Is the Use of DPP-4 Inhibitors Associated With an Increased Risk for Heart Failure? Lessons From EXAMINE, SAVOR-TIMI 53, and TECOS

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Diabetes Care 2016;39(Suppl. 2):S210–S218 | DOI: 10.2337/dcS15-3009

About 40 years ago, the Framingham study first documented that the risk for heart failure (HF) in patients with diabetes was about twofold higher in men and fivefold in women compared with individuals without diabetes (1). The UK Prospective Diabetes Study (UKPDS) reported that the incidence of hospital admission for HF was similar to that of nonfatal myocardial infarction and nonfatal stroke (2). A more recent 6-year follow-up study of 65,619 patients with type 2 diabetes treated with insulin reported that the hospital admission rate due to HF (243 of 10,000) was higher than that due to myocardial infarction (97 of 10,000) or stroke (151 of 10,000) (3). The pathogenesis of HF in diabetes is multifactorial but can largely be attributed to four key factors: coronary artery disease (CAD), hypertension, diabetic cardiomyopathy, and extracellular fluid volume expansion (4,5). Remarkably, type 2 diabetes itself is a recognized risk factor for HF, independent of CAD and hypertension (4), suggesting that glycemic control may influence the development of HF. Hyperglycemia can exert deleterious effects on the myocardium and has been shown to increase oxidative stress, promote accumulation of advanced glycation end products, and cause interstitial fibrosis (6). Hyperglycemia has also been associated with myocardial lipotoxicity, mitochondrial dysfunction, abnormal substrate metabolism, and impaired calcium handling (7). Epidemiological evidence indicates that HbA_{1c} and the risk of HF are significantly related. A cohort study of ~49,000 patients with type 2 diabetes showed that each 1% increase in HbA_{1c} was associated with an 8% increased risk of HF and that an $HbA_{1c} \geq 10$ relative to $HbA_{1c} < 7$ was associated with 1.56-fold (95% CI 1.26–1.93) greater risk of HF (8). A more recent meta-analysis (9) of 178,929 subjects with diabetes and 14,176 incident chronic HF cases showed an overall adjusted risk ratio for HF of 1.15 (95% CI 1.10–1.21) for each percent (point higher) increase of HbA_{1c}. In a recent Scottish study (10), 8% of 8,683 patients with type 2 diabetes developed HF during a 5.5-year follow-up, and both low HbA_{1c}, <6% (hazard ratio [HR] 1.60 [95% CI 1.38–1.86]; $P < 0.0001$), and high HbA_{1c}, >10% (1.80 [1.60–2.16]; $P < 0.0001$), were independently associated with the risk of HF.

Owing to the significant contribution of diabetes to the pathogenesis of HF, the effect of the various antihyperglycemic agents on HF must be assessed and balanced with their benefit in glucose reduction (11–13). Thiazolidinediones may cause HF, the main mechanism being fluid retention (13), and are generally contraindicated in patients with New York Heart Association (NYHA) class III–IV HF (14). Insulin has been associated with an increased risk of HF in several studies (15), though in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial no such signal was observed (16). A study that assessed the association of antidiabetes medications with the risk of hospitalization for HF showed inferiority of sulfonylurea or insulin to metformin therapy (17). Metformin is now considered the safest therapeutic alternative for individuals with HF (18). A recently published cardiovascular (CV) outcome study with empagliflozin demonstrated a 35% relative risk (RR) reduction of hospitalization for HF with the drug versus placebo (19), and it remains to be seen whether this effect exists in additional drugs in the class.

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This publication is based on the presentations at the 5th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from AstraZeneca.

The glucagon-like peptide 1 receptor agonist lixisenatide has demonstrated in its recently presented randomized controlled trial (RCT) no increase in the risk of hospitalization for HF versus placebo (20).

