Cardiovascular Disease and Type 2 Diabetes Mellitus: Regulating Glucose and Regulating Drugs

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Type 2 diabetes mellitus is a major and increasingly prevalent independent risk factor for cardiovascular morbidity and mortality worldwide. Glycemic control is a target of therapy and a principal marker of therapeutic success in diabetes, but whether lowering glucose is accompanied by a commensurate reduction in cardiovascular risk is a matter of ongoing controversy. It has become increasingly apparent from recent large-scale clinical outcome trials that glucose lowering is a poor predictor of cardiovascular outcome, and several instances of unexpectedly increased cardiovascular risk with antihyperglycemic drugs have sounded the alarm with regulatory agencies. This article reviews the critical facts that have led to a recent shift in the regulation of glucose-lowering drugs and makes the case for why new and existing antidiabetic medications should be assessed in clinical trials of cardiovascular outcome.

Introduction

Having type 2 diabetes mellitus (T2DM) more than doubles an individual's risk of death resulting from heart disease or stroke [1]. Of the 284,000 deaths attributable to diabetes in the United States in 2007, approximately two thirds had either cardiovascular disease (CVD) or cerebrovascular disease as the primary cause of death [2], yet half a century after the approval of the first noninsulin antihyperglycemic agent by the US Food and Drug Administration (FDA), we still have no conclusive evidence of macrovascular risk reduction with any of the cornucopia of drugs—individually or in combination—presently approved for use in the treatment of patients with T2DM.

Regulatory agencies around the world base T2DM drug approval and labeling primarily on changes in glycometabolic biomarkers (glycosylated hemoglobin [HbA1c] being the most widely used) [3], with the assumption that benefits on vascular risk (microvascular and macrovascular) will track accordingly. The use of HbA1c as a surrogate marker of clinical outcome has become a de facto standard based on the beneficial effects of improved glycemic control on diabetic symptoms and microvascular complications (nephropathy, retinopathy, and neuropathy) [4,5••], with scant data available with regard to macrovascular complications. In other words, an evidence base supports microvascular risk reduction that is associated with HbA1c reduction to normal or near-normal values, but HbA1c remains of unproven value as a surrogate marker for the reduction of macrovascular complications—the principal driver of morbidity and mortality in T2DM. The importance of this distinction, highlighted by the reported results of recent randomized clinical trials [6,7•,8•,9••–11••], merits academic discussion and has catalyzed a recent paradigm shift in the regulatory approach to T2DM drugs in the United States and Europe.

The Jekyll and Hyde of Surrogate Markers

A *surrogate* as defined by *Webster's Dictionary* is quite simply "one that serves as a substitute" [12]; as used in the context of clinical research, a *surrogate marker* has been defined as "a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effects of the therapy" [13]. Although the research use of surrogate markers in lieu of primary clinical end points has obvious practical justifications (eg, limiting study time, sample size, and costs; streamlining drug development; allowing assessment of drug response in individual patients), surrogates require critical appraisal and careful scrutiny before they can be taken at face value.

An ideal surrogate should fulfill two fundamental criteria: 1) it should track with the outcome of interest without deviation and thus should accurately predict disease

outcome; and 2) the response of an ideal surrogate to an intervention should fully reflect the intervention's effect on the clinical outcome [14]. The latter criterion is clearly the most difficult (and in some cases, outright impossible) to test, but is also the most important. The failures of many proposed surrogate markers over the history of clinical research, both remote and recent, bear witness to the fact that logic and sound biologic underpinning are no substitute for clinical outcomes evidence. The cardiovascular arena is scattered with examples of such failure. For example, inotropic drugs, when administered to patients with heart failure, improved cardiac performance, acute symptoms, and exercise tolerance (all logical choices as potential surrogate markers) and were vested with high expectations of decreased mortality, but in subsequent clinical trials, the effect on mortality was unexpectedly the opposite [15–17]. Oral glycoprotein IIb/IIIa antagonists effectively and predictably provided stable, long-term intermediate level of inhibition of platelet activation and aggregation, yet they failed to improve (and actually worsened) clinical outcomes [18–22]. More recently, the cholesteryl ester transfer protein inhibitor torcetrapib was expected to reduce major cardiovascular events in at-risk patients based on its ability to markedly increase high-density lipoprotein (HDL) cholesterol and modestly lower low-density lipoprotein (LDL) cholesterol. Despite a 72% increase in circulating HDL cholesterol and a 25% reduction in LDL cholesterol observed with torcetrapib in a large-scale, international, randomized clinical outcomes trial, the drug was actually shown to increase mortality, which resulted in early discontinuation of the trial [23•], as well as termination of the torcetrapib development program. Yet another example (more relevant to the T2DM field) is that of muraglitazar, a dual peroxisome proliferator-activated receptor (PPAR) agonist with affinity for both PPAR-γ and PPAR-α that was expected to improve clinical outcomes by simultaneously targeting hyperglycemia and diabetic dyslipidemia. However, its development was halted after a quantitative summary analysis of phase 2 and phase 3 clinical trials showed a statistically significant increase in the risk of the composite end points of heart failure, major cardiovascular events, and death [6].

