Cardiovascular Outcome Studies With Novel Antidiabetes Agents: Scientific and Operational Considerations

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The requirement from several health authorities to demonstrate cardiovascular (CV) safety of new antidiabetes drugs represents both an opportunity and a challenge. In a few years, this requirement may avail to regulatory agencies and the medical community data from large, prospective clinical trials assessing the benefits and risks of such drugs in high–CV risk patients with diabetes. These studies may also provide an opportunity to assess safety signals beyond CV. However, these studies pose significant challenges, including study design, long-term retention of patients, the risk of missing data, and varying regulatory requirements among countries and regions. In addition, these trials cost hundreds of millions of dollars. This significant investment may potentially detract from the investigation of other drug-specific risks or benefits. In this article, we discuss considerations in the design and execution of CV outcome studies in diabetes.

The goals of antidiabetes treatment are to avert the untoward metabolic effects of high glucose concentrations and prevent microvascular and macrovascular complications. Compelling data in type 2 diabetic patients support the conclusion that improved long-term glycemic control reduces the risk of microvascular complications (1–3). Based on several large outcome studies, including the seminal Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS), HbA_{1c} was established as a surrogate biomarker of glycemic control and therapeutic goals were set accordingly (4).

Based on the proven correlation between HbA_{1c} and microvascular complications and inconclusive data on CV benefits, most clinical development programs for antidiabetes drugs have focused on glucose lowering. While confirmatory studies in these clinical development programs were being conducted to establish the glucose-lowering properties of novel drugs, CV safety assessment has been limited. CV safety concerns have been raised with respect to several antidiabetes compounds approved or under development for the treatment of type 2 diabetes. In July 2008, the U.S. Food and Drug Administration (FDA)'s Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of CV assessment in the pre- and postmarketing settings. Subsequent to the Endocrinologic and Metabolic Drugs Advisory Committee recommendation, the FDA determined that concerns about CV risk should be more thoroughly addressed during antidiabetes drug development. The 2008 guidelines resulted in profound changes in the ways new antidiabetes drugs are evaluated and brought to market (5):

1. An upper bound of the 95% CI for the risk ratio of important CV events of <1.3 should be used as a key criterion for excluding unacceptable CV risk for new treatments of type 2 diabetes.
2. Study patients must include those with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.
3. A minimum of 2 years' CV safety data must be provided.
4. All phase 2 and 3 studies should include a prospective, independent adjudication of CV events. Adjudicated events should include CV mortality, myocardial infarction (MI), and stroke and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other end points.
5. For satisfaction of the new statistical guidelines, the analysis of CV events may include a meta-analysis of all placebo-controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy), and active-controlled trials or an additional single large safety trial may be conducted that alone, or added to other trials, would be able to satisfy this upper bound before New Drug Application/Biologic License Application submission.

As a result, a number of large outcome studies are now underway (Table 1). The purpose of this article is to describe challenges that the pharmaceutical industry is facing as a result of the FDA guidance with respect to the conduct of CV outcome studies.

Outcomes studies for new antidiabetes drugs: opportunity and challenge

Large drug-specific CV outcome studies in diabetes provide a unique set of opportunities and challenges (Table 2). One needs to distinguish these studies from glycemic control–focused studies such as the UKPDS, Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), which used multiple treatment modalities to achieve glycemic targets (2,6,7).

The new studies will provide the medical community with prospective, long-term blinded data on the efficacy

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This publication is based on the presentations from the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Ethicon Endo-Surgery, Janssen, Medtronic, Novo Nordisk, Sanofi, and Takeda.
DOI: 10.2337/dcS13-2041

Table 1—*Examples of ongoing pre- and postapproval outcome studies

Trial name	Drug	Primary end point	No. of subjects (length of study in years)
EXAMINE	Alogliptin	MACE	5,400 (5)
CANVAS	Canagliflozin	MACE	4,500 (4)
CAROLINA	Linagliptin	MACE + unstable angina	6,000 (7)
ALECARDIO	Aleglitazar	MACE	6,000 ACS (4.5)
TECOS	Sitagliptin	MACE + unstable angina	14,000 (5)
SAVOR	Saxagliptin	MACE	16,500 (5)
EXSCEL	Exenatide LAR	MACE	12,000 (5.5)
LEADER	Liraglutide	MACE	9,000

