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-7) will undoubtedly contribute to theFDA deliberations, which are likely to conclude with one oftwo possible courses of action concerning rosiglitazone. Oneoption is to recommend removal of rosiglitazone from the USmarket and the termination of the TIDE trial. Under this scenario,GSK loses, but clinicians and patients still have pioglitazoneas an option, and public safety is prioritized over the desirefor certainty about the safety of rosiglitazone relative topioglitazone. A second option is to do nothing for now otherthan await the results of the TIDE trial. If the FDA electsthis course of action, regulators around the world are likelyto follow their lead, and millions of patients will continueto receive rosiglitazone (assuming GSK continues to market thisdrug). Under this scenario, the desire for certainty trumpssafety, patients may lose, and an ethically questionable trialwill continue to seek participants who, it seems, may not fullyappreciate the potential risks of participation.

The epilogue of the rosiglitazone story has yet to be written,but a few observations can now be made with confidence. First,there is no direct evidence that rosiglitazone prevents vascularevents in patients with diabetes. Second, converging lines ofevidence suggest that rosiglitazone is less safe than pioglitazone,whereas no data suggest that the converse might be true. Third,because the evidence to date is not conclusive, differing viewshave emerged on how to proceed in the face of uncertainty. Aconsensus panel of the American Heart Association and the AmericanCollege of Cardiology Foundation has called for more controlledclinical trials,[5](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-5) whereas the American Diabetes Associationand its European counterpart have advised against the use ofrosiglitazone.[19](http://jama.ama-assn.org/cgi/content/full/jama.2010.954%22%20%5Cl%20%22REF-JED05041-19) The latter view incorporates a simple factthat has frequently gone overlooked: rosiglitazone confers notherapeutic advantage over pioglitazone. Whether rosiglitazoneand pioglitazone really do have different cardiovascular safetyprofiles is an intriguing question but one with a misplacedfocus. Accumulating concerns about rosiglitazone make it difficultto advance a cogent argument regarding why, exactly, a patientmight want to receive the drug or why a physician would chooseto prescribe it when there is an available and quite possiblysafer alternative.

**AUTHOR INFORMATION**

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