Rosiglitazone and Cardiovascular Outcomes:
Is There a Clear Answer?

Running title: Gerstein; Rosiglitazone & outcomes: Is there a clear answer?

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Journal Subject Codes: [190] Type 2 diabetes, [121] Primary prevention, [122] Secondary prevention

Key words: Dysglycemia, Editorial, diabetes mellitus, clinical trial, cardiovascular outcomes, drug trials
Diabetes 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\textsuperscript{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, epidemiologic studies and analyses of administrative databases have repeatedly shown that people with diabetes are 2-3 times more likely to experience fatal and nonfatal cardiovascular outcomes than people without diabetes\textsuperscript{2}. This high risk was the basis for the intentional inclusion of ambulatory adults with diabetes in a large number of recent cardiovascular outcomes trials that either recruited large subpopulations or people with diabetes or were wholly restricted to people with diabetes. These trials showed that therapies that were shown to be cardioprotective in people without diabetes will also reduce cardiovascular outcomes in ambulatory people with diabetes. These include blood pressure lowering\textsuperscript{3}, LDL lowering with statins\textsuperscript{4}, ACE inhibitors\textsuperscript{5} or angiotensin receptor blockers\textsuperscript{6} and bypass surgery\textsuperscript{7}. During the same period other therapies were shown to have a neutral effect on cardiovascular outcomes in people with diabetes including vitamin E\textsuperscript{8}, omega 3 fatty acids\textsuperscript{9}, and basal insulin\textsuperscript{10}.

Implementation of the results of these trials may account for the decline in absolute risk of cardiovascular outcomes and death in people with diabetes over time\textsuperscript{11,12}. However, both the inability of these trials to reduce this risk to levels seen in people without diabetes\textsuperscript{6} and the inability of traditional risk factors to completely explain the high cardiovascular risk associated with diabetes points to additional factors that are unique to people with diabetes. The many studies showing that different measures of glucose elevation above normal (including HbA1c levels, and fasting, post-load, 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\textsuperscript{2,13}. Moreover, a recent report showing that genetic variants that predict elevated random glucose levels also predict cardiovascular outcomes further highlights the importance of dysglycemia and/or genetically determined biologic abnormalities closely linked to dysglycemia in the etiopathogenesis of cardiovascular outcomes\textsuperscript{13}. This has focused attention on the effect that glucose-lowering and/or glucose-lowering drugs that target glucometabolic abnormalities (e.g. insulin resistance or beta 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 have been formally assessed in 4 large randomized controlled outcomes trials: 1 in people with newly diagnosed type 2 diabetes and 3 in people with established type 2 diabetes\textsuperscript{14}. Whereas 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 due to a 15\% relative reduction in total (fatal or nonfatal) myocardial infarctions\textsuperscript{14}. Combined with a concomitant clear reduction in eye and/or kidney disease in 3 of these trials, these findings also suggest a delay in any benefit of glucose lowering on cardiovascular disease (5 or more years) compared to small vessel disease. Notwithstanding the foregoing, an unexplained increase in cardiovascular mortality in one of these trials\textsuperscript{15} 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 (\textbf{Tables 1 and 2})\textsuperscript{10,16-20}. The BARI 2D trial was one such large outcomes trial\textsuperscript{7}. 
Conducted in 2368 people with angiographically documented coronary artery disease, this trial allocated participants to 2 different glucose lowering approaches, both targeting a HbA1c <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%) and/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 HbA1c levels that differed by less than 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.

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 Federal Drug Administration to restrict the drug’s availability and suspend its approval for a large ongoing cardiovascular outcomes trial pending further cardiovascular safety data21.

The post hoc epidemiologic analysis of the BARI 2D trial reported in this issue of the journal22 provides data that are pertinent to this issue. In this report the investigators used 2 different approaches to assess the cardiovascular effects of rosiglitazone during 3025 patient-years follow-up of participants exposed to rosiglitazone versus 7146 patient-years follow-up of participants with no thiazolidinedione exposure during the study. First, using regression models that adjusted for differences in baseline characteristics and use of other glucose-lowering drugs,
they observed that rosiglitazone was not associated with death (HR 0.83, 95% CI 0.58 - 1.18; P=0.29) and was associated with a reduced hazard of the composite cardiovascular outcome (HR 0.72, 95% CI 0.55 to 0.93, p=0.01). Second, using a propensity-matched approach that compared incident cardiovascular outcomes in participants taking rosiglitazone during the first 6 months of the trial to participants on no thiazolidinedione during that time but who were estimated to have the same propensity for being prescribed rosiglitazone, no differences in any cardiovascular outcome was observed. Both approaches reported nonsignificant increases in incident heart failure and significant increases in fractures with rosiglitazone.