Dipeptidyl peptidase (DPP)-4 inhibitors are extensively used in the treatment of diabetes and were prescribed in 21% of treatment visits in the U.S. in 2012 (21). The effect of DPP-4 inhibitors on the risk for hospitalization for HF has been extensively discussed in several observational studies and meta-analyses. The publication of three randomized controlled trials of CV outcomes with saxagliptin (22) and alogliptin (23) and most recently with sitagliptin (24) versus placebo revealed contradictory results that merit renewed discussion regarding the potential association between the use of DPP-4 inhibitors and HF.

DPP-4 Inhibitors and HF: Evidence From Observational Studies

Several observational studies have attempted to assess the association between the use of DPP-4 inhibitors and hospitalization for HF (25–29) (Table 1). The studies have generally used propensity score matching, with varying success at matching the groups, and applied a Cox proportional hazards model or a conditional logistic regression to adjust for further confounding. These studies demonstrate conflicting results, with some pointing to a potential hazard associated with the use of DPP-4 inhibitors (25,26), others demonstrating a neutral effect (28,29), and one showing a possible benefit associated with the use of DPP-4 inhibitors—in those with no baseline CV disease [CVD]—compared with the use of sulfonylureas (27).

Observational studies are generally limited by missing data; e.g., in the study by Giorda et al. (29) no data regarding metabolic control, blood pressure, renal function, or valvular heart diseases were available, and thus risk was not adjusted for these variables. Additionally, observational data often entail confounding by indication, e.g., those who are prescribed DPP-4 inhibitors may suffer from less comorbidity, and although outcomes are evaluated by propensity score matching, this is usually done only for several clinical variables. Further multivariable adjustment can correct for additional clinical variables to some extent; however, it cannot fully correct for significant baseline differences in the population. Since the prescription patterns are related to disease severity and often to socioeconomic status, the outcomes are thus related to the variable studied, which is a major confounder not easily overcome even by multivariable adjustment. Additionally, as these are not randomized data, residual confounding may remain unadjusted for due to either the lack of data or confounders that were not considered.

DPP-4 Inhibitors and HF: Evidence From Meta-analyses

Wu et al. (30) analyzed 50 trials comparing DPP-4 inhibitors with comparators (placebo or active comparator) enrolling 55,141 participants; however, mean follow-up was only 45.3 weeks. Treatment with DPP-4 inhibitors compared with placebo showed no increase in risk with regard to all-cause mortality, CV mortality, acute coronary syndrome, or stroke but a statistically significant increased risk of hospitalization for HF outcomes (n = 39,953) (RR 1.16 [95% CI 1.01–1.33]; P = 0.04) (Fig. 1). This meta-analysis was mainly influenced by the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) trial (22), contributing 66.2% of the weight in the analysis, with EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) (23) contributing 21.3% and the VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) (31) trials contributing 6.9%. The results were similar compared with a placebo comparator (n = 27,818) (RR 1.17 [95% CI 1.01–1.34]; P = 0.03) and were not significant compared with the active comparator (n = 12,563) (0.80 [0.35–1.81]; P = 0.59). The result lost statistical significance when only trials with low risk of bias were included (n = 30,429) (1.15 [0.98–1.34]; P = 0.09).

Monami et al. (32) analyzed 82 trials enrolling 69,615 patients; since 45 trials reported zero events, the principal analysis was performed on only 37 trials, reporting 448 and 361 cases of acute HF in DPP-4 inhibitor and comparator groups, respectively. The overall risk of acute HF was higher in patients treated with DPP-4 inhibitors in comparison with those treated with placebo or other active comparators (odds ratio 1.19 [95% CI 1.03–1.37]; P = 0.015). When SAVOR-TIMI 53 (22) and EXAMINE (23), which accounted for the majority of the overall result, were removed from the analysis, no signal of risk was detectable in the other trials, which were designed for non-CV outcomes. The meta-analysis of Savarese et al. (33), analyzing 94 trials enrolling 85,224 patients, arrived at similar results. Compared with control subjects, treatment with DPP-4 inhibitors did not affect all-cause or CV mortality or stroke, but long-term treatment with DPP-4 inhibitors was associated with a 15.8% increased risk of hospitalization for HF (RR 1.158 [95% CI 1.011–1.326]; P = 0.034). No heterogeneity among studies or publication bias was detected.

