

# More Than 7 Years of Hindsight: Revisiting the FDA's 2008 Guidance on Cardiovascular Outcomes Trials for Type 2 Diabetes Medications

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■ **IN BRIEF** Concerns raised about the cardiovascular safety of type 2 diabetes medications such as rosiglitazone prompted the U.S. Food and Drug Administration to issue draft guidance in 2008 that, in practice, has required large cardiovascular outcomes trials (CVOTs) for all new type 2 diabetes therapies. After more than 7 years and six completed and published trials to date, this is an opportune time to consider whether these studies, as currently designed and conducted, accurately assess the long-term benefit/risk profile of new therapies and whether they represent an optimal use of limited health care resources. This article presents and contextualizes opinions on CVOTs from 10 thought leaders in diabetes. It is intended to inform an exploration of the costs, medical ethics, and effectiveness of using large-scale CVOTs to assess the safety of new diabetes therapies.

Diabetes represents a significant and growing burden in the United States. According to the most recent estimates by the Centers for Disease Control and Prevention, 29.1 million people, or 9.3% of the U.S. population, have diabetes (1). Both type 1 and type 2 diabetes put patients at risk for acute medical emergencies resulting from hypoglycemia or hyperglycemic crisis, while in the long-term raising the risk of complications, including cardiovascular disease (CVD), vision loss, kidney disease, and lower-limb amputations. Type 2 diabetes in particular imposes a disproportionate burden on racial/ethnic minorities, with higher prevalence rates among Native Americans (15.9%) and black (13.2%) and Hispanic (12.8%) Americans compared to non-Hispanic white Americans (7.6%) (1). In addition to the medical burden, the American Diabetes Association (ADA) estimated the economic costs of diabetes at \$245 billion in 2012, including \$176 billion in direct medical costs and \$69 billion in lost

productivity (2). These expenditures are forecast to reach nearly \$500 billion annually by 2030 if current cost trends continue (3).

Despite the numerous approved treatments for type 2 diabetes, new therapies that produce sustainable improvements in glycemic control without undue health risks are needed. Many current medications have serious drawbacks, including hypoglycemia, weight gain, diminishing efficacy over time, and unpleasant side effects that negatively affect adherence. Given the complexity of the disease, the size and diversity of the affected population, and the fact that type 2 diabetes is progressive and multiple therapies are needed over the course of the disease, patients benefit from a wide range of treatment options and from continued efforts to develop products with more favorable benefit/risk profiles.

Because CVD is the leading cause of death among people with type 2 diabetes, meaningful reduction of adverse cardiovascular outcomes

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through glucose lowering is a compelling goal for scientists, clinicians, and pharmaceutical manufacturers. Unfortunately, although the correlation between poor glycemic control and cardiovascular risk is clear, it has proven difficult to demonstrate a causal relationship between improved diabetes control and reduced cardiovascular risk in type 2 diabetes.

According to its mission statement, the U.S. Food and Drug Administration (FDA) has a dual mission with regard to new therapies: 1) “protecting the public health” by ensuring the safety and efficacy of new products and 2) “advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable” (4). Finding the balance between these two goals and defining a safety threshold above which patients and health care providers can make individual assessments about a drug’s advantages and disadvantages is a continuing challenge.

Currently, there are only two diabetes pharmacotherapies (metformin and sulfonylureas) available in comparatively less expensive generic formulations, both of which have side effect challenges. We support the development of more therapies so that, ultimately, there will be more approved therapeutic choices available in generic form.

### Background

Before 2008, new medications for type 2 diabetes were approved based on improvements in glycemia—namely, A1C, a surrogate for improved microvascular outcomes as demonstrated by the U.K. Prospective Diabetes Study (UKPDS)—and the safety profile demonstrated in phase 2 and phase 3 clinical trials (5). The trials conducted to support approval typically lasted 6 months, often with an open-label extension period, and typically enrolled patients with a relatively short history of diabetes. Existing CVD often was an exclusion criterion. A new medication’s impact on cardiovascular safety was assessed

through investigator-initiated adverse event reports, with no central, blinded adjudication process or prespecified analyses required (6).

