Regulating Drugs that Regulate Glucose: Cardiovascular assessment of type 2 diabetes medications

Darren K. McGuire, MD, MHSc
Professor of Medicine
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This is to acknowledge that Darren K. McGuire, M.D, M.H.Sc.. has disclosed that he does have financial interests or other relationships with commercial concerns related directly to this program. Dr. McGuire will be discussing off-label uses in his presentation.

Darren K. McGuire, MD, MHSc
Professor of Medicine; Division of Cardiology

Dr. McGuire holds the Dallas Heart Ball Chair for Research on Heart Disease in Women, directs the UTSW Division of Cardiology Clinical Trials Unit, and is the Lead Physician of the Parkland Hospital and Health System Outpatient Cardiology clinics. His expertise is in clinical outcomes trial design and execution, and registration/regulation of drugs, focusing on the nexus of type 2 diabetes (T2DM) and cardiovascular disease. He presently has leadership roles for numerous international cardiovascular clinical outcomes trials, including T2DM, obesity, and lipid trials. Dr. McGuire recently completed a 4-year term on the FDA Cardiovascular and Renal Drugs Advisory Committee and remains an FDA *ad hoc* consultant. He is clinical trials editor of *Diabetes and Vascular Disease Research,* associate editor of the *American Heart Journal*, and co-editor of the textbook: *Diabetes in Cardiovascular Disease: A Companion to Braunwald's Heart Disease*.

Purpose and Overview:

This presentation reviews the epidemiology of diabetes and its cardiovascular complications, the history of diabetes drug development, and the challenges to consideration of glycated hemoglobin (HbA1c) as a surrogate marker for clinical efficacy. These considerations set the backdrop for the recent paradigm shift in the regulatory requirements for the development of anti-hyperglycemic drugs for type 2 diabetes, presenting the case for why both new and existing anti-hyperglycemic medications must undergo assessment in clinical trials of cardiovascular outcomes. Finally, in the wake of this new guidance, the present cardiovascular outcomes trial landscape for patients with type 2 diabetes will be reviewed.

Educational objectives

- To understand the increasing incidence and prevalence of T2DM and its cardiovascular complications.
- To understand the anti-hyperglycemic drugs presently approved for T2DM and their lack of cardiovascular outcomes data.
- To understand the history of the regulatory requirements for new drug application and approval for T2DM medications, recent changes in such requirements, and their influence on drug development
- To understand the present landscape of randomized clinical trials completed and ongoing evaluating the cardiovascular safety and efficacy of T2DM medications.

Dr. McGuire discloses honoraria for trial leadership and consultation from GlaxoSmithKline, Takeda, Novo Nordisk, Orexigen, Cubist, Janssen, Eli Lilly, Bristol Myers Squibb, Astra Zeneca, Boehringer Ingelheim, Merck, Regeneron, Lexicon, Eisai

Introduction

Type 2 diabetes mellitus (T2DM) is a strong and increasingly prevalent independent risk factor for cardiovascular (CV) morbidity and mortality worldwide. Glycemic control is both a target of therapy and a principal marker of therapeutic success in T2DM. Clear associations have been consistently observed between worsening glycemic control and worsening CV risk, but whether pharmacologically lowering glucose is accompanied by a commensurate reduction in CV risk is a matter of ongoing controversy. It is notable that half a century after the approval of the first non-insulin anti-hyperglycemic agent in the US by the Food and Drug Administration (FDA), and subsequent approvals of over 40 drugs/formulations comprising 12 classes of medications, we still have no conclusive evidence of CV risk reduction with any of the drugs, individually or in combination, presently approved for use in the treatment of patients with T2DM.

