Abstract: Prevalent and incident heart failure (HF) is increased in people with type 2 diabetes mellitus, with risk directly associated with the severity of hyperglycemia. Furthermore, in patients with type 2 diabetes mellitus, mortality is increased ≈10-fold in patients with versus without HF. Reducing HF with antihyperglycemic therapies, however, has been unsuccessful until recently. In fact, HF as an important outcome in patients with type 2 diabetes mellitus seems to be heterogeneously modulated by antihyperglycemic medications, as evidenced by results from cardiovascular outcome trials (CVOTs) and large observational cohort studies. Appropriately powered and executed CVOTs are necessary to truly evaluate cardiovascular safety and efficacy of new antihyperglycemic medications, as reflected by the guidance of the US Food and Drug Administration and other regulatory agencies since 2008. In light of the best available evidence at present, metformin and the sodium-glucose-co-transporter 2-inhibitor empagliflozin seem to be especially advantageous with regard to HF effects, with their use associated with reduced HF events and improved mortality. Acarbose, the dipeptidyl-peptidase 4-inhibitor sitagliptin, the glucagon-like peptide 1-receptor agonist lixisenatide based on presently available CVOT results comprise reasonable additional options, as significant harm in terms of HF has been excluded for those drugs. Additions to this list are anticipated pending results of ongoing CVOTs. Although no HF harm was seen in CVOTs for insulin or sulfonylureas, they should be used only with caution in patients with HF, given their established high risk for hypoglycemia and some uncertainties on their safety in patients with HF derived from epidemiological observations. Pioglitazone is contraindicated in patients with HF>New York Heart Association I, despite some benefits suggested by CVOT subanalyses. (Circ Res. 2016;118:1830-1843. DOI: 10.1161/CIRCRESAHA.116.306924.)

Key Words: antihyperglycemic agents ■ cardiovascular disease ■ diabetes mellitus, type 2 ■ heart failure
Over the past 20 years, during which increasing attention in the field of type 2 diabetes mellitus (T2DM) has focused on atherosclerotic complications, heart failure (HF) has emerged as another serious complication occurring significantly more frequently in people with T2DM. A multitude of factors, including T2DM-related autonomic neuropathy, microangiopathy, cardiomyopathy, and renal glucotoxicity with hyperfiltration and expansion of intravascular volume contribute to HF in T2DM patients beyond the consequences of ischemic heart disease, hypertension, and neurohormonal overdrive, all of which are more common in persons with versus without T2DM. They constitute an ominous octet in the often unrecognized transformation of the heart in T2DM from ailing to failing (Figure 1). Observations on HF risks of antihyperglycemic therapies in patients with T2DM derive from many cohort studies and randomized clinical trials (RCTs) and highlight the importance of HF in the context of T2DM, as well as the effects of various antihyperglycemic medications on HF risk. A spectrum of effects of antihyperglycemic medications on risk for hospitalization caused by HF (hHF) have been observed from RCTs, with some increasing hHF risk, some with neutral effects, and one trial demonstrating superior outcomes for hHF with the study therapy. Most of these RCTs have been conducted in response to changes in the regulatory guidance of the United States Food and Drug Administration (FDA), with similar changes by the European Medicines Agency, that require demonstration of cardiovascular safety of new antihyperglycemic medications. Although such safety analyses have focused on atherosclerotic vascular disease outcomes, it has become clear that assessment of HF effects is of similar importance. The present article summarizes epidemiological associations between T2DM and HF, and where available, the effects of current antihyperglycemic medications on HF risk reported to date.

**Methods**

A systematic search in PubMed, Embase, Clinical trials.gov, and other sources yielded a total of 38 Cardiovascular Outcome Trials (CVOTs) designed to evaluate antihyperglycemic medications (Online Data Supplement). Six of those were performed in patients with impaired glucose tolerance, beyond the focus of this article, and were excluded. Of the remaining 32 trials, 20 have reported primary cardiovascular outcomes in patients with T2DM, constituting the core material for the present article, noting that numerous antihyperglycemic CVOTs are still ongoing.

**Results**

**Epidemiological Underpinnings**

Among the first studies to report an increased HF risk associated with T2DM was the Framingham Heart Study, in which HF events occurred 2.5× more often in men and 5× more often in women with versus without diabetes mellitus. A multitude of factors, including T2DM-related autonomic neuropathy, microangiopathy, cardiomyopathy, and renal glucotoxicity with hyperfiltration and expansion of intravascular volume contribute to HF in T2DM patients beyond the consequences of ischemic heart disease, hypertension, and neurohormonal overdrive, all of which are more common in persons with versus without T2DM. They constitute an ominous octet in the often unrecognized transformation of the heart in T2DM from ailing to failing (Figure 1). Observations on HF risks of antihyperglycemic therapies in patients with T2DM derive from many cohort studies and randomized clinical trials (RCTs) and highlight the importance of HF in the context of T2DM, as well as the effects of various antihyperglycemic medications on HF risk. A spectrum of effects of antihyperglycemic medications on risk for hospitalization caused by HF (hHF) have been observed from RCTs, with some increasing hHF risk, some with neutral effects, and one trial demonstrating superior outcomes for hHF with the study therapy. Most of these RCTs have been conducted in response to changes in the regulatory guidance of the United States Food and Drug Administration (FDA), with similar changes by the European Medicines Agency, that require demonstration of cardiovascular safety of new antihyperglycemic medications. Although such safety analyses have focused on atherosclerotic vascular disease outcomes, it has become clear that assessment of HF effects is of similar importance. The present article summarizes epidemiological associations between T2DM and HF, and where available, the effects of current antihyperglycemic medications on HF risk reported to date.

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Among the first studies to report an increased HF risk associated with T2DM was the Framingham Heart Study, in which HF events occurred 2.5× more often in men and 5× more often in women with versus without diabetes mellitus. Results from a landmark study by Nichols et al demonstrated an increased HF risk for participants with versus without T2DM across all age groups studied, with an inverse association between age and magnitude of incremental HF risk, ranging from an 11-fold increased HF risk in the youngest age group <45 years, to a 2.8-fold increased risk in the oldest group 65 to 74 years. Similar observations have been reported from more contemporary
cochets, such as the REduction of Atherosclerosis for Continued Health (REACH) Registry, in which patients with versus without T2DM had a 33% greater incidence of hHF (9.4% versus 5.9%; adjusted hazard ratio [HR], 1.33; 95% confidence interval [CI], 1.18–1.50). Both the incidence of hHF and its incremental risk associated with T2DM observed in the REACH registry are of similar magnitude as for the outcome of cardiovascular death in the same study (8.9% versus 6.0% in participants with versus without T2DM; adjusted HR, 1.38; 95% CI, 1.26–1.52). Likewise, in other studies, the incidence of hHF among patients with T2DM has been reported as comparable to that of acute myocardial infarction (MI).