As this is an epidemiologic analysis of data collected within a randomized controlled trial, it provides a lower level of evidence than could be provided by a carefully done prospective randomized controlled trial. Indeed, like all epidemiologic analyses it cannot definitively separate the effect of the drug from the reasons that the drug was prescribed and may therefore provide a biased estimate of the drug’s effect on cardiovascular outcomes. Indeed, the confounding that is inherent in all such analyses is the likeliest explanation for discordant cardiovascular effects of rosiglitazone observed in the published epidemiologic analyses. However, the fact that these data were collected for the specific purpose of assessing cardiovascular effects along with pertinent cardiovascular risk factors and co-interventions 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 RECORD cardiovascular outcomes 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\textsuperscript{19}, and which recently underwent rigorous independent scrutiny, reanalysis and confirmation\textsuperscript{21}. 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 its long-term effect 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 FDA Advisory Committee Meetings and that both committees expressed the need for more cardiovascular data highlights this point. Second, they 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 epidemiologic analyses or small trials done for other reasons which were subsequently shown to have different effects when tested within large outcomes trials\textsuperscript{23}. The unfortunate withdrawal of regulatory approval and subsequent discontinuation of a trial designed to clearly answer this question\textsuperscript{24} means 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 FDA-mandated large cardiovascular outcomes trials are currently being conducted of promising new glucose-lowering drugs for people with diabetes (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.
Conflict of Interest 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. 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.

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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&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Diabetes, IGT, IFG</td>
<td>Glargine</td>
<td>12537</td>
</tr>
<tr>
<td>Meglitinide&lt;sup&gt;16&lt;/sup&gt;</td>
<td>IGT</td>
<td>Nateglinide</td>
<td>9306</td>
</tr>
<tr>
<td>Prandial Insulin&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Diabetes</td>
<td>Lispro</td>
<td>1115</td>
</tr>
<tr>
<td>TZD&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Diabetes</td>
<td>Pioglitazone</td>
<td>5238</td>
</tr>
<tr>
<td>TZD&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Diabetes</td>
<td>Rosiglitazone</td>
<td>4447</td>
</tr>
<tr>
<td>2 Drug Strategies&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Diabetes</td>
<td>Insulin sensitizing &amp; Insulin Supplying Drugs</td>
<td>2368</td>
</tr>
<tr>
<td>Biguanide&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Diabetes</td>
<td>Metformin</td>
<td>1704</td>
</tr>
</tbody>
</table>

TZD – thiazolidinedione; IGT – impaired glucose tolerance; IFG – impaired fasting glucose;

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</td>
<td>saxagliptin, sitagliptin, alogliptin, linagliptin, MK3102</td>
<td>50,000</td>
</tr>
<tr>
<td>GLP1a</td>
<td>Diabetes</td>
<td>lixisenatide, liraglutide, exenatide (extended), dulaglutide, semaglutide</td>
<td>40,000</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>Diabetes</td>
<td>canagliflozin, empagliflozin, dapagliflozin</td>
<td>25,000</td>
</tr>
<tr>
<td>PPARαγ</td>
<td>Diabetes, Prediabetes</td>
<td>aleglitazar</td>
<td>25,000</td>
</tr>
<tr>
<td>AGI</td>
<td>IGT</td>
<td>acarbose</td>
<td>7,500</td>
</tr>
<tr>
<td>TZD</td>
<td>Insulin Resistance</td>
<td>pioglitazone</td>
<td>4,000</td>
</tr>
<tr>
<td>GPR40</td>
<td>Diabetes</td>
<td>fasiglifam</td>
<td>5,000</td>
</tr>
</tbody>
</table>

DPP4i – dipeptidyl peptidase-4 inhibitors; GLP1a – glucagon-like peptide 1 analogue; SGLT2i – sodium-glucose linked transporter 2 inhibitor; PPARαγ - peroxisome proliferator activated receptor alpha-gamma; AGI – alpha glucosidase inhibitor; TZD – thiazolidinedione; GPR40 – G protein-coupled receptor 40; IGT – impaired glucose tolerance
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Circulation. published online July 15, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
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