Glucose control is a key aspect of diabetes management. After concerns about the cardiovascular safety of several classes of antihyperglycemic agents, culminating with concerns about thiazolidinediones, the US Food and Drug Administration implemented a guidance statement in 2008 (strongly) recommending the demonstration of cardiovascular safety of new antihyperglycemic medications. Practically, these must be tested prospectively in randomized, controlled trials to “definitively show that the upper bound of the two-sided 95% confidence interval for the estimated risk ratio for important cardiovascular events is less than 1.3,” meaning that their use does not result in a >30% increase in the risk of major cardiovascular events. The European Medicines Agency next issued similar, although less-stringent, requirements. There was an ensuing flurry of cardiovascular safety trials for all new antihyperglycemic agents. These trials typically compared the new agent with a control group using a matching placebo, with glucose control intended to be managed the same in both arms with other class(es) of antihyperglycemic medications. Therefore, these really are, in fact, placebo-controlled, noninferiority trials using a margin of 1.3. If noninferiority is achieved, one can claim to have established cardiovascular safety in the sense implied by regulators, which can be reformulated as the strange concept of demonstration of noninferiority to placebo.

There are some important benefits to these cardiovascular safety trials. It is always valuable to gather data on the safety and efficacy of drugs such as antihyperglycemic medications, which are used in large numbers of patients, often indefinitely. Indeed, these trials have uncovered unanticipated signals of cardiovascular harm (such as an increase in the risk of heart failure with some but not all dipeptidyl peptidase 4 inhibitors) or benefit (such as the marked but yet not fully understood cardiovascular benefit of empagliflozin in the EMPA-REG OUTCOME trial [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients]), although other signals of benefit or harm (such as the identification of harm with the peroxisome proliferator-activated receptor α/γ agonist aleglitazar or the benefits of pioglitazone after stroke) were derived from trials done outside the scope of the guidance. Additionally, top-line results of the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) with liraglutide and the SUSTAIN 6 trial (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) with semaglutide suggest cardiovascular benefits.

However, implementation of the US Food and Drug Administration and European Medicines Agency guidance for the cardiovascular safety trials of antihyperglycemic agents is not without problems. For one, it is unclear the extent to which the trials are relevant to the population concerned. The concerns about cardiovascular safety pertain to the hundreds of millions of patients with type 2 diabetes mellitus without established cardiovascular disease who are exposed for many years to treatment with new glucose-lowering agents. However, the trials have generally aimed to enroll patients at very high cardiovascular risk (typi-
cally acute myocardial infarction survivors or patients with established cardiovascular disease) to accrue a sufficient number of events within a short time horizon. In addition, the typical population of these trials has long-standing diabetes mellitus, often for >10 years. The pathophysiology of recurrent cardiovascular events in these survivors of myocardial infarction with long-standing diabetes mellitus treated for a few months may be very different from that of inaugural events in patients with recently diagnosed diabetes mellitus without overt cardiovascular disease treated for many years. Soon after myocardial infarction, thrombosis, particularly stent thrombosis, plays a relatively greater role in the genesis of cardiovascular events than does atherosclerotic disease progression, whereas the converse is true in patients without established cardiovascular disease.

A second issue is cost. It is estimated that >150,000 patients have been enrolled worldwide in completed or ongoing cardiovascular safety randomized trials. Is this the best use of resources, given the enormous cost of these trials? Could the funds be directed to better use in the discovery of novel therapeutic approaches for diabetes mellitus? Prospective, randomized, clinical trials are the most rigorous method for assessing the efficacy and safety of new therapies. However, alternative study designs using careful observational studies that can accrue important information in more relevant patient populations at a minimal fraction of the cost of randomized trials may provide better value. The increasing ability to tap into very large and representative patient databases from large healthcare organizations (sometimes from entire countries) must affect our perspective of the comparison of observational versus randomized studies.