Not only is HF risk increased in the setting of T2DM, but once present, HF adversely impacts prognosis. In patients with T2DM in the REACH registry, those with versus without HF at baseline had increased risk for cardiovascular death (adjusted HR, 2.45; 95% CI, 2.17–2.77) and hHF (adjusted odds ratio, 4.72; 95% CI, 4.22–5.29). In subgroups of patients with T2DM enrolled into RCTs, such as the Losartan Intervention for End Point Reduction in Hypertension Study (LIFE) or the Reduction of End Points in Noninsulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) trials, HF at baseline was associated with up to 12× higher death rates than T2DM individuals without baseline HF.

Furthermore, the composite of hHF and cardiovascular death occurred 75% more often in patients with versus without T2DM (28.5% of the cohort) in the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials program (7599 patients with HF with up to 3.5 years of follow-up), irrespective of whether HF was caused by ischemic heart disease. In terms of death, T2DM patients with ischemic HF in the CHARM trial program experienced a doubling compared with patients without T2DM and with nonischemic HF. In contrast, T2DM patients with nonischemic HF had comparable death rates to patients without T2DM who had ischemic HF.

In analyses from the CHARM program stratified by T2DM status and by baseline HF with preserved ejection fraction versus reduced ejection fraction, T2DM patients with HF with reduced ejection fraction compared with HF with preserved ejection fraction patients without T2DM had 2.5× higher incidence for both, the composite of cardiovascular death and hHF and for total death. Those with T2DM and HF with reduced ejection fraction experienced 40% mortality at a follow-up of 3.5 years. Patients with T2DM and HF with preserved ejection fraction had comparable risk for these selected outcomes to patients without T2DM who had HF with reduced ejection fraction. From these iterative subanalyses from the CHARM program, it seems that T2DM imparts similarly poor prognosis as does ischemic versus nonischemic cause of HF and reduced versus preserved systolic function.

**Association With Hyperglycemia**

In observational analyses among patients with T2DM, HF risk varies in continuous relationship to the degree of hyperglycemia. For example, in the United Kingdom Prospective Diabetes Study (UKPDS), a trial of 4000 patients with newly diagnosed T2DM followed up for a median of 10 years, there was a continuous relationship between hemoglobin A1c (glycated hemoglobin [HbA1c]) and incident HF when the cohort was analyzed independent of randomized treatment assignments. The Reykjavik study, a population-based cohort study in Iceland that recruited 19381 participants aged 33 to 84 years from 1967 to 1997, demonstrated a stepwise increase of baseline HF prevalence from participants with normal glucose tolerance to impaired glucose tolerance/abnormal glucose regulation to overt T2DM.

Importantly, although the observational associations between worsening glycemic metrics and increasing HF risk, intensification of glucose control has not been shown to affect HF risk. For example, in the UKPDS, when HF outcomes were analyzed by randomized trial treatment assignments of conventional versus more intensive glucose control (achieved HbA1c 7.9% versus 7.0%, respectively), intensive glucose control did not significantly affect the risk of HF. Subsequently, intensification of glycemic control versus usual care has failed to reduce HF risk in patients with T2DM in the Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Intensification of Blood Glucose Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT). Meta-analyses of trials comparing more versus less intense glucose control, with an average of 0.9% lower HbA1c in the intensive arms, confirmed no benefit on HF risk.

It remains unclear whether HF is a consequence of T2DM or perhaps vice versa. For example, it is unknown whether insulin resistance contributes to HF risk or is rather a physiological adaptation in response to HF, or in the setting of hyperglycemia, dyslipidemia, and increased circulating free fatty acids, adaptation to prevent adverse myocardial substrate metabolism and myocardial fuel overload. Given the failure of glucose control to improve HF risk, it is also important to note the complex metabolic milieu of T2DM, including dyslipidemia, inflammation, endothelial dysfunction,
and other potential mediators of HF risk not directly affected by glucose control,1–3,5,35,42–48 again underscoring the complex pathophysiology of insulin resistance and HF, addressed elsewhere within this Compendium. Increased HF risk associated with T2DM is also affected by concomitant coronary artery disease, hypertension, and obesity (Figure 1), and targeting these specific comorbidities may favorably influence HF risk independent of glucose control.

Hyperglycemia may induce irreversible changes in terms of advanced glycation end-product formation and tissue deposition, disordered extracellular matrix synthesis, and epigenetic alterations of the heart. For example, advanced glycation end-products increase collagen crosslinking in the myocardial extracellular matrix, contributing to cardiac stiffening and diastolic dysfunction, the commonest myocardial abnormality seen in T2DM.26,49 Epigenetic changes of the mitochondrial p66Shc promoter in the setting of T2DM drive persistent oxidative stress and endothelial dysfunction that seem to be resistant to glycemic control.50 Finally, the possibility exists for direct myocardial metabolic effects of T2DM medications that may be beneficial or adverse and may or may not be related to the primary mechanism of action of the medications.

In summary, the beneficial effects of glucose lowering may theoretically be offset by adverse pleiotropic drug effects, but conversely, may also be enhanced. Such potential for antihyperglycemic therapies affecting T2DM-associated HF risk requires further evaluation, most importantly by more systematic assessment of HF outcomes in ongoing and future RCTs.

### Classic Antihyperglycemic Medications and Some Unresolved Issues on HF

Subsequent to the UKPDS trial with its primary results published in 1998,22 and prior to the 2008 modification of the FDA guidance for development of antihyperglycemic medications requiring CVOTs,16,18 a series of trials assessing the effects of antihyperglycemic medications and strategies on cardiovascular outcomes in patients with T2DM have been completed: The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive),7 the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial,8 ORIGIN,12 ADVANCE,31 ACCORD,30 and VADT32 (Table 1). The trials of specific medications explored their effectiveness versus placebo added to background standard glucose management,7,8,12 with other trials evaluating the cardiovascular effects of more intensive glucose control versus contemporary standard of care.22,30–32 Although each of these trials primarily assessed atherosclerotic cardiovascular complications, they also each reported effects on HF outcomes, with noted variability in HF data collection, in HF definitions used, and variable use of central blinded adjudication for HF outcomes. Analyses of HF effects across these trials are further challenged by the broad variation in patient populations enrolled. For example, the UKPDS excluded patients with previous macrovascular disease,22 PROactive enrolled only patients with prevalent atherosclerotic cardiovascular disease (CVD),7 and the remainder of the RCTs accrued about one third of patients with prevalent macrovascular disease at baseline (Table 1). The results from the HF analyses of these trials have been analyzed in several meta-analyses,6,33,34 with highlights of observations from each of these trials with regard to HF efficacy and safety discussed below.