ACS, acute coronary syndrome; CANVAS, CANagliflozin cardioVascular Assessment Study; EXAMINE, Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome; EXSCEL, EXenatide Study of Cardiovascular Event Lowering; LAR, long-acting release; TECOS, A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control. *Accessed through http://www.clinicaltrials.gov/.

and safety of new antidiabetes drugs. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial, for example, will provide data that are ~3–4 times greater than the entire phase 3 development program for saxagliptin (8). The large outcome studies may also allow assessment of emerging non-CV safety signals and, in particular, rare events that may be difficult to discern in the postmarketing setting from nonrandomized, nonblinded data.

CV and other outcomes in dysglycemia were assessed in the ORIGIN trial. When used to target normal fasting plasma glucose concentrations for more than 6 years, insulin glargine had a neutral effect on CV outcome and cancers (9). The latter finding is of importance in understanding insulin glargine's overall safety profile, as observational studies have previously linked insulin glargine to increased cancer risk (10).

Challenge of design: study design considerations

CV outcome studies to address the requirements of the 2008 FDA guidance (11) are typically event-driven, i.e., designed to accrue a predefined number of end point events. These end point events, as per the guidance, should include CV mortality (CV death), MI, and stroke and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other end points such as hospitalization for heart failure. CV death, MI, and stroke are generally referred to as major adverse CV events (MACEs). In the majority of ongoing studies, MACE has been selected as the primary end point (Table 1). MACE is considered a more stringent end point with arguably less ambiguity and bias and more certain ascertainment than some "softer" end points. The guidance also states that these end points should be prospectively adjudicated in a blinded fashion by an independent CV end points committee.

The number of events is an important component of the design and the basis for determining the trial's size and duration. Trials to assess a novel antidiabetes drug's effect on CV events can be divided into two major categories according to the primary end point assessment: noninferiority and superiority. The primary goal of noninferiority trials is to address the FDA's requirement to definitively demonstrate that the upper bound of the two-sided 95% CI for the estimated risk ratio of the drug is <1.3. It has been proposed that the required number of events for such a trial would be ~600–700 (12). The rationale to conduct a superiority trial can include hypothesis-generating data from meta-analyses of CV events (done to address premarketing FDA requirements) from studies conducted preapproval, effects on CV risk factors beyond HbA_{1c} reduction; a postulated mechanism directly impacting CV disease, or other considerations. For a superiority trial, however, the required number of events may be considerably larger than for a noninferiority trial and would depend on the size of the drug's postulated effect on CV events versus the chosen comparator(s) (the hazard ratio or relative risk).

The number of end point events is thus based on whether the trial is designed as a noninferiority or superiority trial and, in the latter case, on the predicted relative risk reduction. It should be noted that some trials (e.g., CAROLINA [13]) are designed to test for noninferiority first and, if successful, subsequently test for superiority. The desired power to demonstrate the effect will impact the targeted number of events. If interim analyses are planned for the trial, their number and the associated α spending function have to be taken into account in the sample size determination. Other predicted variables, including the yearly event rate (which may differ based on the patient population) and patient dropout rate from the study, may affect the sample size and duration of the trial. The type of events chosen as end points may also have a bearing on the trial size; limiting events to MACE may require more patient-years to accrue compared with a broader spectrum of qualifying events. Finally, the absolute difference in risk is another statistical factor to consider when potential benefits of a study drug are being assessed.

Generally, the larger the required number of events, the larger or longer the trial needs to be. Larger and longer trials are more expensive, complex, and difficult to conduct, as we will further discuss below. As the trials are event driven, however, they would be stopped when the predefined number of adjudicated events had been reached, regardless of the predicted duration. If, for

Table 2—*Outcomes studies for new antidiabetes drugs: opportunity and challenge*

Opportunities	Challenges
• Large data from randomized prospective clinical trials	• Patient retention and handling of missing data
• Assessment of benefit/risk in high-risk diabetic patients	• Regional- and country-specific considerations in global studies
• Opportunity to assess non-CV and rare safety signals	• Cost

example, a study meets its recruitment goals ahead of schedule or the actual event rate is higher than predicted, a study could reach its end prior to the planned timelines and vice versa. Thus, the size and predicted duration of the trial are useful primarily for planning purposes.