A meta-analysis, which included >17,000 patients in the development program of vildagliptin (phase III and IV studies), assessed the CV safety and HF profile of vildagliptin. The analysis included 9,599 patients receiving vildagliptin and 7,847 subjects receiving placebo in trials with a median duration of nearly 1 year. CV events were adjudicated by an independent committee in a preplanned fashion as secondary end points of these trials. Confirmed HF events were reported in 41 patients in the vildagliptin group (0.43%) and in 32 patients in the comparator group (0.45%) (RR 1.08 [95% CI 0.68–1.70]) (34).

Meta-analyses of studies from the development programs of linagliptin, sitagliptin, and alogliptin, which assessed the incidence of major adverse CV events (MACEs), did not include HF events (35–37). (In the alogliptin study, HF events were collected as part of the "adjudicated serious non-MACE CV events" [37].) A meta-analysis from the development program of saxagliptin reported the prevalence of MACE and HF events, which, however, were not adjudicated and analyzed separately. HF was reported in 21 of 6,045 patients allocated to saxagliptin and in 18 of 2,862 patients allocated to the comparator (RR 0.55 [95% CI 0.27–1.12]) (38).

Overall, these meta-analyses included many studies that were underpowered to assess CV end points, and additionally these events were often not adjudicated. Therefore, the information that can be obtained from meta-analysis of

Table 1—Summary of observational studies on DPP-4 inhibitor use and incident HF

Reference	Patient population	Methodology	Selected outcome measures and results	Additional comments
Wang et al. (25)	Taiwan National Health Insurance research database: 16,576 patients with diabetes (8,288 matched pairs). Median follow-up 1.5 years.	Propensity score matching (1:1) for multiple clinical and demographic variables and medication use. Cox proportional hazards model to estimate HR (95% CI).	Sitagliptin use vs. no DPP-4i use: first HHF, 1.21 (1.04–1.42); all-cause mortality, 0.87 (0.74–1.03)	For every 10% increase in adherence to sitagliptin, the risk for HHF increased (HR 1.09 [95% CI 1.06–1.11])
Weir et al. (26)	U.S. claims database (Clinformatics DataMart, OptumInsight Life Sciences); 7,620 patients with diabetes who were treated with metformin or SUR and no TZDs and had documented HF; median follow-up 1.4 years	Nested case-control population, matched by age and sex (1:10). Conditional logistic regression adjusted to multiple confounders to obtain estimate of the OR (95% CI).	Sitagliptin users (887) vs. nonusers (6,733): all-cause mortality, 1.16 (0.68–1.97); HHF or mortality, 1.34 (0.93–1.92); HHF, 1.84 (1.16–2.92)	Large differences between sitagliptin users and nonusers, such as prevalence of IHD (45.3 vs. 40.5%), GFR $<$30 mL/min (1.9 vs. 4.1%)
Fu et al. (27)	U.S. claims database (Truven Health MarketScan Commercial and Medicare Supplemental databases). Patients with diabetes and baseline CVD, 54,598 (27,259 pairs); patients without CVD, 164,038 (82,019 pairs). Comparison between saxagliptin and sitagliptin users (13,042 and 43,402 pairs with and without CVD, respectively).	Propensity score matching (1:1) use of DPP-4 inhibitors vs. use of SUR. Cox proportional hazards model applied to propensity score–matched samples were used to estimate HR (95% CI).	HHF, DPP4i vs. SUR: baseline CVD 0.95 (0.78–1.15), no baseline CVD 0.59 (0.38–0.89). HHF for saxagliptin vs. sitagliptin: baseline CVD 0.95 (0.70–1.28), no baseline CVD 0.99 (0.56–1.75).	
Yu et al. (28)	U.K. Clinical Practice Research Datalink, connected to the Hospital Episode Statistics database. New users of antidiabetes drugs: 1,118 patients with HHF events and 17,626 matched control subjects. Mean follow-up 2.4 years.	Nested case-control analysis (1:20) matched by age, diabetes duration, treatment duration, year of cohort entry. Conditional logistic regression was used to estimate OR (95% CI).	HHF: DPP-4i vs. use of $>$2 OADs, 0.88 (0.63–1.22)	Case and control subjects were not matched by multiple characteristics, i.e., BMI, renal failure, IHD. Low rates of DPP4i use.
Giorda et al. (29)	Piedmont region in Italy. 14,613 patients with HHF and 146,130 patients without.	Nested case-control study 1:10 matched by age, sex, and disease duration. Conditional logistic regression models adjusted for confounders: history of IHD, use of insulin, or SUR were used to calculate OR (95% CI).	Any HHF: DPP4i use (in last 6 months) vs. no use, 1.00 (0.94–1.07)	Missing data on metabolic control and renal function