It has become increasingly apparent from recent large-scale clinical outcome trials of patients with T2DM that the degree/intensity of glucose lowering poorly predicts CV outcomes, and many instances observed of increased cardiovascular risk in clinical trials of antihyperglycemic drugs/intensive glucose lowering strategies, invalidating HbA1c as a surrogate for CV efficacy or safety, have raised the alarm with regulatory agencies. These observations have led to a sea-change in the regulatory requirements for the development and evaluation of anti-hyperglycemic drugs used and being developed for the treatment of T2DM. Specifically, this uncertainty has prompted regulatory agencies in both the United States and in Europe to revise the regulatory requirements for new drug application and approval of T2DM medications, to at a minimum prove CV safety within a pre-defined margin of statistical certainty.[1]

This grand rounds presentation reviews the background and observations that have led to this paradigm shift in the regulation of anti-hyperglycemic drugs for T2DM, and presents the case for why both new and existing anti-hyperglycemic medications must undergo assessment in clinical trials of cardiovascular outcomes.

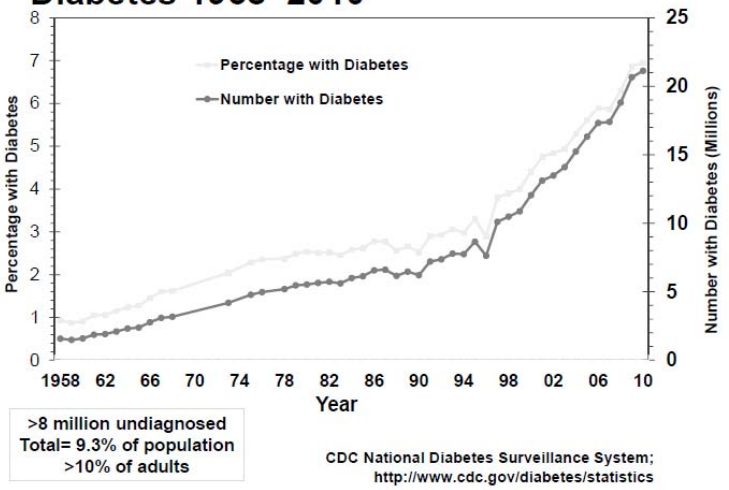
The "Perfect Storm" Underpinning Regulatory Revision for T2DM Drug Development

Though many factors have contributed to the evolution of regulatory guidance for T2DM drug development, the following 5 conditions are key considerations comprising the “perfect storm” yielding the imperative for the present regulatory focus on and requirement for CVD safety assessment of drugs for T2DM.

Increasing incidence and prevalence of T2DM

Diabetes is a grave and growing public health problem, with 29.1 million people estimated to have DM in the United States (9.3% of the population; >10% of the adult population),(http://www.cdc.gov/diabetes/pubs/statsreport14.htm; Accessed 0ctober 8, 2014; **Figure 1**) and 366 million worldwide.[2] In addition, the global burden of DM is projected to continue to increase to a affect a projected 552 million people by 2030,[2] driven primarily by the increase in T2DM.

Figure 1. US Population with Diagnosed Diabetes 1958–2010

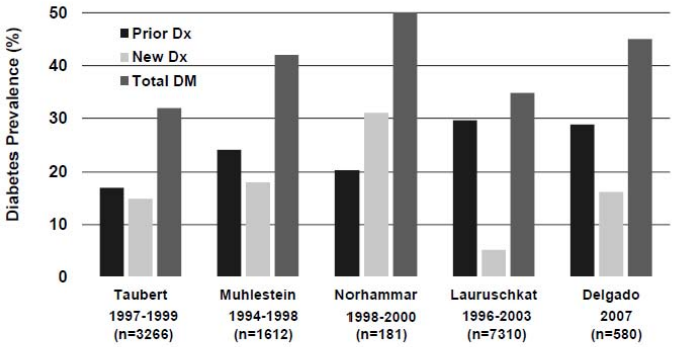


Increasing awareness of the CV consequences of T2DM

Having T2DM more than doubles the risk of dying of heart disease or stroke.[3] Of the 284,000 deaths attributable to DM in the U.S. in 2007, about 2/3 had CV disease as the primary cause of death,[4] with CVD listed as the cause of death in ~65% of people with DM, compared with ~25% in the general U.S. population. Likewise, 30-50% of unselected patients in CV clinical cohorts have concomitant diabetes (**Figure 2**).