Why do such failures happen? Simply put, it is because surrogate markers are but individual elements in the vast and immensely complicated network of interacting physiologic and pathophysiologic phenomena whose functions integrated over time determine clinical outcome. The closer the surrogate is to the outcome in this complex biologic network, and the more causally specific the link between the surrogate and the outcome is, the more accurate and applicable the surrogate marker will be for the purpose of clinical research.

A theoretical overview of how surrogate markers may fail encompasses at least four possible scenarios:

1. The surrogate and the outcome are associated but not mechanistically or causally linked. For example, although gray hair (or balding or wrinkling of the skin) may temporally associate with increased CVD risk, virtually any intervention aiming to reverse hair graying (short of affecting the aging process itself) is highly unlikely to influence CVD risk. In this example, the proposed surrogate (gray hair) and the clinical outcome (CVD risk) may have a distant common antecedent with a partially causative role (aging), but such a highly variable and extremely remote relationship disqualifies the surrogate from relevant clinical use.
2. The surrogate and the outcome are linked via close common causal antecedents, but effects on one do not affect the other, as they both result from a common underpinning. For example, it is possible that hyperglycemia and atherosclerosis are the results of insulin resistance and/or lipotoxicity, and treating hyperglycemia (surrogate marker) may not affect CVD risk (outcome) unless such treatment is targeted at the underlying pathobiology. A similar scenario may account for the fact that although elevated circulating C-reactive protein is associated with atherosclerosis and cardiovascular events [24–26], several anti-inflammatory interventions failed to materially improve (and in some cases, worsened) aggregate CVD risk [27–30].
3. The surrogate and the outcome are mechanistically linked but only partially or in the context of a redundant system, such that effects on the surrogate only partially (or do not at all) affect the outcome. The redundancy of the system for platelet activation and aggregation and its clinical applicability provides an example of this phenomenon. Drugs that affect the "upstream" regulators or activators of platelets (eg, aspirin, thienopyridines, and most recently the experimental thrombin receptor antagonists) can only partially antagonize platelet function and can be overcome by platelet activation via parallel pathways that remain unaffected by these drugs [31,32]. This phenomenon is the biologic underpinning for the development and basis for clinical use (and clinical efficacy) of antagonists of the platelet glycoprotein IIb/IIIa receptor, the common denominator in the parallel pathways of platelet aggregation. However, as mentioned previously, oral formulations of these drugs also failed to improve cardiovascular outcome.
4. The surrogate and the outcome are mechanistically linked, and effects on the surrogate affect the outcome, but the magnitude of the effect is modulated by "off-target" effects of the intervention, either adversely (ie, adverse side effects) or favorably (often referred to as *pleiotropic effects*). This is perhaps the most common way in which surrogates fail, and there are multiple examples of adverse side effects—virtually always completely

unexpected—leading to the doom of otherwise promising drugs in the cardiovascular field. Several inotropic agents turned out to be proarrhythmic [16,17]: the first-generation thiazolidinedione troglitazone was plagued by hepatic toxicity [33], and the cholesteryl ester transfer protein inhibitor torcetrapib led to increased mortality and morbidity of unknown cause (but possibly related to an off-target effect on the aldosterone axis, electrolyte handling, and blood pressure [23•]), just to highlight two examples. On the positive side, some drugs may improve outcome to a greater extent than their effect on surrogate markers. As examples of such pleiotropic effects, statins may improve clinical outcome beyond their effect on LDL reduction [34,35], and the magnitude of observed cardiovascular benefit with metformin exceeds the expected effect based on the relatively modest effect on HbA1c [5••,36].

