The diabetes pandemic is currently among the most challenging noncommunicable disease threats to public health. It is estimated that 382 million people worldwide have diabetes mellitus, and the majority will likely die of cardiovascular disease. Diabetes mellitus is an independent risk factor for atherosclerotic cardiovascular disease and heart failure, with a 5-fold increased risk of heart failure in women with diabetes mellitus and a 2.4-fold increased risk in men.1–3 In patients with diabetes mellitus, the prevalence of heart failure is between 10% and 22%, 4 times higher than that of the general population.2 The degree of glycemic control in patients with diabetes mellitus has been demonstrated to be associated with the risk of atherosclerotic cardiovascular disease and new-onset heart failure.1,4 It has been a widely held belief that lowering hemoglobin A1c levels with glucose-lowering medications in patients with diabetes mellitus would result in clinical benefits, including a reduction in atherosclerotic cardiovascular events. Lowering of the hemoglobin A1c levels by glucose-lowering medications in patients with diabetes mellitus has been used as a surrogate measure of their benefit, including the potential to reduce cardiovascular risk, by clinicians, guideline writing groups, and regulators.5

There is, however, little evidence from randomized, clinical trials of substantial cardiovascular risk reduction with improved glycemic control in patients with type 2 diabetes mellitus. Trials of individual glucose-lowering medications and trials comparing more intensive and standard glucose-lowering strategies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Administration Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease (ADVANCE) trials, have, despite their large sample sizes and follow-up for up to 5 years, demonstrated no or very modest reductions in cardiovascular events.5–9 After the publication of a meta-analysis suggesting that one of the thiazolidinedione medications may have increased the risk of myocardial infarction and the resulting controversy, regulatory agencies revised the process for approval of new medications to treat diabetes mellitus and require demonstration that cardiovascular risk is not above certain specified levels.3,10 The US Food and Drug Administration now requires that clinical trials done before the approval of a diabetes drug show a 2-sided 95% confidence interval upper boundary of 1.8 for the risk ratio for major adverse cardiovascular events compared with the placebo/usual-care control group, with subsequent outcomes trials having an upper boundary of 1.3 for major adverse cardiovascular events.11 The focus of the US Food and Drug Administration and other regulators has been on major adverse cardiovascular events (the composite of cardiovascular death, myocardial infarction, or stroke).10,11 Heart failure events were not included as part of the requirements to demonstrate cardiovascular safety, and as a result, none of the large-scale, randomized, clinical trials evaluating the cardiovascular safety of new diabetes medications have included heart failure in the primary cardiovascular end points, and many have not included heart failure events as secondary end points.11 However, patients with diabetes mellitus, including those enrolled in these cardiovascular safety trials, face a substantial risk of heart failure. As noted by McMurray and colleagues,11 the rates of heart failure events have actually exceeded that of acute myocardial infarction in many of the diabetes medication trials. Furthermore, when patients in trials developed heart failure hospitalizations, their subsequent risk of mortality greatly exceeded that of patients hospitalized with myocardial infarction.11

It had also been hypothesized that an improvement in glycemic control would be beneficial to reduce the initiation and progression of myocardial dysfunction, reducing the risk of heart failure events. Metabolic control has been shown to enhance myocardial contractility parameters, possibly as a result of more efficient myocardial energy substrate use and improved microvascular perfusion.12 However, results from recent trials have challenged this assumption. In ACCORD, VADT, and ADVANCE, stricter glycemic control was not associated with a reduced risk of heart failure.7–9 In the Diabetes Mellitus and Diastolic Dysfunction (DADD) study, neither insulin nor oral agents were associated with an improvement in diastolic function despite a reduction in hemoglobin A1c.13 Trials with thiazolidinediones have shown substantially increased heart failure event rates. The use of rosiglitazone and pioglitazone has been associated with a >2-fold increased risk of heart failure, including heart failure hospitalizations, caused by fluid retention and peripheral edema, even in patients without preexisting left ventricular systolic dysfunction, and the risk increased further in patients with a history of heart failure.5,6

Recently, the cardiovascular efficacy and safety of the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin was
evaluated in 16,492 patients with diabetes mellitus and cardiovascular risk factors in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial. The primary or secondary cardiovascular end points were similar between saxagliptin and placebo control during a median of 2.1 years of follow-up. However, in this trial, heart failure hospitalizations were collected prospectively, and there was a 27% relative risk increase (hazard ratio, 1.27; 95% confidence interval, 1.07–1.51; \( P<0.007 \); absolute risk, 0.7%) for hospitalization for heart failure.14 In this issue of Circulation, Scirica and colleagues further analyze the heart failure risk in this trial in detail.15 The risk of heart failure hospitalization with saxagliptin was found to be most prominent in the first 12 months of treatment. It was also shown that patients at the greatest risk for hospitalization for heart failure had prior heart failure, elevated baseline levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), or chronic kidney disease.15 Patients with or without these risk factors experienced a similar relative risk increase for heart failure hospitalizations with saxagliptin compared with placebo, but the highest absolute risk was observed in those with a greater number of heart failure risk factors. Interestingly, treatment with saxagliptin was not associated with increased risk of peripheral edema, adverse event reports for edema, or differences in body weight at 1 year compared with placebo.15 Although baseline NT-proBNP levels were associated with increased risk of heart failure hospitalization, NT-proBNP levels increased only modestly in both the placebo- and saxagliptin-treated patients, with a slightly greater increase in placebo-treated patients.