DPP4i, DPP-4 inhibitors; GFR, glomerular filtration rate; HHF, hospitalization for HF; IHD, ischemic heart disease; OADs, oral antidiabetes agents; OR, odds ratio; SUR, sulfonylurea; TZDs, thiazolidinediones.

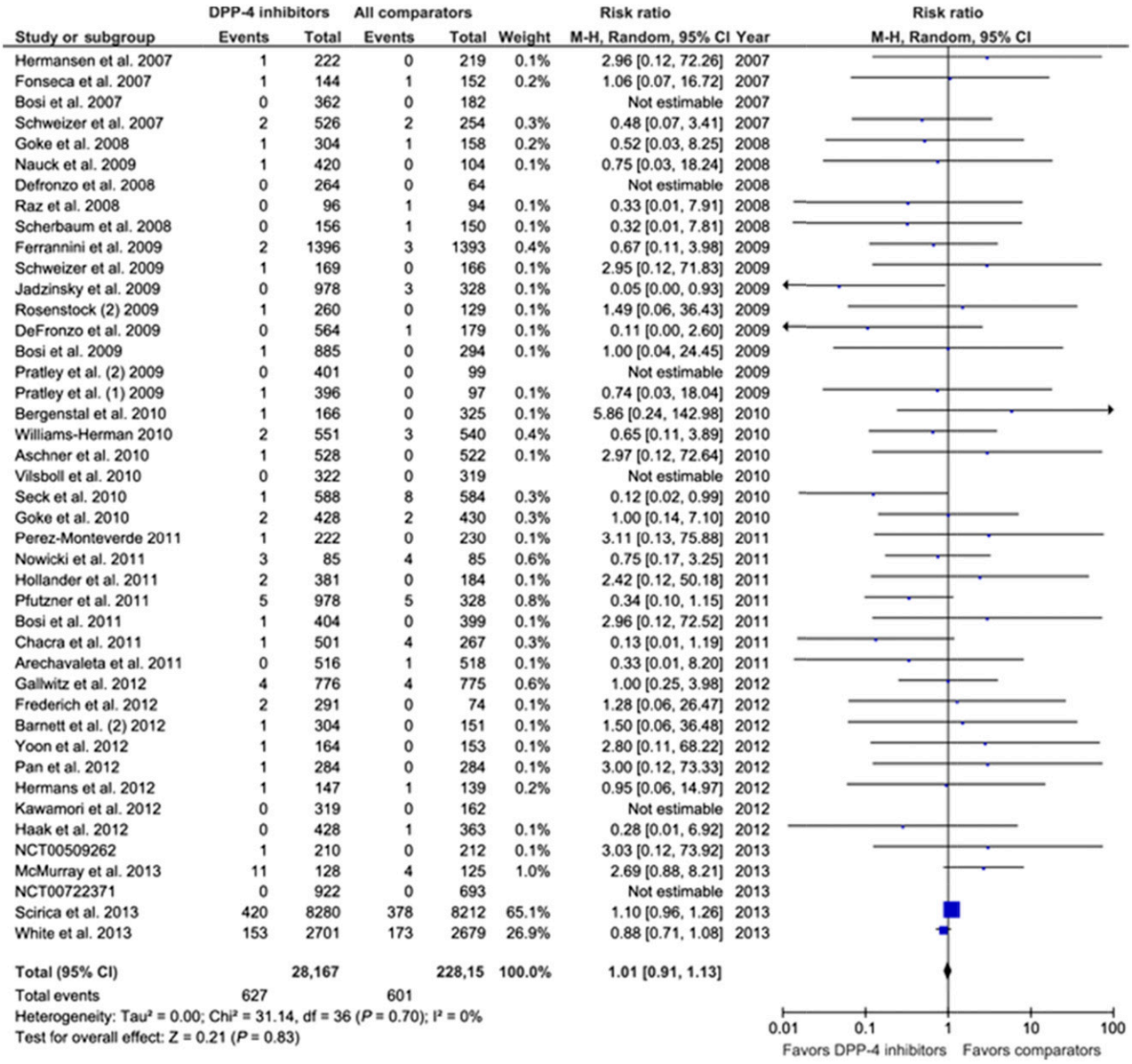

Figure 1—DPP-4 inhibitors and CV outcomes: meta-analysis of randomized clinical trials with 55,141 participants. DPP-4 inhibitors vs. all comparators: HF outcomes (30). M-H, Mantel-Haenszel. Reprinted with permission from Wu et al. (30).

these small studies is limited and more focus should be placed on the larger trials that were designed to assess CV safety.

Figure 2 shows a meta-analysis of the hospitalization rate for HF of the three large RCTs with alogliptin, saxagliptin, and sitagliptin versus placebo (EXAMINE, SAVOR-TIMI 53, and TECOS [Trial Evaluating Cardiovascular Outcomes with Sitagliptin]), which were primarily designed to assess CV safety. Hospitalization for HF was reported in 3.4% (623 of 18,313) of patients receiving a DPP-4 inhibitor and in 3.0% (546 of 18,230) of subjects in the placebo arm. The HR of 1.14 (95% CI 0.97–1.34) did not reach significance. The test for heterogeneity of the three trials was also not significant ($P = 0.178$, $I^2 = 42\%$); yet, since the analysis included three trials with discordant results, they will be discussed in detail in the following section.

DPP-4 Inhibitors and HF: Evidence From Large CV Randomized Controlled Outcome Trials

In 2008, the U.S. Food and Drug Administration and the European Medicines Agency simultaneously revised their approval processes for all new glucose-lowering therapies to require a demonstration of CV safety. In the last 2 years, three CV outcome studies evaluating three different DPP-4 inhibitors (alogliptin, saxagliptin, and sitagliptin) were completed, and the findings were reported in detail (22–24).

SAVOR-TIMI 53 was designed to evaluate the long-term CV safety of saxagliptin in patients with diabetes at high risk for CV events (22). The study enrolled 16,492 high–CV risk patients with type 2 diabetes, who were followed for a median of 2.1 years. Saxagliptin was noninferior to placebo in lowering the risk of the composite primary end point of CV death, myocardial infarction, or stroke; however, there was an

