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fter the fall of the Roman Empire, the developed
doctor entered centuries of intellectual darkness
marked by minimal scientific progress, a period often
called the “Dark Ages.” After many centuries, progress re-
sumed and eventually accelerated during the Renaissance.
In a similar fashion, knowledge about the comparative ef-
fectiveness of drugs to treat type 2 diabetes is finally begin-
ing to emerge from 40 years of stagnation. This period of
darkness and the current reawakening provide critically im-
portant lessons for contemporary medicine about the use
of surrogate end points in drug development, regulatory
oversight, and the hazards associated with reliance on com-
mercial funding for pivotal clinical trials.

The diabetes Dark Ages began in 1961 with the initi-
ation 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 treat-
ment groups: variable-dose insulin, fixed-dose insulin, tol-
butamide, phenformin, or diet alone. In 1970, the tolbu-
tamide group discontinued therapy because of an increase
in all-cause and cardiovascular (CV) mortality compared with
the other treatment groups (1). The makers of tol-
butamide 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 sim-
ply stopped performing RCTs comparing CV outcomes
for alternative diabetes treatment strategies. In 2007, a sys-
tematic 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 anarchistic 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 crit-
icized the reliance on biochemical measures as a surrogate
for clinical benefit, because numerous surrogates have failed
to show a consistent link with actual clinical out-
comes (4). However, regulatory policy for diabetes drug
development remained essentially static for 50 years.

A series of traumatic shock waves ultimately was re-
quired to shake the complacency of the diabetes com-
munity 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 muragli-
tazar, the first dual (α and γ) peroxisome proliferator–
activated receptor modulator to reach an advanced stage of
development. The biochemical effects of muraglitazar, in-
cluding 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 de-
velopment 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 re-
vealed that the company had completed its own internal
analysis 2 years before our publication, confirming a sig-
nificantly 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 con-
cealing 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 lower-
ing 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 two 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 sulfonyl-ureas, this question must be resolved with high-quality evidence. Continued darkness is not an acceptable option.

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

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