Critical Appraisal of the Validity of Using HbA1c as a CVD Surrogate

Could hyperglycemia be a valid surrogate marker for CVD risk in T2DM? The first criterion for surrogate validity (surrogate correlates with clinical outcome) appears to be satisfied through several epidemiologic studies of association between a variety of glucose metrics and CVD risk [37–40]. Evaluating the second criterion (effect of intervention on surrogate fully predicts effect on clinical outcome) has been much more difficult, with a mix of positive and negative signals scattered throughout the literature and a paucity of large-scale clinical trials to specifically test the impact of glycemic intervention on cardiovascular outcome.

The recently announced results of three major trials shed new light on this issue. The ACCORD [9••], ADVANCE [10••], and VADT trials [11••] together randomly assigned more than 23,000 patients to intensive versus standard glycemic control strategies based on HbA1c targeted levels, with the expectation that lowering blood glucose to normal or near-normal levels in the intensive control groups would yield CVD risk reduction and less mortality. However, none of the three studies met this expectation. Even more strikingly, the ACCORD trial showed significantly increased cardiovascular and all-cause mortality in the intensive treatment group, prompting its early termination, and the VADT trial revealed a similar (although not statistically significant) trend. Although there are many differences among the three trials, and ample room exists for interpretation of the results, one overarching conclusion is that HbA1c as a surrogate marker fails to reflect the intervention's effect on cardiovascular and mortality outcomes among patients with advanced T2DM and increased CVD risk, by virtue of prevalent CVD or additional CVD risk factors at study entry.

Diabetes Drugs and CVD: Where Do We Go From Here?

In spite of the evidence (summarized previously) from recent trials of glucose control yielding disappointing results with regard to CVD risk modification, the proven benefit of glucose management in T2DM for the purpose of modifying microvascular disease risk and ameliorating symptoms of hyperglycemia maintains a pivotal role for the use of therapeutic interventions (lifestyle and pharmaceutical) to treat hyperglycemia associated with T2DM. Therefore, from a cardiovascular standpoint, perhaps the principal therapeutic consideration for glucose-lowering medications should be *primum non nocere* ("first do no harm"): are the diabetes drugs that we use (and drugs in development) at least safe from a CVD perspective? This question is most acutely highlighted by the published meta-analysis by Nissen and Wolski [7•] that demonstrated a cardiovascular safety signal associated with the use of rosiglitazone, with an apparent increase in atherosclerotic CVD complications. In the wake of these results, the concerning safety signal for rosiglitazone has been supported by observations from some studies but not by others [8•,41–43]. Perhaps the most valid of the analyses to date derive from the interim results of the prospective RECORD trial, in which rosiglitazone was associated with an increased risk of heart failure but no statistically significant increased risk of major atherosclerotic cardiovascular events or death [8•]. Although each of the published studies has important shortcomings, yielding a dataset on aggregate that is not conclusive, these studies and the academic debate that has followed acutely highlight the clinical uncertainty in the diabetes field, underscoring the imperative for systematic evaluation with regard to cardiovascular efficacy and safety of drugs, both experimental and approved, to treat T2DM.

The FDA and its European counterpart, the European Medicines Agency, recently addressed the need to re-evaluate the process of T2DM drug approval and have called meetings of their respective advisory committees. The FDA Endocrinologic and Metabolic Drugs Advisory Committee met in early July 2008 with the stated purpose of discussing "the role of cardiovascular assessment in the preapproval and postapproval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus"; the detailed proceedings from that meeting are publicly available [44]. In December 2008, the official FDA guidance with regard to CVD assessment of drugs for diabetes was made public, deriving in large part from the proceedings in July. At that time, new guidance for the industry was issued, recommending that new antidiabetic therapies be tested in clinical trials to demonstrate that they do not increase cardiovascular risk [45]. The full text of this nonbinding recommendation is available from the FDA [46]. Although it was a clear step toward the regulatory requirement for the assessment of cardiovascular effects of T2DM drugs, the nonbinding nature of the guidance preserves some potential discord between

the recommended components of drug evaluation and the law that governs the activity of the agency [47]:

> FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate end point that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit … Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate end point to clinical benefit ...

