

2. Horton JC, Chambers WA, Lyons SL, Adams RD, Kjellberg RN. Pregnancy and the risk of hemorrhage from cerebral arteriovenous malformations. *Neurosurgery* 1990;27:867-71.

THE AUTHOR REPLIES: Horton correctly points to the conclusion from a study he coauthored stating that there is no apparent increase in the rate of hemorrhage of unruptured arteriovenous malformations during pregnancy. There is significant controversy among clinicians who manage arteriovenous malformations in pregnant patients, and it is for this reason that I placed this discussion in the Areas of Uncertainty section of my article. As stated in the last American Heart Association Scientific Statement on the manage-

ment of brain arteriovenous malformations, "The data regarding AVM [arteriovenous malformation] hemorrhage risk during pregnancy are inconclusive."¹ Notwithstanding the controversy, I regret any confusion regarding the reference to the article by Horton et al.

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1. Ogilvy CS, Stieg PE, Awad I, et al. AHA scientific statement: recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. *Stroke* 2001;32:1458-71.

Rosiglitazone and the FDA

TO THE EDITOR: In his Perspective article (Aug. 30 issue),¹ Dr. Rosen discusses the recent Food and Drug Administration (FDA) advisory committee meeting on rosiglitazone. He also calls for approval of antidiabetic drugs based on long-term clinical outcomes, not on the surrogate of glycated hemoglobin, a measure of glycemic control. Although he does not describe a specific study, we assume he is suggesting that approval should require evidence that cardiovascular events, a major long-term complication of diabetes mellitus, are reduced. This change could have major implications for the availability of treatments for type 2 diabetes.

All drugs currently approved for the treatment of diabetes are indicated to improve glycemic control. Reductions in glycated hemoglobin levels directly reflect improved glycemic control, leading to a lessening of hyperglycemic symptoms, including polydipsia, polyuria, and blurred vision. In this respect, the FDA views a reduction in the level of glycated hemoglobin as a well-validated surrogate for a beneficial effect on the immediate clinical consequences of diabetes.

There are reasonably strong data supporting a reduced risk of microvascular complications with improved long-term glycemic control,^{2,3} although not for most individual drugs, and no drug carries a claim for such an effect. Clear evidence of a reduced risk of macrovascular complications in type 2 diabetes associated with any antidiabetic

agent has yet to be established.⁴ Because patients with type 2 diabetes have progressive worsening of glycemic control over time, long-term trials will probably need to compare one drug within a multidrug regimen with other available therapies, making demonstration of the effect of any single drug a formidable task.

A proposal to base future approvals on evidence of long-term cardiovascular benefit would significantly delay the availability of new drugs for the treatment of diabetes and might make development of new drugs impossible. One would also need to question why existing therapies, all lacking such evidence of benefit, should persist. This concern does not minimize the importance of determining whether the treatment of diabetes with antidiabetic drugs reduces long-term cardiovascular complications. Such an effect is, after all, one of the major intents of the treatment of diabetes.

A separate issue raised in the case of rosiglitazone, but one that is not limited to treatments for diabetes, is whether a drug might have adverse cardiovascular effects. For rosiglitazone, the recommendations of the advisory committee are currently under consideration by the FDA. The FDA considers cardiovascular safety matters during premarketing review and postmarketing activities, particularly when there is a safety signal that raises a concern. For this very reason, we recently requested a phase 3 clinical outcome trial of an investigational antidiabetic drug on the basis of

safety concerns noted in preclinical and phase 2 studies, despite evidence of an effect on glycemic control.

We agree that a better understanding of the cardiovascular benefits and risks of antidiabetic drugs is needed. For new antidiabetic drugs, a reasonable approach might be to approve new entities on the basis of improved glycemic control and to ensure that well-designed, long-term studies comparing the new treatment with established therapy, with cardiovascular outcomes as end points of interest, are conducted in a timely manner after approval. This approach merits further discussion.

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1. Rosen CJ. The rosiglitazone story — lessons from an FDA advisory committee meeting. *N Engl J Med* 2007;357:844-6.
2. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53. [Erratum, *Lancet* 1999;354:602.]
4. *Idem*. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65. [Erratum, *Lancet* 1998;352:1558.]

This letter (10.1056/NEJMc076347) was published at www.nejm.org on August 29, 2007.

TO THE EDITOR: I believe that the Perspective article by Dr. Rosen about the July 30 committee meeting to advise the FDA on myocardial ischemic events during treatment with rosiglitazone leaves readers with a misconception about the committee's advice. Dr. Rosen states that the committee concluded that rosiglitazone "was associated with a greater risk of myocardial ischemic events than placebo, metformin, or sulfonylurea." Although the advisory committee voted 20 to 3 that rosiglitazone increases cardiac risk in patients with type 2 diabetes, many members of the committee made statements accompanying their votes

that drew a distinction between the risk as compared with placebo and the risk as compared with other antidiabetic drugs.