In 2007, a controversy surrounding the thiazolidinedione rosiglitazone put pressure on the FDA to more rigorously scrutinize whether new diabetes medications could have an adverse impact on patients’ cardiovascular outcomes. The controversy was ignited by the publication of a meta-analysis of 43 fairly small trials that found a significant 43% increased risk of myocardial infarction ( $P = 0.03$ ) and a non-statistically significant 64% increased risk of cardiovascular death with rosiglitazone ( $P = 0.06$ ) (7). This controversial publication generated enormous publicity, including a congressional investigation, with many accusing the FDA of abdicating its duty to protect public safety (8). In response to these and other concerns, in July 2008, the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee voted 14-2 in favor of recommending a long-term cardiovascular safety trial or other “equivalent evidence” to rule out unacceptable cardiovascular risk for all new glucose-lowering agents (9).

In December 2008, the FDA released a guidance document that established new expectations for evaluating the cardiovascular safety of these therapies. The agency advised that pre-marketing interim outcomes data should rule out a hazard ratio of 1.8 (based on the upper bound of a two-sided 95% confidence interval) for major cardiovascular events (typically cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), in the context of a “reassuring” point estimate, which was not explicitly defined. If the pre-marketing data had not already ruled out a hazard ratio of 1.3, a drug approved based on interim outcomes data would be required to continue the outcomes trial to do so after approval. The final document suggested that a meta-analysis of phase 2 and phase 3 clinical trials would

be the default option to satisfy these requirements and that an additional dedicated safety trial would only be needed if data were insufficient (10).

The reality has been very different, however. In practice, every novel antidiabetic agent approved since 2008 has undergone a dedicated cardiovascular outcomes trial (CVOT), typically involving 5,000–15,000 people with type 2 diabetes and high cardiovascular risk and planned to last 3–5 years; the actual length of the trials was determined by event rates, and some of the trials completed to date have lasted only 1.5–2 years. Six of these trials have reported results, and at least 10 others are ongoing, with most scheduled to report within the next 5 years. Although the FDA guidance said that insulin would not be subject to the CVOT requirement, multiple insulins in development since 2008 have been subject to the standard outlines in the guidance.

With the benefit of hindsight, it is worthwhile to reexamine the original rationale for the 2008 FDA guidance, as well as its practical consequences. Exclusively for this article, we interviewed 10 experts in the diabetes and cardiovascular fields, including Drs. Ian de Boer (University of Washington), John Buse (University of North Carolina), Robert Eckel (University of Colorado), Michael Farkouh (University of Toronto), Hertzfel Gerstein (McMaster University), Silvio Inzucchi (Yale University), Lawrence Leiter (University of Toronto), David Nathan (Harvard University), Steven Nissen (Cleveland Clinic), and Robert Ratner (ADA). These interviews revealed a wide array of opinions about the FDA’s policy, ranging from strong support for the rationale to criticism based on the lack of conclusive evidence against rosiglitazone and its eventual exoneration by the FDA (11).

Drawing from these interviews, we discuss below some of the key issues relating to the FDA’s 2008

guidance. The discussion is divided into five questions:

1. What are we learning from CVOTs?
2. Are there any limits of CVOTs as currently designed?
3. What are the costs of conducting CVOTs?
4. How do the benefits of CVOTs as currently designed compare to the costs?
5. What are some alternative policies?

### 1. What are we learning from CVOTs?

Since the FDA issued its guidance in 2008, a number of dedicated CVOTs for new type 2 diabetes medications have been initiated, and six have reported full results: SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus), for the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin (Onglyza; AstraZeneca) (12); EXAMINE (Examination of Cardiovascular Outcomes: Alogliptin vs. Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome), for the DPP-4 inhibitor alogliptin (Nesina; Takeda) (13); TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), for the DPP-4 inhibitor sitagliptin (Januvia; Merck) (14); ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome), for the glucagon-like peptide 1 (GLP-1) receptor agonist lixisenatide (Lyxumia; Sanofi) (15); EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) for the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (Jardiance; Lilly/Boehringer Ingelheim) (16); and LEADER (Liraglutide Effect and Action in Diabetes) for the GLP-1 receptor agonist liraglutide (Victoza; Novo Nordisk) (17). All of these trials achieved their primary objective of demonstrating cardiovascular noninferiority compared to placebo (added

to standard care). Their results provided a high degree of certainty that these new, widely prescribed medications do not result in increased cardiovascular risk, even in patients at high baseline risk of CVD.