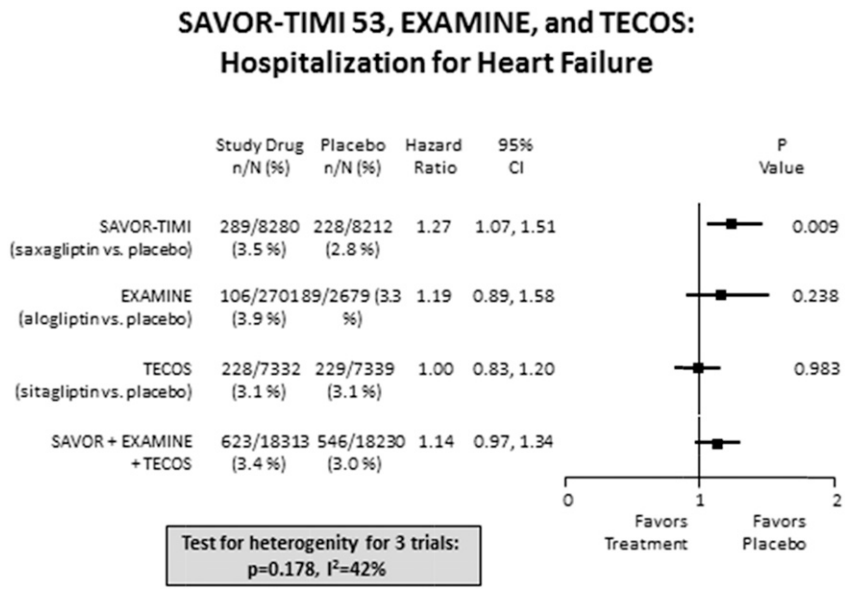

Figure 2—SAVOR-TIMI 53, EXAMINE, and TECOS: hospitalization for HF.

unexpected 27% increase in the RR (and 0.7% absolute risk over 2 years) of hospitalization for HF in patients assigned to saxagliptin (22). Hospitalization for HF was a predefined component of the secondary end point. Over 2 years of follow-up, more patients in the saxagliptin group (289 of 8,280 [3.5%]) were hospitalized for HF compared with the placebo group (228 of 8,212 [2.8%]) (HR 1.27 [95% CI 1.07–1.51]; P = 0.009). The corresponding rates at 6 months were 1.1 vs. 0.6% (1.80 [1.29–2.55]; P = 0.001) and 1.9 vs. 1.3% (1.46 [1.15–1.88]; P = 0.002) at 12 months and were balanced thereafter (HR 1.09; P = 0.51) (39).

In the subgroup of patients without a history of HF at baseline, the risk of hospitalization for HF with saxagliptin versus placebo was significantly increased (2.3 vs. 1.7%) (HR 1.32 [95% CI 1.04–1.66]). An increase in the risk of hospitalization for HF with saxagliptin versus placebo was also observed in the subgroup of patients with a prior history of HF (11.7 vs. 10.2%) (HR 1.21 [95% CI 0.94–1.58]), and though this increase did not reach statistical significance the P for interaction of prior HF with the risk for HF with saxagliptin was not significant (P = 0.67). Subjects at greatest risk for hospitalization for HF regardless of treatment allocation were those who had prior HF, chronic kidney disease (estimated glomerular filtration rate $<$60 mL/min), and/or elevated baseline levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP) (39). The absolute risk excess for HF with saxagliptin was the greatest in the highest NT-proBNP quartile. However, even in patients at high risk for hospitalization for HF, the risk of the primary and secondary end points was similar between treatment groups.

In the EXAMINE trial (23), which enrolled 5,380 patients with type 2 diabetes and a recent acute coronary syndrome event, alogliptin was noninferior to placebo in lowering the risk of the composite primary end point of CV death, myocardial infarction, or stroke (11.3 vs. 11.8%; HR 0.96, upper boundary of the one-sided 95% CI 1.16). As part of EXAMINE, the authors investigated the outcome of hospitalization for HF in a prespecified exploratory analysis and in post hoc analyses (40). Overall, more patients had admissions for HF in the alogliptin group (106 of 2,701 [3.9%]) compared with the placebo group (89 of 2,679 [3.3%]), but this difference was not significant (HR 1.19 [95% CI 0.89–1.58]). In the subgroup of patients with a history of HF, the admission rate for HF was not higher in the alogliptin group (63 of 771 [8.2%]) versus placebo group (65 of 762 [8.5%]) (HR 1.00 [95% CI 0.71–1.42]); however, in patients without a history of HF the admission rate for HF was significantly higher in the alogliptin group (43 of 1,930 [2.2%]) compared with the placebo group (24 of 1,917 [1.3%]) (HR 1.76 [95% CI 1.07–2.90]) (P for interaction 0.07) (40). The risk of CV events was substantially higher in patients with a history of HF at baseline than in those with no history of HF.