Continued efforts at reconciling such apparent discordance, and the interpretation and application of such guidance in the planning of drug registration programs for experimental and, ultimately, existing diabetes drugs remain notable challenges for the years to come.

In this context, lessons learned from the drug development program for torcetrapib may be particularly informative. As previously mentioned, the development of the HDL-raising drug torcetrapib was halted based primarily on observations during the ILLUMINATE trial, a CV morbidity and mortality trial comprising more than 15,000 patients at high CVD risk that assessed the drug effects on a composite of coronary heart disease death, myocardial infarction, stroke, and unstable angina [23•]. The study was terminated prematurely due to adverse clinical outcomes observed with torcetrapib versus placebo, including a 25% increased risk for major adverse cardiovascular events and a 58% increased risk for all-cause mortality. Most importantly, these observations occurred in the setting of more than a 70% increase in HDL and a 25% decrease in LDL associated with torcetrapib assignment. Due to its very large size, coupled with the systematic collection and adjudication of clinical events, this clinical trial had adequate power to detect relatively small absolute (but sizable relative) increases in CVD risk and mortality that would have been very difficult, if not impossible, to detect based on the present model of ad hoc postmarketing pharmacovigilance. Although the torcetrapib experience was wholly disappointing from a clinical and scientific perspective, not to mention from the drug development perspective, the lessons learned from this experience are invaluable and forcefully underscore the imperative for ongoing critical appraisal of the validity of surrogates and, in place of reliance on such, the regulatory imperative of morbidity and mortality trial assessments for therapeutics intended for diseases as common and as morbid as T2DM and CVD.

Conclusions

It is truly an exciting and dynamic time in the realm of T2DM drug regulation, with the present evolution of the regulatory landscape having direct and important clinical correlations. The imperative for CVD assessment of drugs for T2DM has never been so objectively apparent as it is now, and given the global burden of T2DM, never has it been so important. These considerations are complemented by a rapidly evolving therapeutic milieu. We are quickly evolving from a "seller's market," in which as recently as 1995, there were only a few treatment options for T2DM (insulin, sulfonylureas, acarbose, metformin), to an exploding "buyer's market," presently with more than 30 drugs and formulations available in the United States indicated for the treatment of T2DM—comprising nine different drug classes—complemented by the evaluation of at least 12 novel classes of medications for T2DM in advanced clinical testing. These remarkable advances afford us some luxury to transition toward clinical outcomes appraisal to assess emerging (and existing) therapies.

As we move forward, uncertainties remain: should T2DM drug regulation require (instead of "recommend") cardiovascular outcomes assessment? If so, would this apply only to drugs in development or also to drugs already approved and in clinical use? If it were the latter, who would be responsible for funding the vast and very expensive clinical research efforts required to rigorously assess the CVD effects of drugs that are now generic? If cardiovascular outcomes assessment becomes a regulatory imperative, would the requirement for cardiovascular outcomes data apply prior to or following drug registration (ie, approval)? With recent guidance on these issues, the FDA (with similar guidance forthcoming from the European Medicines Agency) is taking a critically important step toward the requirement for cardiovascular outcomes assessment of drugs for T2DM. This is presently focused on developing, at a minimum, evidence excluding incremental CVD risk of relevant magnitude at the time of new drug application, with an expectation for subsequent definitive assessment of CVD effects through larger, more robustly powered cardiovascular clinical outcomes trials. Although the rebuttal from industry and academia alike to such propositions has commonly been "we cannot afford to do this," it is increasingly evident from the clinical perspective that we cannot afford not to do it.

Clinical Trial Acronyms

ACCORD—Action to Control Cardiovascular Risk in Diabetes; ADVANCE—Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ILLUMINATE—Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events; RECORD—Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; VADT—Veterans' Affairs Diabetes Trial.

Disclosure

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a consultant for Novo Nordisk, Tethys Bioscience, and AstraZeneca and has received research grant support from GlaxoSmithKline. No other potential conflicts of interest relevant to this article were reported.

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