A Perspective on the American Heart Association/American College of Cardiology Science Advisory on Thiazolidinedione Drugs and Cardiovascular Risks

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Controversies are rampant surrounding topics that affect the care of patients with diabetes. With 3 recent trials that failed to find a benefit in reducing glycated hemoglobin levels below 7 mg/dL, the assumption about lower being better is now in question, at least at stringent targets.1–3 While this issue is being debated, a related controversy that is also the subject of a recent American Heart Association/American College of Cardiology Foundation Science Advisory4 addresses whether the choice of medication to control blood glucose levels has an adverse effect on patient cardiovascular risk: specifically, whether there is a relationship between thiazolidinedione drugs, including the type of thiazolidinedione drug, and cardiovascular risk. The verdict of the advisory is that there is inconclusive evidence for potential cardiovascular harm from rosiglitazone but not pioglitazone.

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Until recently, although diabetes medications were viewed as having some minor differences, no particular medication or combination of medications was considered superior. The focus was on the glycated hemoglobin level with regard to the medication strategy used. Quality measures echoed this focus, with no agnosticism about the choice of medications.

Peroxisome proliferator-activated receptors (PPAR) are nuclear transcription factors that mediate the expression of some genes. PPAR-γ agonists increase insulin sensitivity and are the mechanism by which thiazolidinedione drugs are thought to be effective. The first drug in the class, troglitazone (Rezulin, Warner-Lambert, New York, NY) was approved in early 1997 and was off the market by 2000 because of concerns about hepatotoxicity. The drug was approved, as were subsequent thiazolidinedione drugs, on the basis of its ability to reduce blood glucose levels. Rosiglitazone (Advandia, GlaxoSmithKline, Philadelphia, Pa) and pioglitazone (Actos, Takeda, Cambridge, Mass) were approved in 1999. Another drug, muraglitazar, which has both PPAR-α and PPAR-γ agonist effects, never received approval because of evidence of an increased risk of death and major cardiovascular events.5 Meanwhile, rosiglitazone and pioglitazone became quite popular.

The advisory is particularly welcome in light of the confusion engendered by the conflicting studies and the safety alert from the Food and Drug Administration6 that raises concerns about possible increased cardiovascular risks with thiazolidinedione drugs. The document clearly reveals the lack of definitive information about the comparative effectiveness of drugs intended to reduce risk in diabetes by improving glycemic control. It states explicitly that “there remains an inadequate foundation of randomized clinical trials to properly judge the safety or efficacy of either agent [rosiglitazone or pioglitazone] with respect to IHD [ischemic heart disease] events.”

How did we find ourselves in this predicament? A reliance on the surrogate end point of glycemic control has produced drugs in the pharmacy that are effective in lowering glucose levels. Millions of people take the drugs but remarkably, more than a decade after approval, the medical community is still uncertain about the effects on patient outcomes. Moreover, we lack strong comparative effectiveness studies that could provide the evidence we need to make the right choices for our patients.

With millions of patients treated, how is it possible to miss an important risk? Even with the trials, should such risks be evident? It is problematic that cardiovascular risk in these patients is difficult to detect because cardiovascular disease is common. If the drugs caused an uncommon adverse effect such as pulmonary fibrosis, detection would be easy. If they caused people to turn blue, we would immediately recognize the risk. However, an increase in the risk of a commonly occurring outcome actually obscures the problem. No physician is surprised to see a patient with diabetes suffer from a cardiovascular event. Even a doubling of that risk would be difficult to detect in clinical practice. Clinical trials that carefully collect adverse outcomes data are the best way to detect risk. High-quality observational data can be helpful. In any case, the risk will not be apparent to the casual observer.

We were fortunate that this issue was raised so that available evidence could be discussed. The ability to conduct a meta-analysis of the cardiovascular risk of rosiglitazone would not have been possible without litigation forcing the manufacturer to place its trial results in the public domain and an alert investigator who seized the opportunity to disseminate the information.7 We have seen other examples in which company data that are not in the public domain contain information about safety. Information relevant to patient safety8,9 must be available to the public.10

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The advisory also raises the issue of the level of evidence necessary to change practice. Should we change practice with the suggestion of risk in a drug class that has alternatives without an indication of harm? Do we require definitive proof of harm? Does the amount of evidence required become less for a medication that thus far lacks evidence for improving patient outcomes? It may be that efficacy claims require strong proof but safety alerts and warnings require lesser degrees of evidence—and the amount of evidence necessary is context-dependent. Moreover, in our evaluations of efficacy, we may favor specificity, whereas in evaluating safety, we may favor sensitivity. We are struggling with these issues as exemplified by the recent debates about cancer risk and ezetimibe.8,9

The advisory also comments on the association between thiazolidinedione drugs and heart failure. Interestingly, it conveys that there are some questions about the link based on the current evidence. Nevertheless, the advisory reiterates the warning on the drug label and makes clear that the drug is considered contraindicated for patients with New York Heart Association class III/IV heart failure. The evidence for heart failure risk, as summarized in an American Heart Association/American Diabetes Association scientific statement,11 seems as strong as the evidence addressing cardiovascular risk for rosiglitazone. The advisory, however, does not address the question of why these drugs would be used in patients with or at risk for heart failure, given the alternatives.

The advisory does contain several recommendations that speak to issues beyond the cardiovascular risk of thiazolidinedione drugs. It also addresses first-line agents, secondary agents, and target glycosylated hemoglobin levels.

On the basis of reviews of current data, the advisory finds evidence that metformin reduces cardiovascular risk compared with alternative strategies and endorses its use as a first-line agent. The evidence, however, is more than a decade old and is based on the experiences of participants in the United Kingdom Prospective Diabetes Study (UKPDS) who were newly diagnosed with diabetes. No particular evidence was found to suggest which should be second-line drugs, and the advisory states that their effect on cardiovascular risk is unknown.

The advisory is particularly concerning in its recommendation of a glycosylated hemoglobin level of <7%, which is at odds with the recent trials. Although it states that the recommendation is to achieve that level without causing hypoglycemia and that it may be more beneficial if accomplished early in the disease, the only 3 trials of this strategy failed to find a meaningful benefit, and 1 trial identified an increased risk of death. Admittedly, these trials were conducted in patients with long-standing diabetes, and it is unknown whether the findings would have been different in a population of newly diagnosed patients. Suffice it to say, this topic remains controversial and consensus is elusive.

Nevertheless, the article is extremely useful in consolidating the evidence and illuminating the remaining quantity of unanswered questions. Our current uncertainty is almost definitely costing lives and resources. Given the growing population of patients with diabetes and the consequences of the disease, an urgent need exists for additional studies to address the keys areas of uncertainty in treatment.

In the meantime, with the limited evidence available, the advisory states that there is inconclusive evidence that rosiglitazone, but not pioglitazone, increases cardiovascular risk. The constant challenge is determining how best to communicate this information to the public. Given the uncertainty, there is no compelling reason to alarm patients. They should, however, be informed that there may be differences in the risk profiles of the thiazolidinedione drugs. The information is laden with nuance and concise messages are difficult. Nevertheless, the message that emerges from this advisory is that given the choice of various thiazolidinedione drugs, it is hard to make a case for rosiglitazone. Thus, the simplest message might suggest the avoidance of rosiglitazone until more reassuring evidence for the drug becomes available.

Disclosures
Dr. Krumholz chairs a cardiac scientific advisory board for UnitedHealthcare.

References

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