Longer trials may have a better chance of demonstrating a drug's CV effect over time; it has been postulated that changes in HbA_{1c} may require long-term follow-up prior to demonstrating benefit—the effect referred to as "metabolic memory" (14). In the 10-year follow-up to the UKPDS trial, the effect of intensive blood glucose control on CV risk appeared to be improving with time (15). On the other hand, longer trials are considerably more expensive, are marred with patient retention concerns (which may impact the interpretability of the results as described below), and cause a delay in obtaining an answer to the question the trial is designed to address. Therefore, duration of trials, similar to other important design elements, has to be optimized between the desirable and the practical.

Large outcome trials provide an opportunity to obtain important safety information about the drug being studied. Outcome studies testing antidiabetes agents are often several-fold larger than the drug's entire clinical development program, as mentioned above. But while it may be tempting to try to use such studies to address a wide range of safety questions, one must remember that CV outcome studies should be designed to address the primary objective, which is to evaluate whether the drug causes no CV harm (noninferiority) or confers CV protection (superiority) compared with either placebo or a comparator with an established safety and efficacy profile. Important safety information should, of course, be obtained, but the trial should be adequately powered to address the primary objective. Increasing trial size to assess secondary or exploratory end points such as various safety parameters should be avoided, as it unjustifiably exposes a larger number of patients than is necessary.

Finally, most ongoing CV outcome studies have been designed to test the drug versus placebo on top of standard of care. One exception is the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) study (13), where the sulfonylurea glimepiride is the active comparator. This design may offer an additional benefit of testing efficacy parameters of linagliptin versus glimepiride in a long-term, head-to-head comparison; however, an FDA review had raised concerns related to the unknown CV effect of glimepiride, subsequently notifying the sponsor of their requirement to conduct a CV safety study with linagliptin versus placebo (16).

Challenge of patient retention

Poor patient retention threatens the scientific integrity of the study and the interpretability of data and has been widely recognized as a challenge in long-term studies (17). Patient retention is comprised of two main components: *1*) discontinuation of study drug, where patients continue study follow-up, and *2*) discontinuation from the study, where patients either withdraw their consent to any follow-up or are lost to follow-up.

Discontinuation from the study may result in missing data specifically of importance in outcome studies. (See below.) Discontinuation of study drug may result in dilution of the results related to the objectives of the study. Discontinuation of study drug may also lead to selection bias if the dropout population is unequal among the cohorts, creating an imbalance in one or more baseline characteristics.

In addition, study results may be affected by the "drop in" phenomenon, where patients during the course of the study begin taking medications of a similar class or with an effect similar to that of the drug being evaluated in the study. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, the effect of long-term fenofibrate therapy on CV events was evaluated in 9,795 patients with type 2 diabetes. In that study, a large proportion in each study group discontinued study medication (10% on placebo vs. 11% on fenofibrate), and 17% of patients randomized to receive placebo commenced other lipid treatments, predominantly statins, compared with 8% in the fenofibrate group. The discontinuation of study medication and the drop in may have contributed to the study's failure to meet the primary objective (18). In the Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) study, vital status was unknown in 2.9% of patients and a further 394 (8.9%) were alive but withdrew from some study visits, thereby missing complete CV end point information (19).

The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS-ACS 2 TIMI 51) trial tested rivaroxaban in patients with acute coronary syndrome (20). Among patients who received at least one dose of study drug, premature discontinuation of treatment occurred in 26.9, 29.4, and 26.4% of patients receiving the 2.5-mg dose or the 5-mg dose of rivaroxaban or placebo, respectively. The rates of withdrawal of consent were 8.7, 8.5, and 7.8%, respectively, and the rates of loss to follow-up were 0.2, 0.3, and 0.3% (20). Despite an outcome suggesting a reduction in CV risk, the FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC) recommended against approving rivaroxaban for the indication tested in ATLAS-ACS 2 TIMI 51, voicing concerns with respect to patient retention and subsequent missing data. The FDA followed CRDAC's advice and issued a "complete response letter," requesting more data (21).