Very positively, two of the studies that have been completed went on to demonstrate a cardiovascular benefit. EMPA-REG OUTCOME demonstrated a statistically significant 14% risk reduction for the primary endpoint of major adverse cardiac events (MACE) with empagliflozin, driven by a 38% reduction in cardiovascular death ( $P = 0.04$  for superiority) (16). LEADER also demonstrated a 13% statistically significant risk reduction for the primary MACE endpoint with liraglutide ( $P = 0.01$ ) that was derived from all three MACE components (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) (17).

This is valuable clinical information that may not have been revealed without a requirement for a dedicated CVOT, although the manufacturers may have chosen to perform such a study voluntarily if they believed there was potential for such benefit or to rule out harm. As several experts emphasized, this is information about hard clinical outcomes, which is more clinically relevant than results for surrogate endpoints such as A1C.

These trials also have provided valuable information related to secondary endpoints; indeed, Drs. Ratner, Nissen, Eckel, and Buse all identified this as one of the trials' most interesting components. On the positive side, the lack of a significantly increased risk of pancreatic adverse events in the trials of incretin-based agents (12–15) was reassuring, and reductions in hospitalization for heart failure and all-cause mortality with empagliflozin in EMPA-REG OUTCOME (16) were intriguing findings that will likely lead to future studies. However, the significantly increased risk of hospitalization for heart failure with saxagliptin in SAVOR-TIMI 53

(12) and a nonsignificant imbalance in that direction in EXAMINE (13) have generated much controversy about a potential heart failure risk with DPP-4 inhibitors, given their previously high perceived level of safety and tolerability. The implications of these results remain unclear, particularly because the heart failure results in TECOS, the largest trial in terms of patient-years of follow-up, were neutral across all prespecified subgroups and relevant outcomes.

Undoubtedly, CVOTs have delivered valuable data, including assurance on all medications' safety (so far), evidence of cardiovascular benefit in two cases, and multiple valuable hypothesis-generating findings. However, several limitations are also apparent, including variability among trials and low statistical power for rarer secondary outcomes. It is unlikely that manufacturers will fund large follow-up outcomes trials for their products, and many of the questions raised by the primary outcomes trials may remain unanswered.

### 2. What are the limitations of CVOTs as currently designed?

In our interviews of experts with a variety of views on the current CVOT paradigm, one point garnered near-unanimous agreement: the design of these trials carries significant limitations. The studies enroll very-high-risk patients with multiple cardiovascular risk factors or existing CVD. This is an ideal study population if the primary goal is to evaluate the safety of a medication in the highest-risk patients, as Drs. Leiter and Farkouh suggested should be the case for cardiovascular safety studies. Manufacturers also have an incentive to enroll a population in which events will accrue more rapidly to complete the trials as quickly as possible. However, as Drs. Eckel and Leiter noted, if the goal is to evaluate the effects on cardiovascular outcomes in the broader indicated population, enrolling only high-risk patients is misleading.

Another common critique of the current paradigm was that current studies are not long enough to fully explore the possibility of cardiovascular benefit, which requires greater statistical power than does ruling out cardiovascular risk. As Dr. Buse put it, “At face value [the trials] flunk the sniff test for even trying to show some cardiovascular efficacy in diabetes.” Dr. Nathan offered similar sentiments, stating, “The bottom line here is that, unfortunately, there is not a shortcut. If you are going to do . . . studies of a chronic degenerative disease, you have to be patient, and all of these fast-hit studies don’t tell you much of anything . . . They may show an immediate effect, either a benefit or a risk, but they may not because they are just too short.”

Reliably demonstrating a medication’s cardioprotective effect is especially difficult given that 1) today’s patients are on a background of statins and other standard-of-care medications for nonglucose cardiovascular risk reduction, and 2) in a treat-to-target study design, patients in the placebo arm are more likely to receive more intensive treatment with other glucose-lowering medications.

The results from EMPA-REG OUTCOME and LEADER do suggest that it is not impossible to achieve a positive finding with a median patient follow-up of <5 years. However, it is possible that other trials with neutral findings did not have sufficient duration to demonstrate a benefit. Designing CVOTs to run for longer periods of time would give them a better chance of reliably demonstrating cardiovascular benefits where they exist.

Another key question about CVOTs as they are currently designed is whether they target the most clinically relevant questions. Rarely do clinicians and patients make choices about a given glucose-lowering medication in a vacuum. Instead, they consider which among the many available glucose-lowering medications are best suited to the individual

patient. Outcomes data comparing multiple therapeutic options could provide far more relevant data than the current placebo-controlled trials.