For the trials designed to assess the cardiovascular effects of more intensive versus usual care glucose control, each failed to demonstrate significant effects on HF outcomes. In each trial, the protocol prescribed complex treatment algorithms...
using multiple medications in both randomized treatment arms to achieve HbA1c targets, and most patients were ultimately treated with 3 or 4 antihyperglycemic medications in combination, with or without insulin. This complexity of glucose management makes it impossible to draw meaningful conclusions on the HF effects of individual medications from these trials.

Clinical trials primarily designed to study the effects of antihyperglycemic treatments on HF outcomes, especially in T2DM patients with prevalent HF, are lacking, representing a major unmet clinical need. In this situation, information with regard to efficacy and safety of antihyperglycemic medications for T2DM patients with HF must rely on data extrapolated from trials executed in patients with varying degrees of CVD and risk.

**Thiazolidinediones**

Based on preclinical findings, the insulin-sensitizing peroxisome proliferator-activated receptor-γ agonist class of medications, the thiazolidinediones (TZDs; or glitazones), were anticipated to potentially favorably affect HF risk and outcomes.51–55 For example, the Zucker diabetic fatty rat model of insulin resistance and T2DM predictably develops systolic HF. In this model, the TZD troglitazone prevented left ventricular failure, associated histologically with reduced myocardial triglyceride and ceramide concentrations.59 Other animal studies of TZDs suggested beneficial effects on cardiac hypertrophy, cardiac steatosis, and left ventricular systolic function in models of insulin resistance and T2DM.51–54

In humans, both rosiglitazone and pioglitazone reduce blood pressure—an effect that was anticipated to complement other potentially favorable myocardial effects to improve HF risk.56,57 However, counter to these expectations, randomized trial data have consistently demonstrated increased HF risk with the TZDs. Both pioglitazone and rosiglitazone increase the risk for HF, by 43% for pioglitazone in PROactive,7 and by >100% for rosiglitazone in the RECORD trial and in A Diabetes Outcome Progression Trial (ADOPT).58,59 observations supported by subsequent meta-analysis.59 In each of these trials, despite incremental HF risk with the TZDs, there was no clear difference in rates of HF-associated death although limited by few events in each trial for analysis. The resulting uncertainty with regard to the clinical relevance of the observed TZD-associated increased risk for HF has been explored further in post hoc analyses of the PROactive trial. Despite increased HF risk associated with pioglitazone, among the subset of patients who developed HF, the point estimate of efficacy showed a 15% relative risk reduction for the prioritized secondary composite outcome of cardiovascular death/MI/stroke for pioglitazone versus placebo, that is, an effect comparable with the overall trial population.60

The mechanism of increased HF risk with the TZDs remains uncertain, with most data supporting a mechanism of plasma volume expansion, thought because of increased expression and activity of renal tubular epithelial sodium channels and resultant increased urinary sodium reclamation.61,62 If insulin resistance is adaptive for myocardial metabolism in T2DM as some have proposed,63,64 the insulin-sensitizing effects of TZDs could adversely affect fuel overload of the heart and lead to ventricular dysfunction although no adverse effects of TZDs on cardiac structure, function, or aerobic capacity have been observed.63–65 The discrepancies between TZD cardiac effects in animal models and those observed in humans remain poorly understood. The disconnect between increased HF risk, yet unchanged risk for cardiovascular events and death with TZD use, is not fully elucidated and seems to imply some advantageous effects of this class of drugs on the heart, thus mitigating the adverse consequences of intravascular volume expansion and potential myocardial metabolic substrate overload. In this context, TZD use remains cautioned or contraindicated in patients with or at high risk for HF, and discontinuation of TZD recommended whenever HF signs and symptoms occur.

**Insulin**

As with TZDs, insulin induces sodium retention although controversy remains as to the mechanism of this effect.66–68 Both increased proximal and distal renal tubular sodium reabsorption has been observed after an acute increase of circulating insulin, but long-term sustainability of this effect is uncertain. Insulin, like TZDs, has been shown to stimulate the epithelial sodium channel system,69 although the Na/K ATPase and sodium chloride cotransporter also seem to contribute.70 Concerns have also been raised about possible worsening of HF with insulin therapy, based primarily on epidemiological observations.71 Increased death has been associated with insulin use in T2DM patients with HF compared with T2DM patients with HF not treated with insulin. Marked heterogeneity, however, exists between the groups in terms of duration of diabetes mellitus, coexisting coronary artery disease, hypertension, impaired kidney function, and other comorbidities rendering it difficult to account for all potential confounders, most importantly confounding by indication in patients more likely prescribed insulin with much greater severity of diabetes mellitus.72

The only RCT to date to specifically study the cardiovascular effects of insulin treatment is the ORIGIN trial that evaluated insulin glargine versus placebo in 12,612 patients with or at risk for T2DM. In this trial, in which 66% had baseline CVD, there was no effect—favorable or unfavorable—on the risk for HF outcomes over the median of 6.2 years of follow-up.12

Therefore, based on the best available RCT evidence, insulin has no discernable effect on HF risk (at least insulin glargine). Other potential pitfalls of insulin when used in patients at higher cardiovascular risk than those in the ORIGIN trial, especially T2DM patients with HF, is the increased risk of hypoglycemia ≥2-fold higher in patients with versus without HF.72 Given the neurohormonal activation of the hypoglycemia stress hormone response, such events may pose an exaggerated threat in the setting of HF given the associated risk of inducing QTc prolongation, hypokalemia, increased myocardial oxygen demand from elevated blood pressure and heart rate, arrhythmia and sudden death.2

**Metformin**

No RCTs have specifically assessed the HF effects of metformin and sulfonylureas, either their effects on incident HF or on safety and efficacy in HF patients. Analyses of observational studies comprising approximately 34,500 patients with HF and T2DM,73,74 metformin use (n=6624) was associated with a 20% lower adjusted death rate compared with other antihyperglycemic medications, mainly sulfonylureas (23%...
versus 37%; pooled adjusted HR, 0.80; 95% CI, 0.74–0.87). Conversely, no increased death risk was observed for metformin in those with reduced ejection fraction (pooled adjusted HR, 0.91; 95% CI, 0.72–1.14), nor with metformin in those with HF and chronic kidney disease (pooled adjusted HR, 0.81; 95% CI, 0.64–1.02). Furthermore, metformin was not associated with increased risk of lactic acidosis in this large database,73,74 a similar finding to a systematic review evaluating studies of metformin in the setting of chronic kidney disease.75 Hence, these data have prompted regulatory authorities to remove HF from the earlier list of product-label contraindications for metformin therapy.76

**Sulfonylureas**

By inference, the favorable effects of metformin on HF outcomes deriving largely from active comparator trials of sulfonylureas could also mean that sulfonylureas might be less advisable in patients with HF. However, a recent systematic Cochrane review including 72 RCTs with 22 589 participants, including 9707 randomized to sulfonylureas and 12 805 randomized to placebo or active control, did not consistently show an increased risk of cardiovascular events or all-cause death for patients on sulfonylurea treatment although HF outcomes were not specifically reported.77 Observational data from the UK Clinical Practice Research Datalink, however, suggest that sulfonylurea monotherapy may be inferior to metformin in terms of overall survival.78 The ADVANCE trial assessed HF events as a prespecified secondary outcome in 11 140 patients with T2DM randomized to more intensive glucose control with the addition of gliclazide versus standard glucose control using other agents, excluding sulfonylureas.32 Overall, no significant difference for macrovascular outcomes was observed between the intensive versus standard glucose control arms. Hospitalization was slightly more frequent in the gliclazide group, but there were no other significant differences in secondary end points, including incident HF (3.9 versus 4.1% in the intensive arm and control arm, respectively).