The degree of hyperglycemia as reflected by HbA1c also tracks observationally with the incidence and prevalence of cardiovascular complications and death, but the logical converse that controlling hyperglycemia should proportionally reduce the incidence of these complications has not been clearly demonstrated in large, randomized clinical trials.

Figure 2. Diabetes in Cardiology Cohorts

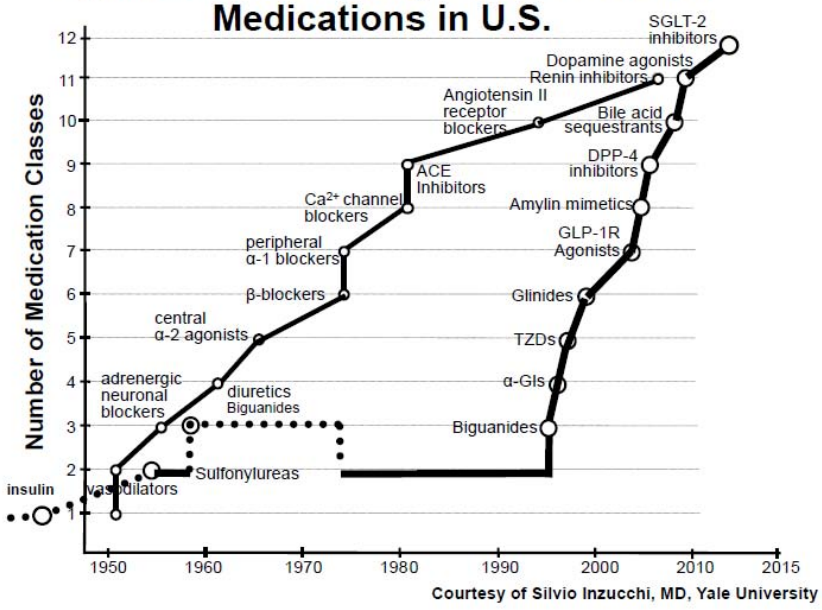


Am Heart J. 2003;145:285-91; *Am Heart J.* 2003;146:351-8;
Circ. 2005;112:2397-2402; *Lancet.* 2002;359:2140;
2007 ADA Scientific Sessions-646-P

Proliferation of Medications Available to treat Hyperglycemia

Over the past 20 years, there has been an explosion of drugs developed for T2DM.[5,6] Until 1995, only insulin and sulfonylureas were available to treat hyperglycemia of T2DM in the US. In 1995, metformin and acarbose were approved. This barren therapeutic landscape underpinned an urgency to develop and bring to market additional thereapeutic options, with focus especially on avoiding hypoglycemia and weight gain associated with insulin and sulfonylureas, and on this basis, provided some support for fairly liberal regulatory guidelines for such drug development. In this context, there are presently >40 formulations in 12 classes of medications approved in the US for the treatment of hyperglycemia in T2DM, thus eliminating the "pressure" to rush new drugs to market (**Figure 3**).

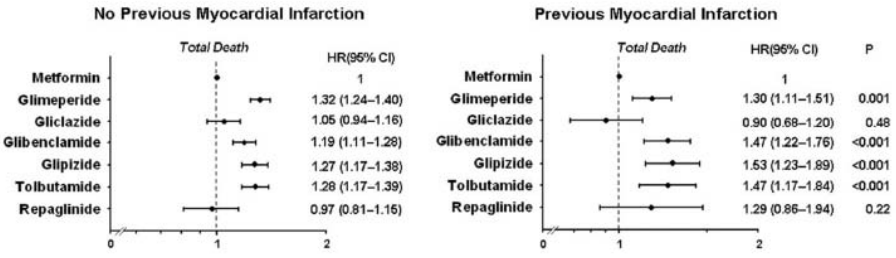
Figure 3. Half-Century of HTN & T2DM Medications in U.S.