The lack of long-term follow-up after the study treatment period ends also limits our understanding of the longer-term effects of new medications.

All of these questions are highly relevant for clinical practice, and it is worth considering whether addressing them would be a more valuable use of public health resources than the current paradigm.

### 3. What are the costs of CVOTs?

As with any large-scale, randomized, clinical trial, the information gained from CVOTs comes at a significant cost. This includes the tens of thousands of patients (almost 50,000 in the six trials that had reported results as of mid-2016) who devote their time to these studies with the knowledge that they are potentially exposing themselves to harm or denying themselves access to a beneficial medication, as well as the researchers, clinicians, statisticians, and other personnel responsible for running the trials and analyzing the results. There is also a substantial financial cost borne by drug manufacturers, which could be passed on to patients through higher medication prices on top of an already high price baseline. Just as negatively for patients, it is possible that the investment burden created by the FDA guidance could steer manufacturers away from diabetes medication development and toward areas with fewer regulatory hurdles; at least one major manufacturer (Bristol-Myers Squibb) has exited the field of diabetes, and others’ investments in the area have fallen because of the high costs.

It is also important to consider the opportunity costs of CVOTs; what other areas of research could be supported with the human and financial resources now dedicated to these trials? The experts we interviewed who most strongly opposed the 2008

guidance (Drs. Ratner, Inzucchi, and Eckel) proposed a number of topics these resources could have been used to investigate, including:

- Comparative effectiveness of different drug classes
- Effects of lifestyle-based approaches to prevention
- Public health and environmental issues contributing to the diabetes epidemic
- Mechanisms of hunger, satiety, and obesity
- Role of blood pressure and lipids in type 2 diabetes
- Long-term durability of the efficacy of type 2 diabetes drug classes
- Preservation of  $\beta$ -cell function
- Effects of diabetes drugs on non-cardiovascular complications

In addition, several experts who at least partly endorsed the current approach suggested that studies primarily intended to evaluate cardiovascular benefit would be a better use of resources than noninferiority trials. Drs. Gerstein and Buse also suggested that cardiovascular safety could be a secondary endpoint in a trial primarily designed to evaluate another question such as a drug’s effect on retinopathy. Other variations of these solutions could include adaptive clinical trials (in which the trial design can be modified based on interim data at a pre-specified point) or passive follow-up after the completion of randomized treatment.

### 4. Are the benefits of CVOTs as currently designed worth the costs?

In 2008, the discussion regarding the costs and benefits of CVOTs was hypothetical and dominated by the rosiglitazone controversy. More than 7 years later and after the exoneration of rosiglitazone by the FDA, the field now has a better sense of the information that can be gained from these trials, as well as their limitations and costs. It is, therefore, worthwhile for the scientific, medical, and regulatory communities to reflect on wheth-

er the benefits of CVOTs as they are typically designed outweigh the costs.

Drs. Nissen and Gerstein both expressed unequivocal support for the value of CVOTs. As the architect of the current paradigm, Dr. Nissen offered the strongest endorsement, saying “We have a disease with a lot of morbidity and mortality . . . that is growing in prevalence around the world, and we do not have good trials of the drugs . . . I am going to fight like a demon against the forces that want to roll back that regulation.”

Conversely, Drs. Ratner and Eckel said that the benefits of these trials do not outweigh the costs as currently structured. Dr. Eckel argued that meaningful safety issues would likely become evident in phase 2 and phase 3 trials and that companies can voluntarily conduct superiority trials if they believe there is potential for benefit. Dr. Ratner summed it up by asking, “What are we going to learn from all of these studies? So far, we have learned very little about cardiovascular disease and much more about secondary considerations like pancreatic disease. The human, time, and monetary costs of these studies are just enormous. The opportunities lost as a result of those demands can only be imagined.”