The findings from SAVOR-TIMI 53 appear consistent with findings from other trials of DPP-4 inhibitors. The Examination of Cardiovascular Outcomes: Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) trial has also preliminarily reported heart failure as part of an exploratory composite outcome, with a greater number of hospitalizations for heart failure in the alogliptin group compared with the placebo group (alogliptin, 3.9% versus placebo, 3.3%; hazard ratio, 1.19; 95% confidence interval, 0.90–1.58), although this difference was not statistically significant.19 A recent meta-analysis of 84 studies showed that the risk of heart failure was higher in patients treated with DPP-4 inhibitors compared with those treated with placebo/active comparators (odds ratio, 1.19; 95% confidence interval, 1.03–1.37; \( P<0.05 \)).17 There was no evidence of heterogeneity among medications of this class. Ongoing trials, including the Sitagliptin Cardiovascular Outcome Study (TECOS; http://www.clinicaltrials.gov; identifier, NCT00790205), which also includes a prespecified end point of heart failure hospitalizations, will add knowledge to these previous findings. Ongoing studies are also investigating glucagon-like peptide-1 agonists as a treatment for established heart failure (Functional Impact of Glucagon-Like Peptide-1 for Heart Failure Treatment [FIGHT]; http://www.clinicaltrials.gov; identifier, NCT01800968).

The possible mechanisms for increased heart failure with DPP-4 inhibitors are not entirely clear. Preclinical studies have not shown cardiotoxicity or impairment of systolic or diastolic function with DPP-4 inhibitors.17 DPP-4 has many substrates, and its inhibition might affect many pathways, including those involving cardiac signaling peptides, cardiac collagen turnover enzymes, and the sodium-hydrogen exchanger in the renal proximal tubule.18 Prior smaller studies with saxagliptin did not suggest an increased risk of weight gain, fluid retention, or new-onset heart failure, nor were there signs of excessive volume overload in SAVOR-TIMI 53.15 Some studies have suggested that BNP is a substrate for DPP-4 inhibitors.18 In SAVOR-TIMI 53, saxagliptin did not increase levels of NT-proBNP. The myocardial effects and energetic consequences of reduced blood and tissue glucose and insulin levels after a prolonged period in which the myocardium had been exposed to elevated glucose and insulin levels might explain the increased risk of heart failure with multiple classes of diabetes medications despite different mechanisms of action. Changes in glucose and insulin levels may unfavorably alter the balance of free fatty acid oxidation and glycolysis. Findings from SAVOR-TIMI 53 do not suggest that there was direct myocardial necrosis or inflammation triggered by the medication because there were no significant differences in levels of high-sensitivity troponin T or high-sensitivity C-reactive protein with saxagliptin compared with placebo.15 Some studies have also suggested worsened endothelial function as assessed by flow-mediated dilation with DPP-4 inhibitors.19 In a 12-month study of the DPP-4 inhibitor vildagliptin in patients with heart failure, New York Heart Association functional classes I through III, and reduced left ventricular ejection fraction, the DPP-4 inhibitor increased left ventricular end-diastolic volumes without changing left ventricular ejection fraction.20 However, it was preliminarily reported that there were numerically more deaths in the vildagliptin arm (n=11) compared with the placebo arm (n=4), raising additional concerns about safety with DPP-4 inhibitors in patients with established heart failure.20 Nevertheless, further studies are necessary to explore the mechanisms that may explain the increased risk of hospitalization for heart failure, as uncovered in SAVOR-TIMI 53 and other studies. As noted by the authors, the decision to choose one anti-hyperglycemic agent over another must balance the potential benefit in reducing microvascular complications via improved glycemic control with the potential adverse events such as hypoglycemia and heart failure.15 Although the potential benefits of these diabetes medications may become manifest with longer-term follow-up, the risk of heart failure appears to emerge very early.11 At the population level, this increased risk of heart failure may be of significant concern. If a quarter of the 25.8 million individuals with diabetes mellitus in the United States had a risk profile similar to that of subjects in SAVOR-TIMI 53 and were treated with saxagliptin, potentially 45,150 excess heart failure hospitalizations over the next 2 years could result. A compelling need exists for well-powered, randomized, clinical trials of diabetes medications that have sufficient follow-up and that more fully integrate all relevant events, including heart failure, into the primary cardiovascular composite end point to more effectively address the crucial questions of net clinical outcomes and the comparative balance of benefit and risk.
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References


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