On- and Off-target Safety Signals of Antihyperglycemic Medications

Weight gain and hypoglycemia risk have long been understood as adverse effects of insulin-providing therapies such as sulfonylureas, meglitinides, and exogenous insulin administration, each of which could influence CV risk.[6] By blockade of ATP-dependent potassium channels, the sulfonylureas could worsen sequelae of acute coronary ischemic events by inhibition of ischemic preconditioning, including increased mortality (**Figure 4**).[6,7]

Figure 4. Associations between Insulin Secretagogues and Mortality

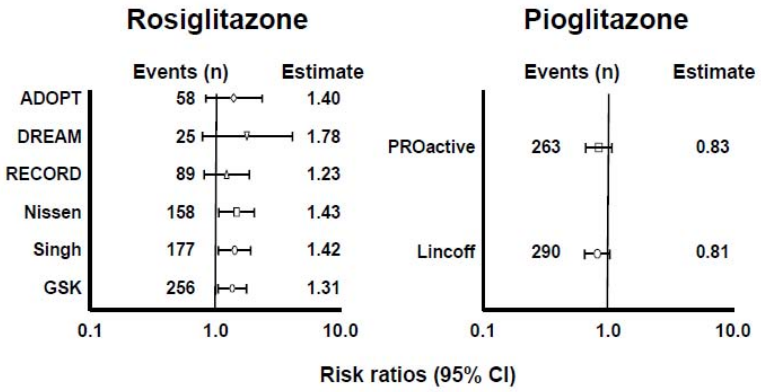


Thiazolidinedione medications have a littany of adverse drug effects related to CV risk, key among them are weight gain, increased risk for incident or worsening heart failure, and for rosiglitazone, increased risk for myocardial infarction.[5] Though potent at reducing HbA1c, the dual PPAR α/γ agonists, 2 of which went through Phase III testing, never reached clinical approval due to increased risk for heart failure and signals for other CV risks as well as increased GI bleeding risk.[8,9] In the DPP 4 inhibitor class, while completely neutral in effect on major adverse cardiovascular outcomes vs.

placebo in the largest T2DM trial executed to date,[10] saxagliptin significantly increased risk for HF hospitalization,[11] with similar trend observed (though not statistically significant) with alogliptin in another trial reporting at the same time.[11,12] Finally, the newest class of T2DM medications available, inhibitors of the sodium glucose cotransporter (SGLT) 2 that inhibit urinary glucose reabsorbtion and increase urinary glucose excretion, may increase risk for symptomatic hypotension, volume depletion events, and some decline in eGFR.[13]

Non-cardiometabolic side effects (i.e. "off-target adverse effects") have also peppered the landscape of T2DM medications, many of which were completely unanticipated, idiosyncratic, and/or unmonitorable. Phenformin was withdrawn from the US market due to increased risk for lactic acidosis; troglitazone for increased risk of fulminant/fatal hepatotoxicity. Rosiglitazone has restricted access based on risk for myocardial infarction (**Figure 5**)[14], and pioglitazone has associated risks of small bone fractures, macular edema, and others. In summary, based on knowledge of mechanism of action and accumulated preclinical and early clinical data, adverse safety signals are often not anticipated and not detectable until thousands (or even millions) of patient-years of exposure are accumulated.

Figure 5. Summary of RCT & Meta-Analysis Data on TZDs and MI Risk



Bidirectional invalidation of HbA1c as a surrogate for CV risk

Definition and overview of "surrogates" in the field of medicine

A surrogate as defined by Webster's Dictionary is quite simply "one that serves as a substitute"; 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 endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effects of the therapy".[15] To have relevance and utility in the research and/or clinical arena, a surrogate must fulfill two fundamental criteria: first, it should track with the outcome of interest without deviation, and thus should accurately predict disease outcome; second, the response of a surrogate to an intervention should fully reflect the effect of the intervention on the clinical outcome. The latter criterion is clearly the most difficult (and in some cases outright impossible) to test and to prove, but is also the most important.[16]

While the research use of surrogate markers in lieu of clinical end-points has obvious practical justifications (e.g. limiting study time, sample size and costs; streamlining drug development; informing dose selection/optimization; allowing assessment of drug response in individual patients; etc.), the problem is that validated surrogates are rare across the spectrum of medicine. That is, few intermediate markers have risen to the level of surrogate, which requires critical appraisal and validation against patient-experienced clinical outcomes before they can be used to demonstrate "efficacy" of a treatment or to inform clinical decision-making.