A third issue is perception. Given the neutral effects on cardiovascular outcomes observed in most trials, which indeed demonstrate cardiovascular noninferiority of novel (and generally costly) drugs compared with placebo, these trials are often misinterpreted as demonstrating lack of efficacy or lack of benefit and generate skepticism about the value of glucose control in diabetes mellitus. This is truly a misinterpretation. The trials were not intended to test the previously established efficacy of antihyperglycemic agents but rather their cardiovascular safety. Observing a lack of benefit on cardiovascular outcomes does not diminish the

Figure. Relation between the differential glycemic exposure between study arms and the hazard ratio for major adverse cardiac events (MACEs; or, when not available, for myocardial infarction) in trials evaluating either intensive vs conventional glucose control or a glucose-lowering agent vs placebo.

Differential glycemic exposure was approximated by multiplying median hemoglobin A1c difference over the study by median length of follow-up or by graphical approximation when required. The line represents the linear fit of the data ($y=-0.013x+0.969; R^2=0.33$). Differential glycemic exposure was minor for most (ELIXA [Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide)], SAVOR [Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications]), TECOS [Sitagliptin Cardiovascular Outcomes Study (MK-0431-082)], EXAMINE [Examination of Cardiovascular Outcomes: Alogliptin vs. Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome]) but not all (EMPA-REG [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients]) of the cardiovascular safety trials and may contribute to cardiovascular protection. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ORIGIN, Outcome Reduction With Initial Glargine Intervention; PRO-ACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events; UKPDS, United Kingdom Prospective Diabetes Study; and VADT, Veterans Affairs Diabetes Trial.
established antihyperglycemic efficacy, just as establishing cardiovascular safety of anticancer drugs does not speak to their efficacy on cancer. Although we remember vividly, as medical students, that diabetes wards in which patients with advanced diabetes mellitus, blindness, and terminal kidney failure requiring dialysis were common, younger physicians may not be as aware of the major benefits of glucose control in the prevention of the microvascular complications of diabetes mellitus\(^5\) and can be legitimately puzzled by the failure of randomized trials testing intensive versus less intensive glucose control in type 2 diabetes mellitus to demonstrate benefits on macrovascular complications.\(^6\) However, glucose control remains one of the major goals in diabetes management and deserves many weapons in our therapeutic armamentarium.

It is ironic that the cardiovascular benefits observed in some recent trials might be, at least partially, explained by the reduction in hyperglycemia. The demonstration of noninferiority to placebo would require the achievement of similar levels of glucose control in both trial arms and, as a consequence, the differential use and dosing of non-study-related antihyperglycemic agents between the 2 groups. Thus, the compound under evaluation is actually compared with a mixture of other antihyperglycemic agents. The treatment strategy used in the control arm may affect the trial outcome because some older medication classes have less firmly established cardiovascular safety than others or may even carry cardiovascular risks (eg, sulfonylureas). Moreover, levels of glucose control in both trial arms are never identical. Although differential exposure to hyperglycemia is sometimes trivial, especially in shorter trials (Figure), this was not the case in the EMPA-REG OUTCOME trial and is not expected to be the case in the LEADER and SUSTAIN 6 trials. How much glucose control per se contributed to the cardiovascular benefits is unknown, but it cannot be ruled out.

Eight years after implementation of the guidance on the evaluation of cardiovascular safety of antihyperglycemic agents, it is time for a first appraisal. No medication withdrawal has been required; secondary safety signals have been sporadically identified; and cardiovascular benefits have sometimes been reported, although this was not the primary purpose of the trials. This policy has resulted in the allocation of enormous resources to try to address the broad cardiovascular safety of drugs, using a focused experimental design in a relatively narrow population. We believe that alternative, more externally valid, and more cost-effective approaches (such as, but not limited to, rigorous, very large population-based observational studies with targeted prospective trials or registry-based trials to test emerging signals) should be explored.

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**REFERENCES**


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**FOOTNOTES**

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