In TECOS, the long-term CV safety of adding sitagliptin versus placebo to usual care was assessed in 14,671 patients with both type 2 diabetes and established CV disease (24). During a median follow-up of 3.0 years, the primary outcome (composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) occurred in 839 patients in the sitagliptin group (11.4%) and in 851 patients in the placebo group (11.6%). Sitagliptin was noninferior to placebo for the primary composite CV outcome (HR 0.98 [95% CI 0.88–1.09]; $P < 0.001$). The rate of hospitalization for HF was similar in the sitagliptin group (228 of 7,332 [3.1%]) and in the placebo group (229 of 7,339 [3.1%]) (HR 1.00 [95% CI 0.83–1.20]). The composite outcome of hospitalization for HF or CV death occurred in 538 patients in the sitagliptin group (7.3%) and 525 in the placebo group (7.2%) (HR 1.02 [95% CI 0.90–1.15]; P = 0.74).

The risk of hospitalization for HF was not consistent across the three large CV outcome studies analyzing the safety of alogliptin, saxagliptin, and sitagliptin. Several explanations for this observation may be proposed and are discussed in the following sections.

Differences in the Characteristics of Patients Enrolled in EXAMINE, SAVOR-TIMI 53, and TECOS

It is important to realize that the trials differed in many aspects, including the following: the patients' severity of disease, comorbidities, and baseline HbA_{1c} and the proportion of patients on multiple daily insulin injections, as well as other baseline characteristics. In addition, sample sizes and duration of follow-up were also different. Table 2 summarizes the baseline characteristics of patients included in SAVOR-TIMI 53, EXAMINE, and TECOS (22–24,39,41). Previous HF was observed in 28% of the patients in EXAMINE but in only 13 and 18% in SAVOR-TIMI 53 and TECOS, respectively. TECOS included patients with a less advanced stage of disease as documented by a relatively

Table 2—Differences in baseline population in SAVOR-TIMI 53, EXAMINE, and TECOS

	SAVOR-TIMI 53	EXAMINE	TECOS
Sample size, *n*	16,492	5,380	14,724
Age	65.0 ± 8.6	61.0*	65.5 ± 8.0
Race			
White	75.2	72.5	68
Black	3.4	4.3	3
Asian	10.8	20.2	22
Other	10.5	2.9	7
Diabetes duration (years)	11.9 ± 8.9	7.1–7.3*	11.6 ± 8.1
HbA_{1c} (%)	8.0 ± 1.4	8.0 ± 1.1	7.2 ± 0.5
Insulin therapy	40.9	29.8	23.2
History of HF	12.7	27.9	18.0
History of CVD	78.3	100	100
GFR 30–50	13.6		9.3
GFR 30–60		26.2	
GFR <30	2.0	2.9	Excluded

Data are percent or mean ± SD unless otherwise indicated. Data are from refs. 22–24,39,41. GFR units are mL/min (SAVOR-TIMI 53) and mL/min/1.73 m^2 (EXAMINE and TECOS). GFR, glomerular filtration rate. *Median.

low HbA_{1c} at baseline (7.2% [range 6.5–8.0]), excluded patients with severe renal failure, and had a lower percentage of patients with moderate renal failure, and only 23% of patients were on insulin therapy at baseline; conversely, ~7% and 40% of the SAVOR-TIMI 53 population had baseline HbA_{1c} <6.5 or >8%, respectively, with higher baseline HbA_{1c} (8%), and almost twice as many (41%) of the patients were already on insulin therapy before saxagliptin or placebo was added, indicating that in SAVOR-TIMI 53 more patients with advanced stages of diabetes were included. However, it should be noted that analyzing the risk of hospitalization for HF with saxagliptin versus placebo in various subgroups revealed an increased risk in all groups (*P* for interaction >0.05 for all subgroups) (Supplementary Fig. 2 in ref. 39). For example, saxagliptin increased the risk of hospitalization both in insulin users (HR 1.19 [95% CI 0.95–1.50]) and in nonusers (1.36 [1.04–1.79]) (*P* for interaction 0.42).