Failures of numerous 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 many examples of such failure of intermediate markers to demonstrate surrogacy for clinical outcomes. Just to name a few in the cardiovascular arena, failed surrogates include HDL-C, triglycerides, ejection fraction, platelet function testing, carotid intima-media thickness, and many others-all consistently associated with disease and risk, yet interventions that "favorably affect" these markers/measures have often (and sometime always) failed to render commensurate changes in clinical outcomes.

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

Scenarios by which proposed surrogate markers may fail

A) The surrogate and the outcome are associated but not mechanistically or causally linked. For example, while graying of hair (or balding; or wrinkling of the skin) may temporally associate with increased CVD risk, interventions to alter hair graying would not be expected 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 (ageing) satisfying the first surrogacy criterion and consisent statistical association between the marker and the outcomes; but such highly variable and extremely remote relationship disqualifies the surrogate from relevant clinical use.

B) 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 both 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 while elevated circulating C-reactive protein is associated with atherosclerosis and CV events, a number of anti-inflammatory interventions failed to materially improve (and in some cases, worsened) aggregate CVD risk.

C) 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 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, such as aspirin, thienopyridines, and most recently, the experimental thrombin receptor antagonists, are able to only partially antagonize platelet function and can be overcome by platelet activation via parallel pathways that remain unaffected by these drugs. 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, yet 4 oral formulations of GpIIb/IIIa antagonists in 5 randomized trial all failed to improve clinical outcomes.

D) 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 (i.e. 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; for example, several inotropic agents turned out to be pro-arrhythmic; the first generation thiazolidinedione troglitazone was plagued by hepatic toxicity; the cholesterylester transfer protein (CETP) inhibitor torcetrapib that potently raised HDL-C led to increased mortality and morbidity of unknown cause, but possibly related to an off-target effects on aldosterone, electrolyte handling, and blood pressure, just to highlight a few of the numerous examples. On the positive side, some drugs may improve outcome to a greater extent than their effect on surrogate markers would predict. As examples of such pleiotropic effects, statins may improve clinical outcome beyond their effect on LDL-C reduction, and the magnitude of observed CV benefit with metformin exceeds the expected effect based on the relatively modest effect on HbA1c.

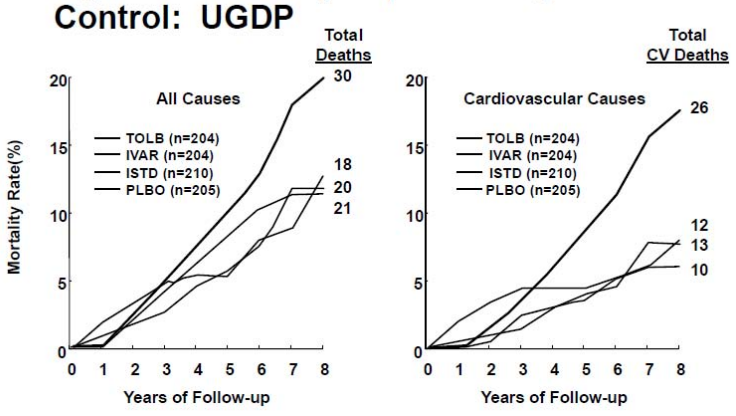
Considering HbA1c as a Surrogate

Could hyperglycemia in general, and HbA1c specifically, be a valid surrogate for CVD risk in T2DM? The 1st criterion for surrogate validity (the marker or measure correlates reliably with clinical outcomes) is well satisfied through numerous epidemiologic studies of association between a variety of glucose metrics and CVD risk.

Evaluating the 2nd criterion (effect of intervention on the surrogate fully predicts effect on clinical outcome), the case for HbA1c simply fails. Until the past decade, there was a paucity of data from large scale clinical trials to specifically evaluate the impact of glycemic intervention on CV outcome. However, numerous examples emerging over the past 10-15 years have unequivocally invalidated HbA1c in this regard-with key regulatory and clinical implications.