The remaining experts landed somewhere in the middle on this question, suggesting that the current approach has value, but that there is ample room for improvement. Dr. Leiter accepted the existing paradigm as a foundation but suggested that those designing the trials could maximize their value by including an active comparator or interesting secondary endpoints such as renal outcomes. Drs. Nathan and Farkouh described the current approach as a “problematic compromise” and suggested that it would be ideal to require the completion of a full CVOT to evaluate both the cardiovascular safety and benefit of a medication before approval, rather than allowing interim data from an ongoing CVOT to secure approval. On this subject,

some said that such a requirement could create large disincentives for companies to invest in diabetes drug development. Dr. Buse was largely content with the current trials but suggested that the primary endpoints and study populations could be made more flexible to answer more relevant questions for each drug. Dr. Inzucchi argued that the financial cost is not an undue burden for manufacturers but that noninferiority studies are not worth the investment for drugs with no worrisome signals in phase 2 or 3 trials. “It just seems to me an enormous waste of time, money, and effort to conduct these large CVOTs to prove cardiovascular ‘safety’ when there was no suspicion of harm in the first place,” he said. However, in light of the impressive results from EMPAREG OUTCOME, Dr. Inzucchi has tempered his views to some degree. He was involved as a steering committee member in that trial and, more recently, suggested that, without the 2008 FDA guidance, it is conceivable that the study might never have happened, although the manufacturer could have chosen to set up a superiority trial if it felt there was potential for a cardiovascular (or renal or other long-term) benefit.

##### **5. What are some alternatives?**

There appears to be a growing consensus in the field that the current paradigm for evaluating the cardiovascular effects of diabetes medications is imperfect, suggesting that now is an opportune time for the FDA to engage in a discussion about making changes to the status quo. These could range from small adjustments to more significant modifications to the existing guidance.

##### ***Standardized Guidance for the Use of Interim CVOT Data to Support Approval of New Drugs***

It was clear from a 2014 FDA public hearing on the confidentiality of interim results of CVOTs that interim data disclosure from ongoing CVOTs is the source of much confusion and

disagreement (18). The 2008 guidance allows for the use of interim data from an ongoing trial to support approval of a new drug as long as it rules out a hazard ratio of 1.8 for the primary endpoint, but broad disclosure of such data can seriously disrupt the integrity of the ongoing trial. This process of systematically reviewing new drug applications (NDAs) based on interim results from ongoing trials is fairly unprecedented.

Even without clear guidance, manufacturers in some cases have successfully navigated this challenge. For example, Novo Nordisk disclosed interim data from the DEVOTE (A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events) trial to only a small group within the company (not including senior management) to support its resubmission of insulin degludec (Tresiba) (19). Other recent cases have not gone as smoothly. For example, Sanofi withdrew its NDA for lixisenatide in 2013 to avoid risks of interim data disclosure from ELIXA (20).

Although there is much disagreement about a solution, a clear consensus emerged at the 2014 hearing that manufacturers and researchers would benefit from more explicit, standardized guidance from the FDA for the use of interim data to support approval. Disclosing interim data only to a small, firewalled, need-to-know team within the sponsor company may be the best solution, although it would preclude the possibility of a public Advisory Committee meeting and require a clear enforcement mechanism to ensure that the data are not disclosed more widely. Another alternative would be to prohibit submissions based on interim data and make the entire CVOT a pre- or postmarketing requirement; as mentioned above, however, requiring a full premarketing trial could have negative implications for investment.

### **Minimum Required Duration for CVOTs**

The most rigorous solution to the issue of limited trial duration would be to require a minimum duration for CVOTs that the FDA and the scientific community deem sufficient to answer the most relevant clinical questions, including whether a medication reduces the risk of CVD. This would certainly increase the ability of CVOTs to reveal beneficial cardiovascular effects and make their results more robust. One important question is what the mandatory minimum duration should be, and the answer to this is subjective. Although almost all of the interviewed experts agreed that trials longer than the current 3–5 years would be more scientifically useful, some suggested that 7 or 8 years would be appropriate, whereas others argued that showing a benefit might require more than a decade. Most, but not all, agreed that final data should not be required before a compound could be approved.

Even more important questions include whether longer studies would be worth the substantial additional cost and who would provide the funding for such studies. An FDA mandate for longer trials may prompt significant backlash if manufacturers were required to fund the studies, and this could become a disincentive for them to develop medications for type 2 diabetes relative to other disease areas that do not carry the same requirements. As with passive follow-up, another option would be for the government or private foundations to fund the studies; given the potential for drugs to show cardioprotection (or renal protection) and the lives that could be saved based on such effects, it seems reasonable to think the return on investment may be worthwhile. Although the total pool of resources may be limited for this at present, it would also be useful to think about presenting the potential return on investment to alternate funders. There also may be room for more public/private partnerships.