Both the RECORD and the ATLAS studies were conducted as a collaboration between pharmaceutical companies as sponsors and leading academic research organizations and illustrate the challenges of retention. Of note, CV outcome studies with antidiabetes drugs may be longer than studies where the anticipated drug effect is relatively short-term (e.g., anticoagulants and antiplatelet agents in acute coronary syndrome), potentially further complicating retention efforts. Finally, although the studies listed in Table 1 are primarily CV outcome studies, they may be perceived by many participating patients as diabetes studies offering control of glycemia, which may not be feasible in such large and long studies, potentially adding to patient dissatisfaction leading to dropout from the studies. Some reassurance, however, may be offered to patients by specifying in the protocol and consent form targets for glycemic control.

Missing data: implications

The scientific integrity of randomized clinical trials relies on random assignment to treatment to reduce potential selection bias in the estimation of treatment effects. Missing data may compromise the benefits of randomization, particularly with respect to outcome data. The importance of understating and dealing with missing data has been recognized in recent years and is increasingly gaining attention (22).

Therefore, the FDA commissioned the Panel on the Handling of Missing Data in Clinical Trials, which was created by the National Research Council's Committee on National Statistics, to author guidance on the subject. The goal of the guidance is twofold: first, to prevent missing data through recommendations on key study design features and subject follow-up methods, and second, to recommend appropriate statistical methods to deal with missing data in clinical trials (17,22).

Missing data are common in clinical research and can complicate interpretation or even invalidate an otherwise important study (20). The National Research Council provided recommendations on the design, conduct, and analysis of studies to minimize that threat (17). Applying these recommendations could be challenging, considering the complexity and long duration of trials, multiple regulatory approaches in different countries, and the unpredictability of participants and investigators. An example of a challenge to obtain information on missing data is the recent change to the U.S. Social Security Administration policies to no longer make public the death records that it receives from the states (23). This will make it much harder to track vital status of U.S. subjects who were lost to follow-up in clinical trials.

Challenges in global studies

As recruitment goals in ongoing CV outcome studies range from 4,500 to 16,500 patients (Table 1), it becomes increasingly difficult to conduct these studies in a limited geographical distribution. SAVOR, for example, is being conducted in 25 countries (8). CAROLINA is using 700 trial centers in 45 countries (13). Competition for sites and patients continues to increase as new studies are being launched for approved drugs as well as for drugs under development or review. As the majority of these studies are being conducted over a long duration, availability of both investigators and patients is further diminished. Moreover, as these CV outcome studies are conducted in patients with diabetes, participating investigators must be well versed in both the CV and the endocrinology disciplines, have appropriate support mechanisms to conduct such studies, and have a pool of patients who meet the specific requirements for such studies, limiting the availability of research centers even further.

Regulatory authorities require that a certain number or proportion of patients from their respective countries participate in such studies as part of the review and approval process. Differences among various geographic regions and countries may lead to difficulties ranging from logistics through study conduct to interpretation of study results. Differences may include patient demographics and disease characteristics; local practices and standard of care; availability of concomitant medications for diabetes and comorbidities (e.g., drugs that are approved in certain jurisdictions but not in others); availability of resources such as invasive therapeutic procedures, imaging modalities, and specialized laboratory tests; means to properly handle drug supplies and laboratory specimens, including storage and transportation; and substantial differences in cost among regions.