First, drugs with moderate to potent effects on HbA1c and strategies that most intensively reduce HbA1c have most commonly failed to improve (and at times, worsen) CV outcomes. In 1971, the University Group Diabetes Project (UGDP) randomized trial reported increased CV and all-cause mortality with tolbutamide, a first generation sulphonylurea (SU) (**Figure 6**),[17] prompting early termination of that arm of the trial and modification of the U.S. product label to include a "special warning on increased risk of CV mortality". Based on presumed within-class similarities with no definitive proof to the contrary, that warning has persisted in the product label of every SU subsequently marketed in the US, although no further signals of adversity have been observed with SUs as a drug class in subsequent larger trials testing 2nd and 3rd generation SU medications,[18,19] while observational analyses maintain concerns about incremental CV risk with SU treatment.[20,21]

Figure 6. Mortality Impact of Glycemic Control: UGDP



More recently, the results of three major glycemic control CV outcomes trials have further contributed to the invalidation of HbA1c as a surrogate for CV risk. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[22] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[19] and the Veterans' Affairs Diabetes Trial (VADT)[23] together randomized over 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 3 studies met this expectation failing to achieve statistical significance in analyses of their primary composite endpoints of major adverse CV events. Even more strikingly, the ACCORD trial showed a significantly increased mortality (CV and all-cause) in the intensive treatment group prompting the trial to be terminated early, and the VADT trial revealed a similar (although not statistically significant) trend. Even though there are many differences between the 3 trials and ample room for interpretation of the results, one overarching conclusion is that HbA1c fails as a surrogate marker for CV outcomes, at least among patients with advanced T2DM and increased CVD risk.

Oppositely, some T2DM medications with less potent effects on HbA1c have demonstrated neutral to favorable effects on CV risk and outcomes. Most notably, metformin in the UKPDS trial yielded only a 0.4% HbA1c contrast compared with the usual care group, yet had statistically significant improvements in risk for MI and for all-cause mortality.[24] This is in contrast with the UKPDS patients randomized to insulin, chlorpropamide, or glibenclamide (aka, glyburide in the US)-a 0.9% HbA1c contrast and no significant difference in any of the major adverse CV outcomes. Similarly, in the PROactive trial of pioglitazone vs. placebo, which achieved HbA1c contrast of 0.4%, the composite of CV death/MI/stroke was reduced by 16%.[25] Therefore, HbA1c has been bi-directionally invalidated by the 2nd criterion for surrogacy, with potent therapies have null (or even adverse) clinical impact, and some lesser potent therapies have exaggerated CV effects.

In summary, the increasing global incidence and prevalence of T2DM coupled with the associated CV consequences represent an international public health crisis, demanding higher levels of certainty and evidence on how most safely and effectively to treat these patients. In addition, myriad on- and off-target adverse effects have been observed across several classes of drugs for T2DM underscoring the importance of safety assessment in large populations over long periods of time. Until 1995, given scarcity of therapeutic options for the treatment of T2DM, quite liberal regulatory guidelines were in place that encouraged drug development and expedited drug approval-now with an extensive arsenal of therapeutic options comprising 12 classes of medications with an indication for T2DM-more classes than are presently available to treat hypertension-such "developmental pressure" no longer exists. Finally, and most importantly, the certain invalidation of HbA1c as a surrogate for CV efficacy and for systemic safety yields the mandate to require clinical outcomes trials, and specifically CV outcomes trials, of T2DM drugs in support of new drug application.

Evolution of the Regulatory Landscape for T2DM Drugs

Until recently, regulatory agencies around the world based T2DM drug approval and labeling primarily on changes in glycometabolic biomarkers (glycosylated hemoglobin, HbA1c,

being the most widely used), with the assumption that benefits on vascular risk (micro- and macro-vascular) would track accordingly. The use of HbA1c as surrogate marker of clinical outcome was the *de facto* standard for new drug evaluation based on the beneficial effects of improved glycemic control on DM symptoms and intermediate measures of microvascular complications (nephropathy, retinopathy, and neuropathy).[18,26] This disconnect between validation of HbA1c as a surrogate for microvascular complications of T2DM but its invalidation as a surrogate for macrovascular risk reduction as discussed above merits ongoing academic discussion and has catalyzed a recent paradigm shift in the regulatory approach to T2DM drugs both in the US and in Europe.