Several interviewed leaders offered intriguing proposals to make longer trials more cost-effective. Dr. Gerstein suggested that companies could contribute to a single fund that would facilitate long-term follow-up in multiple trials. This suggestion was reminiscent of FDA Center for Drug Evaluation and Research Director Dr. Janet Woodcock's broader proposal to create "master protocols," in which dedicated groups of investigators would continuously run multiple trials, drawing from a pool of industry funding (21). Drs. Gerstein and Leiter both suggested that electronic medical records could also be used to facilitate long-term, less expensive trials. Both ideas have merit and represent appealing long-term goals for the U.S. clinical trial process. Dr. Inzucchi also raised the possibility of extending a drug's patent exclusivity if the manufacturer agreed to conduct a longer trial. This would likely ease some of the opposition from industry, although it would require controversial reform of the patent system and would undoubtedly raise concerns about delaying widespread access to new products.

### **Passive Follow-Up After Completion of Randomized Trials**

Passively following study participants after the completion of randomized treatment could be one relatively cost-effective way to address the limitation of the short duration of CVOTs. Although the results may be less conclusive than those from a 10- or 20-year randomized trial, they could explore outcomes that take a long time to emerge (as in the case of cardiovascular benefit in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications [22] and UKPDS [23]) at a much lower cost. Drs. Ratner, Gerstein, and de Boer endorsed passive follow-up as a useful approach. However, Drs. Leiter, Inzucchi, Buse, and Farkouh expressed doubt about the scientific

and clinical usefulness and the practicality of such studies. If such an approach is deemed useful, one key question is whether the FDA should require passive follow-up as a necessary component of CVOTs. This would likely prompt significant resistance from industry for adding additional costs to an already burdensome process. However, as Dr. Inzucchi noted, it is unlikely that companies would voluntarily institute long-term follow-up of patients without a mandate. Another appealing alternative could be for nonindustry sources such as the government or private foundations to provide funding for follow-up; although government resources have been declining, not all sources of funding are so limited.

### **Use of Observational Data to Complement or Replace Randomized Trials**

In an era of increasingly sophisticated data analytics, it should be possible to take advantage of large registries to gain information about the safety of new medications. Drs. Ratner and Eckel both suggested that robust postmarketing surveillance could provide more applicable "real-world" information than a trial in a select group of patients. Both acknowledged that the ability to systematically collect and analyze observational data is currently far too limited in the United States but expressed hope that it could be improved. This would be an intriguing subject for a future FDA meeting. Dr. Ratner highlighted the ADA/American College of Cardiology Diabetes Collaborative Registry (24) and the FDA's Mini-Sentinel initiative (25) as two promising efforts along these lines. With a large national registry, comparable to the T1D Exchange for type 1 diabetes (26), this could be an appealing solution. However, it would raise valid concerns about overstating the robustness of results from observational studies. Dr. Gerstein, for one, strongly argued against this option, saying that replacing randomized,

controlled trials with analyses of “big data” is simply unacceptable.

### **Product-Specific CVOT Requirements**

Rather than imposing the same cardiovascular safety requirements for all new type 2 diabetes medications, the FDA could require CVOTs only for the first product in a new class or in cases in which an adverse event is especially plausible. There is merit to avoiding a one-size-fits-all approach in terms of responsible use of resources, but requiring a trial only for first-in-class products would present several challenges. Multiple products often are submitted to the FDA at about the same time; the policy could hamper innovation by creating a penalty for the first company to pursue a new target; and first-in-class CVOTs would not address concerns about product-specific risks within a given class.

Evaluating the need for a CVOT on a case-by-case basis is a highly appealing solution. The various approved classes of glucose-lowering medications work in markedly different ways, with greatly varying efficacy and side effect profiles. In the case of therapies such as rosiglitazone, for which there is concern about cardiovascular risk because of the mechanism of action or signals in earlier trials, the FDA could require the manufacturer to complete a safety trial. For drugs with hypothesized cardiovascular benefits, incentives could theoretically exist for manufacturers to voluntarily conduct superiority studies, or the FDA could mandate such trials if such incentives do not appear to be strong enough in practice.