The ADOPT trial showed that glibenclamide (also known as glyburide in the United States) was associated with a numerically lower risk of cardiovascular events when compared with rosiglitazone, with similar numbers of events in the metformin and rosiglitazone groups.58 The absolute number of cardiovascular events ascertained, however, was so low as to yield negligible statistical power for comparisons of cardiovascular effects, with most cardiovascular events captured through adverse event reporting and not centrally adjudicated. For example, in terms of incident HF, only 3 events were observed with glibenclamide versus 12 events with metformin, and 12 events with rosiglitazone.

In summary, based on limited evidence, the presence of HF is not a contraindication for sulfonylurea therapy, but an alternative option of using metformin seems preferable. Moreover, as with insulin therapy, severe hypoglycemia is common with sulfonylurea therapy with potential adverse cardiac effects,12,72,79 so that sulfonylurea therapy should be reconsidered in patients with HF if hypoglycemia occurs.

**Alpha-Glucosidase Inhibitors**

The cardiovascular effects of the alpha-glucosidase inhibitor acarbose have been evaluated, including HF outcomes, in a meta-analysis of 7 RCTs.80 Whereas a significant reduction of any cardiovascular event and of MI was found in the group of 1248 patients randomized to acarbose versus 932 patients randomized to placebo, no significant difference was noted in terms of HF outcomes (7 cases on acarbose versus 10 on placebo). Again, the number of events was so low that no firm conclusion can be drawn from these data. Additional data are forthcoming, as HF hospitalization is a component of the primary composite end point in the ongoing Acarbose Cardiovascular Evaluation (ACE) trial.81

**Effects on HF Risk of Novel Antihyperglycemic Medications**

Dipeptidyl-peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors represent novel classes of antihyperglycemic medications with low risk for hypoglycemia and weight gain, with the latter 2 classes actually associated with weight reduction.82–85 As to their main anti-hyperglycemic effects, DPP4 inhibitors block degradation of endogenous GLP1 and glucose-dependent insulinotropic peptide (also known as gastric inhibitory polypeptide), gastrointestinal-derived incretin hormones that mediate physiological insulin release and glucagon suppression. The GLP1 receptor agonists more potently affect GLP1-related pathways including physiological insulin secretion and glucagon suppression at pharmacological GLP1 concentrations, whereas SGLT2 inhibitors significantly reduce hyperglycemia by increasing renal glucose excretion.86–88 Available DPP4 inhibitors comprise alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin; GLP1 receptor agonists presently in clinical use include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. Canagliflozin, dapagliflozin, and empagliflozin are the main representatives of the class of SGLT2 inhibitors. Evidence from meta-analyses of data with each of these medications from rather short-term RCTs with limited numbers of events comprising the phase II/IIIa trial programs used to support new drug applications suggest the potential for each of these classes of medications to favorably affect cardiovascular outcomes.

In 2008 as introduced above, the FDA and the European Medicines Agency released specific guidance to industry for the development of new antihyperglycemic medications that require exclusion of significant cardiovascular harm for drug approval16,17—reflecting the experience with the peroxisome proliferator-activated receptor α agonist muraglitazar,89 the TZD medications,65 and the early sulfonylurea tolbutamide.87 All these compounds had shown signals of adverse cardiovascular effects including increased cardiovascular death, MI, and HF.65,86,87 For penultimate approval, the present guidance requires a HR from noninferiority statistical analyses with an upper bound of the 95% CI of <1.3 for effects on major adverse cardiovascular events (MACE; a composite outcome of cardiovascular death, myocardial infarction, or stroke, with or without hospitalization for unstable angina),...
based on meta-analysis of all cardiovascular events prospectively collected and centrally adjudicated from RCTs during phase II and III of drug development. Failing this criterion, but proving an upper bound of the 95% CI of <1.8 for MACE with otherwise acceptable data allows for marketing approval with a requirement for a postapproval CVOT to establish the penultimate regulatory criterion. This new regulatory guidance has resulted in an impressive series of CVOTs comprising a net population of >200,000 people with T2DM enrolled or planned to be enrolled in global RCTs. As they are designed to assess cardiovascular safety of specific medications and not glycemic control per se, these studies are all designed to target minimal differences in HbA1c between the randomized groups. Open-label use and titration of other antihyperglycemic medications are allowed in each arm of these trials to achieve similar glycemic control in both groups with HbA1c targets in accord with local clinical standards.

Results of 5 of these CVOTs are now available (Tables 2 and 3, summary of design and baseline characteristics), with some discordant findings in terms of effects on HF risk. Each of these 5 trials, however, passed the regulatory threshold of excluding an upper 95% CI of 1.3 for the effect estimate of each medication versus placebo on the primary composite MACE outcomes. So, the medications evaluated in these first 5 cardiovascular outcome trials to report, that is, saxagliptin in Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)—Thrombolysis in Myocardial Infarction (TIMI) 53 trial; alogliptin in Examination of Cardiovascular Outcomes With Sitagliptin Versus Standard of Care (EXAMINE) trial; sitagliptin in Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS); lixisenatide in Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA); and empagliflozin in Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), seem to be sufficiently safe as far as the primary MACE outcome is concerned for continued approval of clinical use.

