After the fall of the Roman Empire, the developed world entered centuries of intellectual darkness marked by minimal scientific progress, a period often called the “Dark Ages.” After many centuries, progress resumed and eventually accelerated during the Renaissance. In a similar fashion, knowledge about the comparative effectiveness of drugs to treat type 2 diabetes is finally beginning to emerge from 40 years of stagnation. This period of darkness and the current reawakening provide critically important lessons for contemporary medicine about the use of surrogate endpoints in drug development, regulatory oversight, and the hazards associated with reliance on commercial funding for pivotal clinical trials.

The diabetes Dark Ages began in 1961 with the initiation of one of the first major randomized, controlled trials (RCTs) in modern medicine, the UGDP (University Group Diabetes Project) study. The design of this study was complex, with patients randomly assigned to 5 treatment groups: variable-dose insulin, fixed-dose insulin, tolbutamide, phenformin, or diet alone. In 1970, the tolbutamide group discontinued therapy because of an increase in all-cause and cardiovascular (CV) mortality compared with the other treatment groups (1). The makers of tolbutamide launched an aggressive campaign to discredit the UGDP study findings by using leading and well-remunerated academics (2). As Schwartz and Meinert (2) described in 2004, “The arguments became increasing ad hominem, eventually challenging the honesty of the UGDP investigators.”

The reaction of the broader pharmaceutical industry to the concern about the CV effects of sulfonylureas was decisive and sustained. For the next 40 years, industry simply stopped performing RCTs comparing CV outcomes for alternative diabetes treatment strategies. In 2007, a systematic review catalogued this unfortunate state of affairs, describing the evidence for comparative effectiveness for CV outcomes with diabetes drugs as “low to very low” (3). An anachronistic regulatory policy requiring only that new diabetes drugs show that they lower blood glucose levels without obvious safety problems, not that they improve clinical outcomes, allowed industry to avoid performing studies on CV outcomes. Thoughtful academics have criticized the reliance on biochemical measures as a surrogate for clinical benefit, because numerous surrogates have failed to show a consistent link with actual clinical outcomes (4). However, regulatory policy for diabetes drug development remained essentially static for 50 years.

A series of traumatic shock waves ultimately was required to shake the complacency of the diabetes community and the regulators. The first of these shocks occurred in 2005 after an advisory panel of the U.S. Food and Drug Administration (FDA) recommended approval of muraglitazar, the first dual (α and γ) peroxisome proliferator–activated receptor modulator to reach an advanced stage of development. The biochemical effects of muraglitazar, including robust reduction in hemoglobin A1c levels, marked increases in high-density lipoprotein cholesterol levels, and substantial decreases in triglyceride levels, were impressive. However, immediately after the panel recommendation, my colleagues and I used the FDA briefing documents to reanalyze the CV outcomes data from the muraglitazar development program and found a doubling of major CV morbidity and mortality (5). The FDA quickly reassessed the drug and declined approval. The makers of the drug soon terminated the development program. Nonetheless, a risky drug came very close to regulatory approval.

The second shock wave occurred in 2007 when my colleagues and I published a meta-analysis of CV outcomes with rosiglitazone based on study-level data that became available after a court settlement required the drug maker to disclose all clinical trial results (6). Thirty-five of the 42 clinical trials used in the analysis were unpublished. The study calculated an estimated 43% increase in the risk for myocardial infarction for rosiglitazone compared with other diabetes drugs or placebo.

The meta-analysis initially met with much controversy (7), but the FDA eventually confirmed the findings by using patient-level data. A Senate investigation later revealed that the company had completed its own internal analysis 2 years before our publication, confirming a significantly increased risk for myocardial infarction (8). By 2010, the evidence for harm was so overwhelming that European authorities forced the company to withdraw rosiglitazone from the market and the FDA restricted its use to patients whose disease was refractory to all other therapies. In 2012, the drug maker paid a record $3 billion fine for civil and criminal penalties, related in part to concealing safety data for rosiglitazone.

The third shock wave occurred in 2008, when the National Institutes of Health terminated a trial designed to compare more-intensive with less-intensive glucose lowering after observing an increase in CV mortality in the more aggressively treated group (9).

These 3 successive shocks finally forced the FDA to reconsider its decades-old policy of approving diabetes drugs primarily on the basis of glucose-lowering effects. An advisory panel, convened in 2008, endorsed an approach recommendation that I presented with support from Dr. Thomas Fleming requiring a 2-stage approval process for diabetes drugs.

In the first step, a CV outcomes trial must rule out an upper 95% CI for a hazard ratio of 1.8 for CV events,
followed by a postapproval study to rule out an upper CI of 1.3 (10). Some critics predicted that this policy would halt the development of diabetes drugs, but it has actually done the opposite. Dozens of new diabetes drugs are now in development with ongoing CV outcomes trials under way. The 40-year veil of darkness has finally begun to lift after this pivotal policy shift.

In this historical context, Roumie and colleagues’ article (11) in this issue renews an old controversy. The findings of the UGDP trial were never refuted by a modern RCT. Instead, we have a series of post hoc analyses of studies never designed to resolve the CV safety concern about sulfonylureas. Some but not all of these studies suggested that sulfonylureas were similar to other diabetes drugs in their effects on CV outcomes.

Because sulfonylureas and metformin were approved during the legacy era in which CV outcomes trials were not required, the new FDA diabetes guidance is not applicable. Accordingly, no financial incentives exist for industry to perform comparative effectiveness trials evaluating these 2 commonly used therapies. We must therefore use observational studies to answer a scientific question first asked in 1961: Do sulfonylureas increase adverse CV events?

Roumie and colleagues’ study (11) is a laudable effort, and the findings have implications for millions of patients worldwide. The authors used many of the best methods available to analyze observational data, including careful adjustment for known confounders, propensity matching, and multiple sensitivity analyses. Despite the recognized limitations of observational studies, the findings are credible and important. Sulfonylureas seem inferior to metformin with respect to CV outcomes. However, in the absence of a modern RCT confirming the findings, we must view these data as hypothesis-generating rather than definitive. As such, the UGDP controversy remains unresolved 51 years after the study was initiated.

How might sulfonylureas increase adverse CV outcomes? One theory focuses on their adverse effects on ischemic preconditioning, an adaptive mechanism that allows the myocardium to resist necrosis after intermittent periods of ischemia (12). Another hypothesis relates to sulfonylurea-induced hypoglycemia, which theoretically may result in myocardial ischemia. Regardless of mechanism, this scientific question demands a definitive answer. In the absence of an industry-sponsored study, public health authorities should conduct such a clinical trial. With more than two thirds of diabetic patients dying of CV causes and millions of patients currently receiving sulfonylureas, this question must be resolved with high-quality evidence. Continued darkness is not an acceptable option.

Steven E. Nissen, MD
Cleveland Clinic
Cleveland, OH 44195

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-2295.

Requests for Single Reprints: Steven E. Nissen, MD, Department of Cardiology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail, nissens@ccf.org.


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