The committee did not draw conclusions about rosiglitazone as compared with other available therapies, as shown in the committee's summary minutes.¹ The FDA's meta-analysis, which included the same 42 trials assessed in the meta-analysis submitted by GlaxoSmithKline, found an overall increased risk of myocardial ischemic events with rosiglitazone, with a hazard ratio of 1.4 (95% confidence interval [CI], 1.1 to 1.8). Further analyses presented by the FDA statistician showed that the increased risk of myocardial ischemic events with rosiglitazone was observed only in placebo-controlled studies; in active-controlled studies, the FDA's analysis showed no excess risk with rosiglitazone as compared with metformin or sulfonylureas (odds ratio, 1.0; 95% CI, 0.5 to 2.0).² Two epidemiology studies presented by GlaxoSmithKline showed that rates of myocardial infarction associated with rosiglitazone fell between the rates associated with metformin and sulfonylureas and that there was no statistically significant difference among the three treatments. In the second epidemiology study (performed on the PharMetrics database), there was no significant difference between rosiglitazone and pioglitazone (hazard ratio, 1.07; 95% CI, 0.89 to 1.27).

After carefully considering the evidence, the committee recommended by a vote of 22 to 1 that rosiglitazone should remain available to physicians and patients and that, as Dr. Rosen points out, physicians and patients should be educated and there should be additions to the label. GlaxoSmithKline has embraced these recommendations and is actively discussing with the FDA additional language for the label along with educational efforts to clarify the potential for myocardial ischemic events.

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1. Food and Drug Administration. Summary minutes of the joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on July 30, 2007. (Accessed October 4, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4308m1-final.pdf>)
2. Mele J. Avandia: FDA meta-analysis. Presented at the joint meeting of the Metabolic & Endocrine Advisory Committee and

the Drug Safety & Risk Management Advisory Committee held on July 30, 2007. (Accessed October 4, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-05-fda-mele.ppt>.)

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THE AUTHOR REPLIES: My intention in my Perspective article was to provide an individual account of an extraordinary FDA advisory committee meeting. As such, those reflections represent my own view, rather than that of the entire committee. In that spirit, the article was designed to illustrate some of the broader issues faced by committee members in respect to drug approval, with a particular emphasis on the approval of drugs used to treat type 2 diabetes.

With respect to the letter from the FDA: I agree and have noted previously that it has yet to be demonstrated that any antidiabetic agent reduces macrovascular risk¹; furthermore, Joffe and colleagues are correct in stating that establishing the efficacy of any single drug for the treatment of type 2 diabetes by long-term comparison with multiple drugs is a formidable task. I disagree that this would delay the availability of new drugs for the treatment of type 2 diabetes. In fact, as noted in my article, larger phase 3 outcome trials for safety are critical before approval. I applaud the FDA for doing just that, as noted in their letter, for a new antidiabetic drug that showed evidence of efficacy but was associated with safety concerns. We differ only in determining when these studies should be conducted.

In response to Krall: as stated in the public record,² the committee voted 20 to 3 that the use of rosiglitazone increased the risk of cardiac ischemic events. What is missing from the end of that voting statement, however, is the question, As compared with what? The meta-analyses of 42 studies, reported by three independent groups, pooled the comparator drugs, including metformin, sulfonylureas, and placebo, and ended up with almost identical results: a 40% increase in the risk of cardiac ischemic events.³ In the overall analyses, there was no interactive effect on ischemic risk for the comparators; however, when a subgroup analysis was performed for trials comparing rosiglitazone with metformin only or with sulfonylureas only, there was no increased risk, although estimates were more imprecise than those from the overall analysis because of the

paucity of events and head-to-head trials. Nevertheless, as Krall notes, minutes from the hearing accurately reflect the concerns of several committee members as well as the complex deliberations that occurred during the meeting with respect to defining the ischemic risk associated with rosiglitazone as compared with the risk associated with the currently available active drug comparators.² Krall notes but does not elaborate on the greater ischemic risk consistently reported when the analyses were confined to trials comparing rosiglitazone with placebo only. Finally, Krall reports that epidemiologic studies found no statistical differences in the rates of myocardial infarction for rosiglitazone as compared with those for metformin or sulfonylureas; however, observational studies, whether from independent sources or from pharmaceutical sponsors, have notable limitations, particularly in terms of adjudication, when reporting very common events (e.g., angina) in large cohorts.

Finally, in relation to safety issues, I believe that the process of reporting adverse events needs improvement. It is critically important that future outcome trials for diabetes drugs be designed so that specific adverse events (e.g., angina) can be more carefully reported and can be evaluated in a comprehensive fashion, with full adjudication. This will require more work at individual investigative sites. It will also require a totally independent data and safety monitoring board so that when approval of a specific drug is requested, those safety issues will be easier to define.

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1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65. [Erratum, *Lancet* 1998;352:1558.]

2. Food and Drug Administration. Summary minutes of the joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on July 30, 2007. (Accessed October 4, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4308m1-final.pdf>.)

3. Mele J. Avandia: FDA meta-analysis. Presented at the joint meeting of the Metabolic & Endocrine Advisory Committee and the Drug Safety & Risk Management Advisory Committee held on July 30, 2007. (Accessed October 4, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-05-fda-mele.ppt>.)

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