**Dipeptidyl-Peptidase 4 Inhibitors**

Among the first trials to report in the wake of the updated regulatory guidance for antihyperglycemic medications is the SAVOR TIMI 53 trial that evaluated saxagliptin versus placebo in patients with T2DM with either atherosclerotic CVD or clustered cardiovascular risk factors at trial entry (Tables 2 and 3). Despite an overall neutral effect on MACE events (HR, 1.0; 95% CI, 0.89–1.12), there was an unexpected finding (Table 4) of a 27% increase in hHF with saxagliptin (HR, 1.27; 95% CI, 1.07–1.51). Increased hHF risk with saxagliptin was a consistent finding across all subgroups analyzed, evident within the first 6 months of the trial with the incremental hazard being relatively constant thereafter, and not confined to the 12.8% of patients with baseline HF.9 Analyses stratified by quartiles of baseline N-terminal-pro-brain natriuretic peptide (BNP) showed that the greatest absolute incremental risk for hHF observed with saxagliptin was observed in the top quartile.9 Overall, the trial demonstrated statistically robust noninferiority but not superiority for the effects of saxagliptin versus placebo on MACE outcomes, in the context of an increased risk for hHF with saxagliptin.9,23

The EXAMINE trial evaluated the cardiovascular effects of alogliptin versus placebo in T2DM patients with a recent acute coronary syndrome, demonstrating robust statistical noninferiority with regard to the primary MACE composite outcome (HR, 0.96; upper bound of the 95% CI, 1.16), with no evidence for superiority. Results of post hoc analyses were subsequently reported, showing a numeric, but nonsignificant, 19% increase of hHF in the alogliptin arm as a whole (Table 4), yet a significant 76% increase for hHF in those on alogliptin without baseline HF.14 Similar to the observation from the SAVOR TIMI 53 trial with saxagliptin, the patients in

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**Table 2. Summary of Recent Cardiovascular Outcomes Trials With Published Primary Outcome Results Using Novel Antihyperglycemic Medications**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>SAVOR TIMI 53</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>ELIXA</th>
<th>EMPA-REG OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main inclusion criteria</strong></td>
<td>Saxagliptin/placebo</td>
<td>Alogliptin/placebo</td>
<td>Sitagliptin/placebo</td>
<td>Lixisenatide/placebo</td>
<td>Empagliflozin/placebo</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>16,492</td>
<td>5,380</td>
<td>14,671</td>
<td>6,068</td>
<td>7,020</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>4P-MACE</td>
<td>4P-MACE</td>
<td>3P-MACE</td>
</tr>
<tr>
<td><strong>Key secondary outcome</strong></td>
<td>Expanded MACE</td>
<td>4P-MACE</td>
<td>3P-MACE</td>
<td>3P-MACE</td>
<td>4P-MACE</td>
</tr>
<tr>
<td><strong>Target number of primary outcome events</strong></td>
<td>1040</td>
<td>650</td>
<td>1300</td>
<td>844</td>
<td>691</td>
</tr>
<tr>
<td><strong>Median follow-up, y</strong></td>
<td>2.1</td>
<td>1.5</td>
<td>3.0</td>
<td>2.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

3P indicates 3 points (CV death, MI, and stroke); 4P, 4 points (CV death, MI, stroke, and unstable angina hospitalization); ACS, acute coronary syndrome; CAD, coronary artery disease; CVD, cardiovascular disease; ELIXA, lixisenatide in the Evaluation of Lixisenatide in Acute Coronary Syndrome trial; EMPA-REG OUTCOME, empagliflozin in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXAMINE, alogliptin in the Examination of Cardiovascular Outcomes With Alogliptin Versus Standard Care trial; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; SAVOR TIMI 53, saxagliptin in the Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction trial; TECOS, sitagliptin in the Trial Evaluating Cardiovascular Outcomes With Sitagliptin; and UA Hosp, unstable angina hospitalization.
the top baseline BNP quartile accounted for two thirds of the HF outcomes in both groups; the top 2 BNP quartiles 90%.9

The TECOS trial11 enrolled patients with T2DM with atherosclerotic CVD randomized to sitagliptin versus placebo. Primary outcome results were similar to the previous 2 DPP4 inhibitor trials, that is, with no effect on 4-point MACE (cardiovascular death, MI, stroke, and hospitalization for unstable angina) outcomes (HR, 0.98; 95% CI, 0.88–1.09), showing statistically robust noninferiority but no evidence for superiority. In prespecified analyses of hHF events, there was no effect with sitagliptin (HR, 1.00; 95% CI, 0.83–1.20), demonstrating that increased risk for hHF is not a class effect of all DPP4 inhibitors (Table 4). Irrespective of previous HF, coronary artery disease, or impaired kidney function at baseline, a balanced distribution of hHF was apparent between the randomized groups. In the vildagliptin arm, there was no statistically significant difference between the randomized groups. In the vildagliptin arm compared with placebo, significant increases of the average left-ventricular end-diastolic and end-systolic volumes were observed, as well as increased stroke volume. Conversely, plasma BNP concentrations fell by 28% in the vildagliptin group and by 14% in the placebo group, a between-group difference that was not statistically significant.91 There was no significant difference in deaths between the groups (4 patients on placebo versus 11 patients on vildagliptin). Importantly, the trial was not powered to detect differences in clinical outcomes and conclusions on the cardiac safety of vildagliptin are limited.

In summary, the DPP4-inhibitors, alogliptin, saxagliptin, and sitagliptin, have proven cardiovascular safety in terms of composite primary MACE outcomes in T2DM patients at high cardiovascular risk although none of the trials demonstrated superiority for these cardiovascular outcomes. Whether similar results might be achieved studying patients at lower cardiovascular risk, shorter duration of T2DM, or in trials of longer duration remains uncertain and potential for future clinical research. There is heterogeneity with regard to DPP4 inhibitor effects on hHF risk: sitagliptin has neutral effects,11,90 saxagliptin is associated with a significant increase in hHF risk,9 and a signal for adverse effects on hHF has been evaluated in a small RCT of patients with T2DM with T2DM in Ventricular Dysfunction Diabetes (VIVIDD) trial, reported to date only in abstract.91

Vildagliptin is another DPP4 inhibitor, with regulatory approval in many countries but not in the United States and has been evaluated in a small RCT of patients with T2DM and systolic HF in the Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) trial, reported to date only in abstract.91 The trial enrolled 254 patients with T2DM, HF with reduced ejection fraction, and New York Heart Association class I–III symptoms, with randomization to vildagliptin versus placebo. Ejection fraction after 1 year on study drug was the primary end point. Both groups showed significant ≈5% absolute increases in ejection fraction at 1 year, with no significant difference between the randomized groups. In the vildagliptin arm compared with placebo, significant increases of the average left-ventricular end-diastolic and end-systolic volumes were observed, as well as increased stroke volume. Conversely, plasma BNP concentrations fell by 28% in the vildagliptin group and by 14% in the placebo group, a between-group difference that was not statistically significant.91 There was no significant difference in deaths between the groups (4 patients