In spite of the evidence summarized above from recent trials of glucose control yielding discordant and often adverse 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 remains pivotal for the use of therapeutic interventions (lifestyle and pharmaceutical) to treat hyperglycemia associated with T2DM. That is, favorable effects on HbA1c remain necessary for a drug to achieve approval for the treatment of T2DM, though no longer is it sufficient.

From a CV standpoint, perhaps the principal therapeutic consideration for glucose lowering medications should be *primum non nocere* (i.e. first do no harm): are the T2DM drugs that we use (and drugs in development) at least safe from a CVD perspective? The increasing awareness of the disconnect between HbA1c effects and CV modification and the corresponding academic debate ongoing acutely highlight the clinical uncertainty existing in the T2DM field, underscoring the imperative for systematic evaluation with regard to CV efficacy and safety of drugs to treat T2DM, both experimental and approved.

Both the US FDA and its European counterpart, the European Medicines Agency (EMEA), addressed this need to re-evaluate the process of T2DM drug approval by convening meetings of their respective advisory committees in early to mid 2008. 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 pre-approval and post-approval settings for drugs and biologics developed for the treatment of T2DM"; the detailed proceedings from that meeting are publicly available (http://www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic. Accessed October 8, 2014).

In December 2008, the official FDA guidance with regard to CV safety assessment of drugs for T2DM was made public, deriving in large part from the proceedings in July. At that time, new guidance for industry was issued recommending that new anti-hyperglycemic therapies for T2DM be tested in clinical trials to demonstrate that they do not increase cardiovascular risk. The full text of this nonbinding recommendation is available from the FDA (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed October 8, 2014).

Recommendations include inclusion of high risk patients (e.g. elderly; women; those with renal impairment); minimum exposure and observation of 2 years; prospective and blinded adjudication of all cardiovascular events in phase II and III trials; and appropriate design of these trials to allow for an adequate meta-analysis of all phase II and III data for major adverse CV events, which would have to show no evidence of increased cardiovascular risk with the new drug within a prespecified statistical margin of certainty. And though not stated, it is implied in the guidance that such trials would be against placebo comparator, as non-inferiority analyses

against active comparator requires that the control therapy have proven efficacy-no such drug exists for T2DM. The FDA will also generally require a post-marketing cardiovascular safety trial of newly approved T2DM drugs if premarketing data indicate a potential but not statistically significant risk (specifically, if the upper bound of the 95% confidence interval for estimated increased risk is greater than 1.3).

Once this new guidance was put forward, simultaneously and harmoniously between the FDA and the EMEA first with public announcement in September 2008 followed by publication and filing of the Guidance for Industry documents in December, 2008, there was a bit of an international uproar among members of industry and academia alike-that this would halt T2DM drug development. Of note, this new guidance was made public at the height of the 2008-09 global financial crisis, making the threat of halting drug development all the more serious. To place this into context, prior to February 2008, a new drug application for a T2DM indication could achieve approval with as little as 200 patient-years of exposure to the investigational drug. In the wake of the revised guidance for CV safety assessments, the requisite exposure for penultimate T2DM drug approval is in excess of 15,000 patient years- >70-fold increased exposure over just 10 months (and likely a similar fold-increment in costs).

