Rosiglitazone, Medical Reversal, and Back to Basics for Diabetes

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Between 2007 and 2013, rosiglitazone (Avandia) was one of several highly publicized medical reversals of interventions thought to have done more harm than good.[1,2] In a prominent meta-analysis from 2007, data first suggested that the widely used diabetes mellitus medication increased the rate of myocardial infarction (odds ratio = 1.43; 95% confidence interval, 1.03 to 1.98; $P = .03$).[3] The conduct of the manufacturer in the wake of the evidence regarding rosiglitazone's putative harms became the subject of a Senate investigation, and the company was widely criticized for decisions made as it sought to protect the market share of a medication that earned $3 billion per year.[4,5]

Then, in 2013, the U.S. Food and Drug Administration (FDA) announced that it would lift restrictions on rosiglitazone after an independent committee conducted a new review and found no conclusive evidence of an increased risk of myocardial ischemia.[6] This review included readjudication of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) clinical trial.[6] Even this double reversal may not be the final word on the subject, however, as some have faulted the most recent decision.[7] Most importantly, no part of this debate changes the fact that rosiglitazone doubles the risk of heart failure leading to hospitalization and death, with no evidence for improved survival—hardly a ringing endorsement.[8]

Rosiglitazone has left a lasting legacy on the approval of diabetes medications. The drug's tumultuous history, in part, led to an FDA requirement that new diabetes drugs undergo testing to rule out excess cardiovascular events.[9] This rule prompted large trials of two other diabetes medications—the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin (Onglyza) and alogliptin (Nesina)—which found that, although both medications lower the A1C level, neither improves cardiovascular outcomes, undermining A1C as a surrogate end point for this purpose.[9] The history of diabetes studies over the past 10 years forces physicians to confront the reality that the best treatment for type 2 diabetes is not clear.

How should the findings of the past 10 years affect clinical care? For too long, the debate in diabetes has centered on the question: Is this medication harmful? It's time to revisit the more fundamental question: Is this treatment beneficial? Available data support use of the mainstays of therapy after lifestyle intervention (i.e., metformin [Glucophage], insulin, and sulfonylureas), and it is preferable for physicians to maximize the use of these agents, employing the newer A1C-lowering drugs as seldom as possible.

Metformin remains the cornerstone of care in the treatment of diabetes, based on the UKPDS (United Kingdom Prospective Diabetes study), which randomized patients with diabetes and obesity to treatment with metformin or one of three other therapies: chlorpropamide (Diabinese), glibenclamide (called glyburide in the United States), or insulin. Patients receiving metformin had a reduction in A1C levels and body weight, and improvement in all-cause mortality.[10] These results have been supported by another randomized trial.[11] In patients whose diabetes remains uncontrolled, insulin, sulfonylureas, or a combination may be added.

It should be noted that intensive targets (A1C level less than 7.0) have been linked to worse overall mortality.[12] Additionally, enthusiasm that strict glucose control improves microvascular end points (e.g., nephropathy, retinopathy, neuropathy) occurring in studies of younger patients (mean age = 53 years)[13] has been more tempered in studies of patients in their 60s. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which involved patients with a mean age of 61.5 years, found ▶

some benefit from intensive glycemic control, reducing albuminuria, the rate of cataract surgery, and some measures of neuropathy. However, no differences were noted in the primary and secondary composite outcome of aggregate microvascular complications, including no differences in renal failure, retinal photocoagulation or vitrectomy, visual acuity, and other measures of neuropathy.[14] These limited benefits do not outweigh the increase in all-cause mortality.

Beyond the choice of metformin, insulin, and sulfonylureas, an abundance of drugs that lower A1C levels are available, representing diverse classes. These include meglitinides, thiazolidinediones, DPP-4 inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide agonists, and amylin analogs. However, no evidence has shown improvement in macrovascular or microvascular outcomes for any of the newer agents. For this reason, once the decision has been made to commence insulin therapy, physicians may consider this an opportunity to minimize use of the newer oral agents, eliminating expensive drugs that lack evidence that they improve hard end points.

Approximately 14% of Americans have diabetes,[15] and this percentage is expected to increase in the coming decades. Despite thousands of studies, fundamental questions about the benefits of treating diabetes remain unanswered in randomized trials. This is a disservice to the millions of Americans with diabetes. The evidence base for diabetes care is particularly weak, even lagging behind lipid-lowering and antihypertensive drugs. Developing strict treatment recommendations and guidance is difficult, because there is considerable ambiguity in the trials we have. Calls for more randomized trials powered for hard end points are laudable and logical,[16] but for the time being we should remember that there is little evidence that the newer diabetes agents are better than the proven ones in regard to the outcomes that matter to patients and physicians.

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