### Table 3. Baseline Characteristics of Recent Cardiovascular Outcomes Trials With Primary Outcome Results Reported

<table>
<thead>
<tr>
<th>Trial</th>
<th>SAVOR TIMI S3</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>ELIXA</th>
<th>EMPA-REG OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>65.1</td>
<td>61.0</td>
<td>65.4</td>
<td>60.1</td>
<td>63.1</td>
</tr>
<tr>
<td>% with prior MI</td>
<td>38.0</td>
<td>87.5</td>
<td>42.7</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>% with prior HF</td>
<td>12.8</td>
<td>27.8</td>
<td>17.8</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>% with prior CVD</td>
<td>78.4</td>
<td>...</td>
<td>73.6</td>
<td>60%</td>
<td>100</td>
</tr>
<tr>
<td>Diabetes mellitus duration,y</td>
<td>10.3</td>
<td>7.3</td>
<td>11.6</td>
<td>9.3</td>
<td>12</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.0</td>
<td>8.0</td>
<td>7.2</td>
<td>7.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>78.3</td>
<td>90.6</td>
<td>79.8</td>
<td>64.1</td>
<td>77</td>
</tr>
<tr>
<td>Anthyyperglycemia therapy,%</td>
<td>Naive 4.1 Metformin 69.9</td>
<td>Naive 1.1 Metformin 65.0</td>
<td>Naive none Metformin 66</td>
<td>Metformin 66 Metformin 77</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SU 40.5 T2D 6.2 Insulin 41.6</td>
<td>SU 46.9 T2D 2.5 Insulin 29.4</td>
<td>Mono therapy 47.7 SU 33 T2D 2 Insulin 39</td>
<td>SU 43 T2D 4 Insulin 49</td>
<td></td>
</tr>
<tr>
<td>Metformin use, %</td>
<td>47.7</td>
<td>41.6</td>
<td>33</td>
<td>66</td>
<td>77</td>
</tr>
<tr>
<td>Insulin use, %</td>
<td>29.4</td>
<td>23.5</td>
<td>39</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>TZD use, %</td>
<td>6.2</td>
<td>3.5</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SU use, %</td>
<td>41.6</td>
<td>60.5</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
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<td>43</td>
<td>43</td>
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</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CVD, cardiovascular disease; ELIXA, lixisenatide in the Evaluation of Lixisenatide in Acute Coronary Syndrome trial; EMPA-REG OUTCOME, empagliflozin in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXAMINE, alogliptin in the Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care trial; GLP1, glucagon-like peptide 1; HR, heart failure; MI, myocardial infarction; SAVOR TIMI 53, saxagliptin in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction trial; SU, sulfonylurea; TECOS, sitagliptin in the Trial Evaluating Cardiovascular Outcomes With Sitagliptin; and TZD, thiazolidinedione.

### Table 4. Hospitalization for Heart Failure in Cardiovascular Outcomes Trials Using Incretin-Based Therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Cases of Incident Hospitalization for Heart Failure Observed in Each Trial With Corresponding HRs/95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPP4-Inhibitor/GLP1 Receptor Agonist</td>
</tr>
<tr>
<td>SAVOR TIMI S3</td>
<td>289</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>106</td>
</tr>
<tr>
<td>TECOS</td>
<td>228</td>
</tr>
<tr>
<td>ELIXA</td>
<td>122</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DPP4, dipeptidyl-peptidase 4; ELIXA, lixisenatide in the Evaluation of Lixisenatide in Acute Coronary Syndrome trial; EXAMINE, alogliptin in the Examination of Cardiovascular Outcomes With Alogliptin Versus Standard Care trial; GLP1, glucagon-like peptide 1; HR, hazard ratio; SAVOR TIMI 53, saxagliptin in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction trial; and TECOS, sitagliptin in the Trial Evaluating Cardiovascular Outcomes With Sitagliptin.
been observed with alogliptin. In each of these trials, there was no heterogeneity of the effects of the DPP4-inhibitor on the primary cardiovascular outcomes within the subsets with previous HF. The mechanisms related to increased hHF risk with saxagliptin and the evident heterogeneity with regard to hHF effects within the DPP4 inhibitor class require further elucidation.

Glucagon-Like Protein-1 Receptor Agonists

The ELIXA trial was the first completed trial assessing the cardiovascular effects of a GLP1-receptor agonist. ELIXA enrolled 6068 patients with T2DM and a recent acute coronary syndrome (<180 days) and analyzed the effects of lixisenatide versus placebo on a 4-point MACE composite outcome (Tables 2 and 3). The primary trial results were almost identical to the 3 DPP4-inhibitor CVOTs reported to date, proving robust statistical noninferiority, but no incremental efficacy of lixisenatide versus placebo (HR, 1.02; 95% CI, 0.89–1.17). Importantly, there was no effect of lixisenatide on hHF events (Table 4; HR, 0.96; 95% CI, 0.75–1.23). Again, patients with previous HF experienced higher rates of the 4-point MACE outcome in both randomized groups, with no difference between the lixisenatide and placebo groups (9.7 versus 10.2%, respectively; HR, 0.93; 95% CI, 0.66–1.3). Although increased heart rate has been observed in some studies of GLP1-receptor agonists, there was no increase in heart rate observed with lixisenatide in the ELIXA trial. Although this finding may be true, it could also be because of the timing of assessment of heart rate in the trial occurring 24 hours after the last injection of lixisenatide and affected by the prevalent use of β-blockers in post–acute coronary syndrome patients.

Limited data are available on the cardiovascular effects of the GLP1-receptor agonist lirarglutide based on an abstract report of a short-term RCT in patients with systolic HF and T2DM, enrolling 300 patients randomized to liarglutide 1.8 mg/d versus placebo and followed for 180 days. No significant difference for the primary composite outcome of death or hHF was found between groups although with a numerically unfavorable trend in the liarglutide arm (HR, 1.30; 95% CI, 0.92–1.83). In addition, a press release has announced a statistically significant reduction in cardiovascular risk observed with liarglutide versus placebo in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial. LEADER enrolled 9340 T2DM patients randomized to liarglutide 1.8 mg/d versus placebo with study participants followed for up to 5 years. As per the press release, liarglutide was associated with a reduction in the primary 3-point MACE outcome of cardiovascular death, nonfatal MI, and nonfatal stroke. Publication of trial results is anticipated later in 2016. With several other GLP1 receptor agonist-based CVOTs ongoing, the impact on cardiovascular outcomes of this class of medications remains to be determined. Particularly, rigorous assessment of HF outcomes and the effects of some GLP1-receptor agonists to increase heart rate will be important.