Table 1. Novel Drugs & Targets in Development for Diabetes

- Bromocriptine
- Colesevelam
- Ranolazine
- Long-acting GLP-1 receptor agonists
- DPP IV inhibitors
- Dual PPAR α/γ agonists
- Pan PPAR $\alpha/\gamma/\delta$ agonists
- Sodium-GLucose coTransporter (SGLT) 2 and 1/2 antagonists
- Glucagon receptor antagonists
- Fructose 1,6 Bisphosphatase inhibitors
- Glucokinase activators
- 11β-hydroxysteroid dehydrogenase (HSD)-1 inhibitors
- Protein tyrosine phosphatase 1B inhibitors
- Acetyl CoA carboxylase-1 and -2 inhibitors
- G-protein coupled receptor (GPR)-40 & -119 Agonists
- Protein Tyrosine Phosphatase (PTB)-1b inhibitors
- Carnitine Palmitoyltransferase (CPT)-1 inhibitors
- Acetyl CoA Carboxylase (ACC)-1 & -2 inhibitors

Now approaching 6 years after the new guidance was put forth, there has been no evident interruption of T2DM drug development (**Table 1**), although exact metrics for scientific assessment of such trends are not readily available. In fact, there are presently >20 novel therapies/therapeutic targets being probed in the drug discovery/development phase for T2DM.[27]

Numerous cardiovascular outcome trials of T2DM drugs are presently underway or in advanced stages of planning (**Table 2**), with completed/ongoing trial programs of antihyperglycemic therapies comprising >210,000 patients and climbing. The output from these trials is expected to lead over the next decade to an exponential growth of the available evidence base, and hopefully lead to better treatment strategies and better cardiovascular outcomes for patients with T2DM.

Table 2. CV Outcomes Trials in T2DM

Trial	Drug	Sample Size	Stage
ORIGIN	Insulin glargine	12,500	Completed
TOSCA IT	Pio vs. SU	3371	Started 9/2008
TECOS	Sitagliptin	14,000	Started 12/2008
ACE	Acarbose	7500	Started 2/2009
TIDE	Rosi/Pio	16,000	Halted
EXAMINE	Alogliptin	5,400	Completed
CANVAS	Canagliflozin	4500	Completed
T-emerge 8	Taspoglutide	2,000	Halted
AleCardio	Aleglitazar	7,000	Halted
SAVOR TIMI-53	Saxagliptin	16,500	Completed
ELIXA	Lixisenatide	6000	Started 6/2010
EXSCEL	Exenatide LAR	12,000	Started 6/2010
EMPA-REG Outcome	Empagliflozin	7000	Started 7/2010
CAROLINA	Linagliptin	6000	Started 10/2010
LEADER	Liraglutide	8723	Started 8/2010
GRAND 306	Tak 875	5000	Halted
AlePrevent	Aleglitazar	19,000	Halted
REWIND	Dulaglutide	9622	Started 7/2011
SUSTAIN 6	Semaglutide	3260	Started 2/2013
DECLARE TIMI 58	Dapaglifozin	17,000	Started 4/2013
CARMELINA	Linagliptin	8300	Started 7/2013
DEVOTE	Insulin Degludec	7500	Started 10/2013
MK-8835-004	Ertugliflozin	3900	Started 11/2013
CANVAS-R	Canagliflozin	5700	Started 12/2013
CREDENCE	Canagliflozin	3700	Started 2/2014

Conclusions

It is a 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 now, and given the increasing global burden of T2DM, never 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; suflonylureas; acarbose; metformin), to an exploding "buyer's market", presently with over 40 drugs and formulations available in the US indicated for the treatment of T2DM, comprising 12 different drug classes, complemented by the evaluation of at least 20 additional novel drugs/drug classes/therapeutic targets in advanced pre-clinical and clinical testing. These remarkable advances afford us some luxury to transition toward clinical outcomes appraisal to assess emerging (and existing) therapies. While the rebuttal from industry and academia alike to such propositions has commonly been "We can't afford to do this", it is increasingly evident from the clinical perspective that…we can't afford not to.

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1. Gore MO, McGuire DK. Cardiovascular disease and type 2 diabetes mellitus: regulating glucose and regulating drugs. Curr Cardiol Rep 2009; 11: 258-63.
2. Gore MO, McGuire DK. Resolving drug effects from class effects among drugs for type 2 diabetes mellitus: more support for cardiovascular outcome assessments. Eur Heart J 2011;32:1832-4.
3. Gore MO, McGuire DK. Drugs for type 2 diabetes mellitus: The imperative for cardiovascular outcome assessment. Diab Vasc Dis Res 2012; 9: 85-8.