### **Wholesale Repeal of the 2008 Guidance**

The FDA could eliminate the CVOT standards for diabetes medications and return to the previous approach of making comprehensive risk/benefit assessments based on surrogate endpoints. This would likely be the most popular solution within the pharma-

ceutical industry, could accelerate the development of new diabetes medications, and would from some perspectives better align the FDA’s policy on diabetes medication approval with its policies on medications for other disease states. However, most experts did not advocate abolishing CVOTs entirely, given the scientific and clinical value of their data. From a practical standpoint, it is very unlikely that the FDA would consider such a wholesale repeal, particularly given the convincing argument that these trials have revealed both risks (heart failure with some DPP-4 inhibitors) and benefits (cardiovascular risk reduction with empagliflozin and liraglutide) that otherwise might not have been known.

### **Conclusion**

Based on conversations with these 10 leading experts and on the past 7 years of gained experience, it appears that the FDA’s 2008 guidance on evaluating cardiovascular risk in new type 2 diabetes therapies may not deliver benefits completely commensurate with its costs. The policy risks imposing a one-size-fits-all expectation for all products in a heterogeneous category, and most trials conducted under the guidance are designed so that neutrality will be the most likely outcome.

Given the immense human and financial resources these studies require, we recommend that the FDA consider whether this approach is producing the most valuable scientific and clinical information possible. The FDA showed some inclination to do this at the August 2014 hearing on interim data disclosure, when FDA Director of the Office of New Drugs Dr. John Jenkins acknowledged that “it may be time to revisit the basis of cardiovascular studies for diabetes drugs” (18).

Although there is no perfect solution, there are a number of steps the FDA could take to improve upon the current approach, including clarifying expectations around interim data

disclosure, considering whether a CVOT should be required on a case-by-case basis, and allowing for greater use of observational data, whether through passive follow-up or robust postmarketing surveillance using large registries. It is also incumbent upon manufacturers, the National Institutes of Health, and private philanthropic foundations to consider how they could contribute resources to enable more cost-effective, informative studies in this area. This would be particularly helpful given that people with type 2 diabetes are living longer, and the “elderly unwell” population is growing. As the diabetes epidemic continues to expand and CVD remains the leading cause of death among people with diabetes, better understanding the relationship between the two diseases should be one of the top priorities for all concerned.

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### **Duality of Interest**

#### **Authors**

Emily Regier, Manu Venkat, and Kelly Close are employees of Close Concerns, a for-profit, private entity that publishes newsletters on the latest research in diabetes and obesity and has ongoing business relationships with companies in the field. Kelly Close is the founder of The diaTribe Foundation, a nonprofit organization funded primarily by the Leona M. and Harry B. Helmsley Charitable Trust and, in part, by sponsors, including companies in diabetes.

#### **Expert Panelists**

Dr. Buse has served as a consultant for and owns stock in PhaseBio and has received research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GI Dynamics, Johnson & Johnson, Lexicon, Novo Nordisk, and Orexigen. He has been an advisor to AstraZeneca, Dance Biopharm, Eli Lilly, Elcelyx, GI Dynamics, Lexicon, Merck, Metavention, Novo Nordisk, Orexigen, and vTv Therapeutics.

Dr. de Boer has served as an advisor to Bayer, Boehringer Ingelheim, and Janssen and received research support from Abbott and Medtronic.

Dr. Gerstein has received consulting fees from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kaneq Bioscience, Lilly, Novo Nordisk, Roche, and Sanofi. He has received lecture fees from Abbott, AstraZeneca, Berline Chemie, and Sanofi. His institution has received support for research or continuing education programs led by him from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, and Sanofi.

Dr. Inzucchi has served as an advisor or consultant for AstraZeneca, Boehringer Ingelheim, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Sanofi, and TransTech Pharma and received research support from Takeda.

Dr. Leiter has served as an advisor to AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Servier. He has participated in clinical trials funded by AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Pfizer, Sanofi, and Servier. He has provided continuing medical education on behalf of AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Servier.

Dr. Nissen reported that the Cleveland Clinic Center for Clinical Research receives funding to perform clinical trials from Amgen, AstraZeneca, Cerenis, Eli Lilly, Esperion, Novartis, Novo Nordisk, Orexigen, Pfizer, Takeda, The Medicines Company, and Vivus. Dr. Nissen is involved in these clinical trials but receives no personal remuneration for his participation. Dr. Nissen consults for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction.

Dr. Ratner is the chief scientific officer of the American Diabetes Association.

No other potential conflicts of interest relevant to this article were reported.

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