Sodium-Glucose Cotransporter 2 Inhibitors

The EMPA-REG OUTCOME trial assessed the cardiovascular effects of empagliflozin (2 doses: 10 or 25 mg daily) versus placebo. The trial enrolled 7020 patients with T2DM and atherosclerotic CVD. With a median follow-up of 3.1 years, a significant 14% relative risk reduction in the primary 3-point MACE outcome was observed with empagliflozin (HR, 0.86; 95% CI, 0.74–0.99). This result was largely driven by a 38% reduction of cardiovascular death in the empagliflozin group (HR, 0.62; 95% CI, 0.49–0.77), with no difference in cardiovascular outcomes between the 2 doses of 10 and 25 mg, whereas the other 2 component end points in the 3-point MACE revealed no statistical differences (nonfatal MI: HR, 0.87; 95% CI, 0.70–1.09; and nonfatal stroke: HR, 1.24; 95% CI, 0.92–1.67). The reduction in cardiovascular death was observed in the context of a similar reduction in hHF (HR, 0.65; 95% CI, 0.50–0.85). To what degree the observed cardiovascular mortality reduction is a result of lower HF risk versus other contributing factors remains uncertain and is the focus of ongoing discussion and considerations for additional trial exploration. Total mortality was also significantly decreased in the empagliflozin group (HR, 0.68; 95% CI, 0.57, 0.82). Furthermore, the benefit in HF outcomes was not confined to the 10% of patients with previous HF at trial entry, but was also apparent in patients without HF at baseline, that is, among those without previous HF, in whom hHF occurred in 1.8% in the empagliflozin group versus 3.1% in the placebo group (HR, 0.59; 95% CI, 0.43–0.82). In this same subset, the composite of cardiovascular death or hHF occurred in 4.5% in the empagliflozin versus 7.1% in the placebo group (HR, 0.63; 95% CI, 0.51–0.78).

Thus, the EMPA-REG OUTCOME trial results represent a clinical breakthrough in treating T2DM warranting a shift in the treatment paradigm to consider treatment with empagliflozin as a first-line therapy along with metformin in patients with T2DM and atherosclerotic CVD. It remains to be established what the effects of empagliflozin might be in T2DM patients without CVD, and importantly, if other SGLT2 inhibitors may have similar cardiovascular benefits, with cardiovascular outcome trials assessing canagliflozin, dapagliflozin, and ertugliflozin presently underway.

In the context of the favorable cardiovascular effects in EMPA-REG OUTCOME, effects of SGLT2 inhibition on tubuloglomerular feedback have emerged as potential contributor to the effects on HF and mortality. Renal glucose reclamation is increased in patients with T2DM, associated with the severity of hyperglycemia, often by up to 40%. Instead of the usual 180 g of glucose filtered and reclaimed daily in normal adults, in the setting of diabetes mellitus, up to 250 g of glucose can be reclaimed daily. In parallel, renal sodium reclamation is also increased because of the cotransport of glucose and sodium by the SGLT2 system. In fact, renal tubular SGLT2 expression and activity are increased in diabetes mellitus in the early stages of diabetic nephropathy when kidneys may be noted to be enlarged yet glomerular filtration remains in the normal (or supranormal) range, findings noted to be a hallmark of subsequent impairment of kidney function. As diminished sodium concentration is sensed by the macula densa in the
juxt glomerular apparatus, dilation of the glomerular afferent arterioles increasing transglomerular pressure and exacerbating hyperfiltration, contributing thus to glomerular damage in diabetic nephropathy. At the same time, the renin–angiotensin–aldosterone system is activated leading to intravascular volume expansion by some 4% to 7%, with associated increases in blood pressure. The partial restoration of these complex renal pathophysiologic perturbations seems to be acutely affected by SGLT2 inhibition, independent of the glucose lowering effect, and may contribute to the beneficial effects observed in EMPA-REG OUTCOME on cardiovascular mortality and hHF, potentially complementing more direct metabolic effects of SGLT2 inhibitors. Clearly, all these aspects will prompt further exploration.

Discussion

Aggregate Conclusions From the CVOT Data to Date

Several conclusions may be drawn from the results of these completed CVOTs evaluating antihyperglycemic therapies. First, despite early evidence derived from phase II/IIIa meta-analyses with regard to possible cardiovascular benefits of these novel antihyperglycemic medications, it is clear that large-scale, adequately powered cardiovascular outcome trials are necessary to truly evaluate cardiovascular effects of new medications. Second, it is possible in such large trials to detect unexpected safety concerns such as the incremental hHF risk with saxagliptin observed in SAVOR TIMI 53, with no preclinical or early clinical observations suggesting such an adverse effect.

Table 5 summarizes the current evidence for using antihyperglycemic medications in patients with T2DM and HF. The partial restoration of these complex renal pathophysiologic perturbations seems to be acutely affected by SGLT2 inhibition, independent of the glucose lowering effect, and may contribute to the beneficial effects observed in EMPA-REG OUTCOME on cardiovascular mortality and hHF, potentially complementing more direct metabolic effects of SGLT2 inhibitors. Clearly, all these aspects will prompt further exploration.

Table 5. Key Classes of Antihyperglycemic Medications for T2DM in the Context of HF and CVD

<table>
<thead>
<tr>
<th>CVD</th>
<th>HF</th>
<th>Hypoglycemia</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>(UKPDS/DIGAMI 2)</td>
<td>Indicated</td>
<td>Low risk</td>
</tr>
<tr>
<td>Acarbose</td>
<td>(MERIA, STOP-NIDDM), ACE ongoing</td>
<td>Can be used</td>
<td>Low risk</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>(PROactive)</td>
<td>Contraindicated &gt;NYHA I</td>
<td>Low risk</td>
</tr>
<tr>
<td>DPP4-inhibitors</td>
<td>No CV harm</td>
<td>Increase in HF? (not sitagliptin)</td>
<td>Low risk</td>
</tr>
<tr>
<td>GLP1 receptor agonists</td>
<td>Emerging CVOT data (ELIXA, LEADER)</td>
<td>Can be used?</td>
<td>Low risk</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>EMPA-REG OUTCOME</td>
<td>Can be used?</td>
<td>Low risk</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>(UKPDS)</td>
<td>(Not recommended)?</td>
<td>↑↑ Risk (↑ related CV risk in ORIGIN)</td>
</tr>
<tr>
<td>Insulin</td>
<td>(UKPDS)</td>
<td>Some adverse effects (DIGAMI 2)</td>
<td>↑↑ Risk (low-related CV risk in ORIGIN)</td>
</tr>
</tbody>
</table>

ACE indicates the Acarbose Cardiovascular Evaluation trial; CV, cardiovascular; CVD, cardiovascular disease; DIGAMI, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 trial; DPP4, dipeptidyl-peptidase 4; ELIXA, lixisenatide in the Evaluation of Lixisenatide in Acute Coronary Syndrome trial; GLP1, glucagon-like peptide 1; HF, heart failure; LDL-C, low-density lipoprotein-cholesterol; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results–A Long Term Evaluation; MERIA, the Meta-analysis of Randomized Intervention Studies with Acarbose trial; NYHA, New York Heart Association; ORIGIN, the Outcome Reduction With an Initial Glargine Intervention trial; PROactive, the Prospective Pioglitazone Clinical Trial in Macrovascular Events; STOP-NIDDM, the Stop Non-insulin Dependent Diabetes Mellitus trial; T2DM, type 2 diabetes mellitus; and UKPDS, the United Kingdom Prospective Diabetes Study.