Differences in demographics and disease characteristics can be illustrated by the following example. In Japan, similar to other Asian nations, BMI is lower than in Western countries. A World Health Organization expert panel, addressing the debate about interpretation of recommended BMI cutoffs for overweight and obesity in Asian populations, concluded that the proportion of Asian people with a high risk of type 2 diabetes and CV disease is substantial at BMIs lower than the 25 kg/m^2 cutoff for overweight, potentially because of differences in body fat distribution (24,25). Type 2 diabetes prevalence, although generally increasing worldwide, still varies greatly among various regions (26); in recent years, there has been rapid growth in diabetes in Japan, rendering it one of the nations most affected by the worldwide diabetes epidemic and leading the Japanese Ministry of Health, Labor and Welfare to identify diabetes as a health care priority: ~13.5% of the Japanese population has been reported to have either type 2 diabetes or impaired glucose tolerance (27). However, Japanese patients with diabetes have a lower HbA_{1c} than patients in Western countries, including the U.S. and the U.K. This may be, in part, because Japanese patients are believed to have better adherence to diet and exercise recommendations than their peers in Western countries (27). While insulin resistance is considered to be the heart of the pathophysiological changes leading to type 2 diabetes, the Japanese Pharmaceuticals and Medicines Development Agency (PMDA) in its guidance for development of oral antidiabetes drugs states that "in some patients type 2 diabetes mellitus may be caused mainly by decreased insulin secretion, while in others it may be caused mainly by insulin resistance resulting in relative insulin deficiency," emphasizing a bigger role for insulin deficiency in the disease's pathophysiology. This view may help explain the fact that unlike in other parts of the world, where metformin is widely accepted as first-line therapy, in Japan sulfonylureas have been the most widely prescribed first-line treatment for type 2 diabetes (27).

Local practices vary widely and are related to availability of drugs in terms of regulatory approval or reimbursement policies, patient education, and adherence to lifestyle and drug compliance, cultural differences, and other factors. Various society guidelines and recommendations also differ among regions, leading to different treatment goals and inconsistencies in local practices. One example is differences between guidelines from the American Diabetes Association and the American Association of Clinical Endocrinologists, both of which are based in the U.S. The American Diabetes Association and the European Association for the Study of Diabetes had discrepancies in their respective guidelines for the treatment of diabetes as well until an effort to harmonize these recommendations resulted in a recent joint position paper consolidating and simplifying the treatment algorithm for hyperglycemia (28). Similarly, from the CV perspective, an effort is ongoing to harmonize definitions of end points for CV outcome studies, including such studies in diabetes (29). While differences in recommendations or end point definitions may be considered insignificant in clinical practice, they pose serious challenges in the conduct and interpretation of outcome studies where a single study protocol has to account for such differences, allow following local practices whenever possible, and, yet, maintain consistency throughout the global study.

As CV outcome studies are designed to address the CV end point for the entire study population, they can neither be powered nor stratified to interpret country- or region-specific results, leading to results that may appear inconsistent across regions and may lead to questions from regulatory authorities about the validity of the results in their specific jurisdiction.

Finally, differences among countries may create technical hurdles, including problems with logistics such as drug and

laboratory kit shipments, all of which have to be conducted simultaneously on a large scale and accommodate for recruitment and stratification goals; a large number of clinic site visits during recruitment and extensive monitoring during the study; language and translational difficulties with various documents such as study protocols, informed consent forms, and manuals; and last but not least, substantial differences in costs incurred, which may become prohibitive to a certain degree for some sponsors and impact their decision to use certain locations.

Global regulatory challenges

Regulatory authorities around the world have adopted different approaches to the review and approval of antidiabetes drugs. FDA requires an upper limit of 95% CI for a hazard ratio of 1.8 (minimum required for premarketing) and ultimately 1.3 in order to demonstrate CV safety (12). As a result, sponsors need to consider, plan, and in some cases launch CV outcome trials during the FDA review of their New Drug Application based on limited data from the clinical development program, thereby adding complexity and substantial expense to the drug's development. In contrast, the European Medicines Agency (EMA) does not require outcome studies based on such criteria. The EMA guidance (30) states, "[Outcome] trials will only be mandatory when specific claims are made or when there are suspicions of a detrimental effect of the tested drug." The FDA's approach is that all antidiabetes drugs are suspected of CV harm unless proven otherwise; the EMA's view is that a drug becomes suspect only after a CV safety signal is detected. However, unless a sponsor is not interested in obtaining approval to market their drug in the U.S. (not the typical scenario), they must demonstrate CV safety based on the relatively proscriptive approach of the FDA; indeed, with the exception of Cycloset, drugs recently approved and others under review had been required by the FDA to have such studies (31). Other regulatory authorities take yet different approaches to assessing CV risk; the Japanese Pharmaceuticals and Medicines Development Agency, for instance, requires no CV risk assessment in the form of an outcome study in order to approve antidiabetes drugs, stating in its guidance that "unlike the U.S. and Europe, focusing on cardiovascular risks may not be appropriate considering the epidemiological evidence showing that the leading cause of death among Japanese patients with diabetes mellitus is malignant tumor rather than cardiovascular diseases" (32).

