Rosiglitazone and Cardiovascular Outcomes
Is There a Clear Answer?

Hertzel C. Gerstein, MD, MSc

Diabetes mellitus is a common chronic disease that is characterized and defined by an elevated glucose level and that has grown in prevalence by 75% in the United States during a 20-year period ending in 2010.1 The exact reason for this rising prevalence is not known with certainty; however, a large body of evidence implicates changes in weight, caloric consumption, reduced physical activity, and migration to urban versus rural dwellings. Regardless of the reasons for this growth, epidemiological studies and analyses of administrative databases have repeatedly shown that people with diabetes mellitus are 2 to 3 times more likely to experience fatal and nonfatal cardiovascular outcomes than people without diabetes mellitus.2 This high risk was the basis for the intentional inclusion of ambulatory adults with diabetes mellitus in a large number of recent cardiovascular outcomes trials that either recruited large subpopulations or people with diabetes mellitus or were wholly restricted to people with diabetes mellitus. These trials showed that therapies that were shown to be cardioprotective in people without diabetes mellitus will also reduce cardiovascular outcomes in ambulatory people with diabetes mellitus. These include blood pressure lowering,3 low-density lipoprotein lowering with statins,4 angiotensin-converting enzyme inhibitors5 or angiotensin receptor blockers,6 and bypass surgery.7 During the same period, other therapies were shown to have a neutral effect on cardiovascular outcomes in people with diabetes mellitus, including vitamin E,8 omega 3 fatty acids,9 and basal insulin.10

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Implementation of the results of these trials may account for the decline in absolute risk of cardiovascular outcomes and death in people with diabetes mellitus over time.11,12 However, both the inability of these trials to reduce this risk to levels seen in people without diabetes mellitus6 and the inability of traditional risk factors to completely explain the high cardiovascular risk associated with diabetes mellitus points to additional factors that are unique to people with diabetes mellitus. The many studies showing that different measures of glucose elevation above normal (including hemoglobin A1c levels and fasting, postload, and random glucose levels) independently predict incident cardiovascular outcomes strongly implicate an elevated glucose level or some factor tightly linked to an elevated glucose level.13 Moreover, a recent report showing that genetic variants that predict elevated random glucose levels also predict cardiovascular outcomes further highlights the importance of dysglycemia or genetically determined biological abnormalities closely linked to dysglycemia in the etiopathogenesis of cardiovascular outcomes.14 This has focused attention on the effect that glucose-lowering or glucose-lowering drugs that target glucometabolic abnormalities (eg, insulin resistance or β-cell dysfunction) might have on cardiovascular outcomes.

The cardiovascular effects of more versus less intense glucose lowering using a variety of therapies in people with type 2 diabetes mellitus have been formally assessed in 4 large randomized, controlled outcomes trials: 1 in people with newly diagnosed type 2 diabetes mellitus and 3 in people with established type 2 diabetes mellitus.15 Although none of these trials reported a clear effect on cardiovascular outcomes, a meta-analysis of their 5-year results identified a consistent but modest 9% relative reduction in cardiovascular outcomes, mainly because of a 15% relative reduction in total (fatal or nonfatal) myocardial infarctions.16 Combined with a concomitant clear reduction in eye or kidney disease in 3 of these trials, these findings also suggest a delay in any benefit of glucose lowering on cardiovascular disease (25 years) compared with small vessel disease. Notwithstanding the foregoing, an unexplained increase in cardiovascular mortality in one of these trials17 means that the clinical relevance of targeting normal versus modestly elevated glucose values remains unclear.

A much larger number of outcomes trials have assessed (or are currently assessing) the cardiovascular effects of drugs that lower glucose levels by targeting a variety of physiologic systems (Tables 1 and 2).10,16–20 The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial was one such large outcomes trial.7 Conducted in 2368 people with angiographically documented coronary artery disease, this trial allocated participants to 2 different glucose-lowering approaches, both targeting a hemoglobin A1c level <7%. The first approach started with drugs that lower glucose levels by increasing the effectiveness of secreted insulin. After 3 years, these included metformin (in 75%) and rosiglitazone (in 55%). The second approach used insulin (in 61%) or drugs such as sulfonylureas (52%) that increase insulin secretion. During a mean follow-up period of 5.3 years, participants allocated to these 2 approaches achieved mean hemoglobin A1c levels that differed by <0.5% and used a similar set of cardioprotective therapies. Most importantly, these 2 different approaches to glucose lowering had similar effects on the primary outcome of death and the secondary composite outcome of death, myocardial infarction, or stroke.
dosage. The results of the BARI 2D trial are of particular interest in light of a highly publicized debate regarding the cardiovascular safety of rosiglitazone and concerns that rosiglitazone may increase the risk of death and myocardial infarctions. These concerns were mainly based on meta-analyses of cardiovascular events collected in small noncardiovascular trials and on analyses of administrative databases. Nevertheless, they received much publicity and led the US Food and Drug Administration to restrict the drug’s availability and suspend its approval for a large ongoing cardiovascular outcomes trial pending further cardiovascular safety data.