Given the available evidence, metformin and empagliflozin seem to be advantageous in patients with HF; whereas acarbose, sitagliptin, and lixisenatide appear as reasonable additional options, as significant harm in terms of HF has been excluded for those drugs. This list might be enlarged for other antihyperglycemic medications pending results of ongoing and planned CVOTs, such as liraglutide as suggested by the press release of the LEADER trial results. Although no clear adverse HF signal was seen in CVOTs for insulin or sulfonylureas, they should be used with caution in patients with HF based on concerns for hypoglycemia and uncertainties on their safety in patients with HF derived from epidemiological observations. Pioglitazone is contraindicated in patients with New York Heart Association HF classes > I, despite some beneficial effects suggested by subanalyses in PROactive, and more recently superiority for MACE events observed in a population of 3895 patients with a recent stroke and having insulin resistance (although not T2DM) randomized to pioglitazone versus placebo in the Insulin Resistance Intervention After Stroke (IRIS) trial, with no significant increase in HF outcomes observed. As for any therapeutic recommendations, the full spectrum of contraindications for each individual therapy must be considered.

One key issue that warrants further attention is the high frequency of patients enrolled into the trials reported to date with no reported history of HF but with elevated circulating BNP and N-terminal-pro-BNP at baseline. According to the 2012 European Society of Cardiology HF guidelines with regard to thresholds of natriuretic peptide levels that should prompt further clinical assessment for HF, and based just on the reported baseline N-terminal-pro-BNP/BNP measurements from SAVOR TIMI 53 and EXAMINE, some 50% of...
patients in SAVOR TIMI 53 and about two thirds of patients in EXAMINE would have warranted further HF evaluation based on their natriuretic peptide levels alone.\textsuperscript{9,11} Although diagnosis of HF might not have been confirmed in all suspected cases, it is clear that the true prevalence of HF must have far exceeded the reported 12.8\% and 27\% in these trials, respectively, and the reported cases of hHF in patients without previous documented HF might have been due in part to undiagnosed HF.\textsuperscript{3,14} No natriuretic peptide levels have been reported to date for the TECOS, ELIXA, or EMPA-REG OUTCOME trials.

**Novelty and Significance**

The CVOTs evaluating antihyperglycemic medications remain as important as ever, and as evidenced by observations from the 5 CVOTs completed and published (and positive results of the LEADER trial announced by press release) since the update of the regulatory guidance requiring cardiovascular safety assessment, sometimes yield unexpected results, especially on HF. The primary objective of the FDA guidance requires CVOTs to establish cardiovascular safety and exclude cardiovascular harm of antihyperglycemic therapies with a focus on atherosclerotic cardiovascular outcomes. In light of the aggregate experience obtained with CVOTs to date, it now seems timely to consider whether the concept of the FDA guidance might need some revision in terms of its focus on patients with T2DM at high risk for CVD or with established CVD, being at high risk for HF events at the same time. To this end, it seems advisable that prevalent HF among patients at trial entry should be more precisely captured at baseline, not only based on previous diagnosis but also on defined N-terminal-pro-BNP/BNP criteria, ideally complemented by imaging for assessment of cardiac structure and function. A 3-point MACE composite outcome of cardiovascular mortality and atherosclerotic cardiovascular events appears to be an appropriate primary outcome for excluding cardiovascular harm (ie, testing for noninferiority) and if excluded, for superiority testing and demonstrating cardiovascular benefit. However, consideration should be given by the regulatory bodies to expand the guidance to also include assessment of HF outcomes, including hHF and a composite of hHF and cardiovascular death as a prespecified secondary outcome and also for predefined subgroups with and without prior HF. Adjudicated events of special interest should include hospitalization for unstable angina, all-cause death, all components of primary and secondary composites, hypoglycemia requiring assistance and sudden death.

**Acknowledgments**

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**Disclosures**

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Heart Failure Considerations of Antihyperglycemic Medications for Type 2 Diabetes
Eberhard Standl, Oliver Schnell and Darren K. McGuire

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Heart Failure Considerations of Antihyperglycemic Medications for Type 2 Diabetes

Online Supplemental Table

Supplementary Table: CVOTs designed to evaluate antihyperglycemic medications

(IGT = impaired glucose tolerance)

ACE = Acarbose Cardiovascular Evaluation (79), in IGT patients

ACCORD = Action to Control Cardiovascular Risk in Diabetes study (30)

ACTnow = Pioglitazone (Actos) for Diabetes Prevention in Impaired Glucose Tolerance, in IGT patients

ADOPT = A Diabetes Outcome Progression Trial (58)

ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled intensification of blood glucose Evaluation trial (31)

ALECARDIO = Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus (13)

CANVAS = CANagliflozin cardioVascular Assessment Study (ongoing study)

CARMELINA = Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (ongoing study)

CAROLINA = Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (ongoing study)

CREDENCE = Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (ongoing study)

DECLARE TIMI 58 = Dapagliflozin Effect on Cardiovascular Events (ongoing study)

DEVOTE = Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (ongoing study)

DIGAMI 1&2 = Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 1 & 2 trial (96)

DREAM = Diabetes REduction Assessment with ramipril and rosiglitazone Medication, in IGT patients

DPP 2 = Diabetes Prevention Program, in IGT patients

ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome trial (17)

EMPA REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (18)
EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial (87)

EXSCEL = Exenatide Study of Cardiovascular Event Lowering Trial (ongoing study)

FIGHT = Functional Impact of GLP-1 for Heart Failure Treatment (92)

HARMONY outcomes trail = A long term, randomised, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in patients with Type 2 diabetes (ongoing study)

HEART2D = Effects of Prandial Versus Fasting Glycemia on Cardiovascular Outcomes in Type 2 Diabetes

LEADER = Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (ongoing study)

MeRia = Meta-analysis of randomized intervention studies with acarbose (78)

NAVIGATOR = Nateglinide and Valsartan Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial, in IGT patients

Omarigliptin OUTCOME = A Study to Assess Cardiovascular Outcomes Following Treatment With Omarigliptin (MK-3102) in Participants With Type 2 Diabetes Mellitus (ongoing study)

ORIGINE = Outcome Reduction with an Initial Glargine Intervention trial (14)

PROactive = PROspective pioglitAzone Clinical Trial In macroVascular Events (10)

RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes trial (11)

SAVOR TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)—Thrombolysis in Myocardial Infarction (TIMI) 53 trial (23)

StopNIDDM = Stop non-insulin dependent diabetes mellitus trial (97), in IGT patients

SUSTAIN 6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (ongoing study)

TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin (16)

TOSCA IT = Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents. Intervention Trial (ongoing study)

UKPDS = United Kingdom Prospective Diabetes Study (22)

VADT = Veterans Affairs Diabetes Trial (32)

VIVIDD = Vildagliptin in Ventricular Dysfunction Diabetes trial (89)