Differences between approaches of regulatory agencies exist in multiple additional aspects related to CV outcome studies. The review process of trial applications itself may differ in timelines, procedures including communication with the sponsor, and transparency of the decision making. For example, the FDA's postmarketing requirement and the EMA's follow-up measures, though similar in concept, vastly differ in procedure. Furthermore, some of the regulatory reviews of CV outcome studies may take place after a drug has been approved; others are ongoing while the drug application itself is still being considered, resulting in added complexity and burden on sponsors to address several communication avenues before and during the study to accommodate demands from all regulatory authorities involved in the approval process of the study. Further still, the Clinical Trial Application and similar review processes also involve potential review, questions, and concerns from local authorities such as ethics committees and institutional review boards, adding hurdles.

Issues and questions that can be raised by various agencies may relate to the choice of patient population, including concerns about local demographic or cultural differences; more specifically, various agencies require a certain extent of subject participation, either numeric or a percentage of the study population, to be enrolled in their respective regions. The FDA, EMA, Chinese State Food an Drug Administration, and others have required such participation across several studies; FDA may question the validity of trial results if a certain proportion of study participants were not recruited from the U.S.

Others issues may include different local practices with respect to trial requirements or procedures; study conduct in certain subpopulations, e.g., minorities or subcategories of patients based on renal function, extent of target-organ involvement, and comorbidities; inclusion criteria or concomitant medications that may be inconsistent with local regulations of best practices; approval of comparator drugs, including customs clearance for drugs allowed for the study but otherwise unavailable in the specific country; and, an important consideration for study result interpretation, the approach to collection of vital status and other medical record data for patients who were lost to follow-up or those who withdrew consent.

Escalating development costs

The FDA requirement of careful assessment of CV risk in antidiabetes drug development may provide substantial amounts of data to the medical community to help estimate CV risk associated with these agents. To meet these requirements, phase 2/3 clinical trial programs have become larger, longer, and more comprehensive and include CV high-risk patients compared with previous development programs, which were in fact criticized for limited exposure (33). In addition, sponsors of most newly approved drugs will be required to conduct postapproval CV outcome studies (12), which are complex and expensive; at a range of 20,000–40,000 USD/patient, these trials reach costs of ≥250 million USD. Very few pharmaceutical companies have the resources, expertise, and financial capability to conduct such studies, and it may no longer be feasible for small biotech and pharmaceutical companies to independently develop and launch antidiabetes medications.

Summary: consequences of CV guidance on type 2 diabetes drug development

The incidence of type 2 diabetes worldwide is increasing, and CV disease remains the leading cause of mortality in diabetes. It is important to clearly define the benefit and risk of new antidiabetes drugs. The FDA guidance to assess CV safety for new antidiabetes drugs will provide data to estimate CV risk associated with these agents. Consequently, phase 3 programs will be much larger in scope, and almost all new agents will be required to conduct postapproval large CV outcome studies. These outcome studies pose substantial design, conduct, and cost challenges. This may lead to limited incentives for sponsors to develop new antidiabetes therapies. While grappling with these challenges, it is important to not lose sight of the reason new antidiabetes medications should be developed. While it is yet to be determined what the macrovascular effects of antidiabetes drugs are, the effect of improved glycemic control on microvascular complications is well established, and in spite of a large and growing armamentarium of

antidiabetes drugs, the majority of patients over time are still not at recommended treatment goals.

Acknowledgments—B.H. and A.K. are employees of AstraZeneca, LLC. No other potential conflicts of interest relevant to this article were reported.

B.H. and A.K. equally participated in the writing, editing, and review of the manuscript. B.H. and A.K. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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