The post hoc epidemiological analysis of the BARI 2D trial reported in this issue of the journal provides data that are pertinent to this issue. In this report, the investigators used 2 different approaches to assess the cardiovascular effects of rosiglitazone observed in the published epidemiological analyses. However, the fact that these data were collected for the specific purpose of assessing cardiovascular effects along with pertinent cardiovascular risk factors and cointerventions overcomes some of the limitations inherent in analyses of data within administrative databases that were collected for other reasons. Moreover, the fact that clinically important outcomes were prospectively collected and blindly adjudicated using predefined definitions and the fact that similar results were obtained using 2 different analytic approaches lend confidence to the findings. These results are also consistent with those from the prospective Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial, which showed that addition of rosiglitazone to either metformin or a sulfonylurea is noninferior to the use of metformin plus a sulfonylurea with respect to death and serious cardiovascular outcomes, and which recently underwent rigorous independent scrutiny, reanalysis, and confirmation. These data therefore provide no support for assertions that rosiglitazone increases deaths or ischemic cardiovascular outcomes and are most consistent with a position of clinical equipoise regarding the long-term effect of rosiglitazone on cardiovascular outcomes.

What are the implications of these new findings in light of the above? First, despite all that has been written about rosiglitazone, we still do not know its long-term effect on mortality or serious cardiovascular outcomes. Indeed, the fact that the cardiovascular safety of this drug was the subject of 2 separate US Food and Drug Administration Advisory Committee Meetings and that both committees expressed the need for more cardiovascular data highlights this point. Second, the meetings highlight the ongoing relevance of large, carefully designed randomized outcomes trials for clearly determining the long-term effects of drugs. There are many examples of drugs for which either harm or benefits were claimed based on epidemiological analyses or small trials done for other reasons that were subsequently shown to have different effects when tested within large outcomes trials.

### Table 1. Completed Large Outcomes Trials of Glucose-Lowering Drugs in Ambulatory Settings

<table>
<thead>
<tr>
<th>Class</th>
<th>Participants</th>
<th>Drugs</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin</td>
<td>Diabetes mellitus, IGT, and IFG</td>
<td>Glargine</td>
<td>12537</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>IGT</td>
<td>Nateglinide</td>
<td>9306</td>
</tr>
<tr>
<td>Prandial insulin</td>
<td>Diabetes mellitus</td>
<td>Lispro</td>
<td>1115</td>
</tr>
<tr>
<td>TZD</td>
<td>Diabetes mellitus</td>
<td>Pioglitazone</td>
<td>5238</td>
</tr>
<tr>
<td>TZD</td>
<td>Diabetes mellitus</td>
<td>Rosiglitazone</td>
<td>4447</td>
</tr>
<tr>
<td>2 drug strategies</td>
<td>Diabetes mellitus</td>
<td>Insulin-sensitizing and insulin-supplying drugs</td>
<td>2368</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Diabetes mellitus</td>
<td>Metformin</td>
<td>1704</td>
</tr>
</tbody>
</table>

TZD indicates thiazolidinedione.

### Table 2. Ongoing/Unreported Large Outcomes Trials of Glucose-Lowering Drugs in Ambulatory Settings

<table>
<thead>
<tr>
<th>Class</th>
<th>Participants</th>
<th>Drugs</th>
<th>Estimated n</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i</td>
<td>Diabetes mellitus</td>
<td>Saxagliptin, sitagliptin, alogliptin, linagliptin, and MK3102</td>
<td>50,000</td>
</tr>
<tr>
<td>GLP1a</td>
<td>Diabetes mellitus</td>
<td>Lixisenatide, lixadonetide, and exenatide (extended)</td>
<td>40,000</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>Diabetes mellitus</td>
<td>Canagliflozin, empagliflozin, and dapagliflozin</td>
<td>25,000</td>
</tr>
<tr>
<td>PPARα/γ</td>
<td>Diabetes mellitus and prediabetes</td>
<td>Aleglitazar</td>
<td>25,000</td>
</tr>
<tr>
<td>AGI</td>
<td>IGT</td>
<td>Acarbose</td>
<td>7500</td>
</tr>
<tr>
<td>TZD</td>
<td>Insulin resistance</td>
<td>Pioglitazone</td>
<td>4000</td>
</tr>
<tr>
<td>GPR40</td>
<td>Diabetes mellitus</td>
<td>Fasiglifam</td>
<td>5000</td>
</tr>
</tbody>
</table>

AGI indicates α-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1a, glucagon-like peptide 1 analogue; GPR40, G protein–coupled receptor 40; IGT, impaired glucose tolerance; PPARα/γ, peroxisome proliferator–activated receptor α-gamma; SGLT2i, sodium-glucose linked transporter 2 inhibitor; and TZD, thiazolidinedione.
subsequent discontinuation of a trial designed to clearly answer this question would mean that cardiovascular effects of both rosiglitazone and this class of drugs are likely to remain unknown.

The quest for metabolic drugs that reduce cardiovascular outcomes continues. With the possible exception of metformin, no such drug has clearly been identified. However, in response to the controversy that arose from rosiglitazone, a plethora of US Food and Drug Administration–mandated large cardiovascular outcomes trials are currently being conducted of promising new glucose-lowering drugs for people with diabetes mellitus (Table 2). This should minimize the possibility of premature claims of harms and allow the clear testing of safety and cardiovascular efficacy of glucose-lowering drugs.

Disclosures
Dr Gerstein was leading the trial mentioned in the editorial that was sponsored by GlaxoSmithKline (the manufacturer of rosiglitazone) and that was assessing the effect of thiazolidinediones on cardiovascular outcomes in people with diabetes mellitus. He has also received consulting fees from Sanofi-Aventis, Novo Nordisk, Lilly, Bristol-Myers-Squibb, Roche, AstraZeneca, Novartis, and GlaxoSmithKline; lecture fees from Sanofi-Aventis; and support for research or continuing education through his institution from Sanofi-Aventis, Lilly, Merck, Novo Nordisk, Boehringer Ingelheim, Bristol-Myers-Squibb, and AstraZeneca.

References

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