Hypoglycemia has been proposed as a possible mechanism for the difference in the risk for hospitalization for HF. In both TECOS and SAVOR-TIMI 53, 40–45% of patients were on sulfonylureas at baseline. It was noted that the addition of saxagliptin in SAVOR-TIMI 53 increased the risk for major hypoglycemia, while in TECOS it did not. Hypoglycemia stimulates the sympathetic system and thus, with chronic stimulation, might have adverse results including progression to symptomatic HF and required admission to hospital in at-risk individuals (42). However, correlation between hypoglycemia and increased hospitalization for HF was not demonstrated in SAVOR-TIMI 53.

We conclude that although there were dissimilarities in the baseline characteristics of the patients enrolled in the studies, none of these plausibly explain the observed differences in the effects of the medication on hospitalization for HF.

Potential Mechanisms for the Increased Risk for HF Associated With the Use of DPP-4 Inhibitors

Multiple pathophysiological mechanisms have been proposed aiming to explain the observation of increased hospitalization for HF with DPP-4 inhibitors.

DPP-4 is a widely expressed enzyme and has been localized also in smooth muscle and endothelial cells in different species, as reviewed by Ussher and Drucker (43). Although the precise biological role of DPP-4 in myocardiocyte and endothelial or coronary smooth muscle cells requires further study, DPP-4 is also a circulating protein, and thus DPP-4 activity in the systemic and coronary circulation may influence intact levels of glucagon-like peptide 1 and other vasoactive DPP-4 substrates reaching the myocardium and vasculature (44). Recently, multiple DPP-4 substrates have been identified, and they act on various peripheral tissues, influencing the CV system. Ou et al. (45) discussed in an elegant review the potential enhancement or inhibition resulting from DPP-4 interactions, with many different regulatory proteins influencing a multitude of different cells, tissues, and organ responses via protein truncation. It is known that DPP-4 inhibition prevents the breakdown of the vasoconstricting neuropeptide Y and, when ACE is inhibited, substance P. In patients with metabolic syndrome, Marney et al. (46) observed an interaction between sitagliptin and high doses of enalapril by showing that blood pressure increased rather than decreased. They found that this interaction was associated with an increase in heart rate and plasma noradrenaline concentrations that reached statistical significance at the highest enalapril dose. The mechanisms underlying this interaction are unclear but might relate to altered degradation of the peptide substance P or neuropeptide Y related to DPP-4 inhibition, ultimately leading to sympathetically mediated vasoconstriction. In addition, Jackson and Mi (47) showed that in a renal perfusion model, enhancement of angiotensin-II–mediated constrictor responses, owing to increases of neuropeptide Y, could be exacerbated by sitagliptin and blocked if sitagliptin were given together with a neuropeptide Y inhibitor, again suggesting enhanced vasoconstriction.

In spite of the growing body of evidence stemming from mechanistic studies, we do not have any direct evidence in humans showing that DPP-4 inhibitors have a direct cardiotoxic or fluid retention effect that is related to reduced heart function or decreased myocardial ejection fraction. In SAVOR-TIMI 53, specifically, no possible pathophysiological mechanism to explain the increase in hospitalization for HF was found. Fluid retention was not demonstrated, as weight gain was similar between the two groups at 1 year, and reporting of edema was balanced between the groups as well. There were no differences between placebo and saxagliptin in the median change in concentrations from baseline to 2 years or end of treatment of high-sensitivity troponin or C-reactive protein. There was a slightly greater increase in NT-proBNP levels in the placebo group versus the saxagliptin group (10 vs. 4 pg/mL; *P* = 0.001) (39). These data do not support a toxic effect

of saxagliptin on the myocardium. The lack of a mechanistic explanation for the observed increased risk of hospitalization for HF in the SAVOR-TIMI 53 trial has raised much speculation regarding the meaning of this finding, with some wondering whether it may have been a play of chance (24).

The VIVIDD Trial

VIVIDD (31) was a small RCT assessing the safety of vildagliptin in individuals with diabetes and established HF. The trial, which included echocardiographic studies of patients with preexisting HF, is further discussed here illustrating the physiological changes associated with treatment with vildagliptin. A total of 254 patients with type 2 diabetes (mean age 63 years, average BMI 29 kg/m^2, HbA_{1c} 6.5–10%) and NYHA class I–III were randomized to either vildagliptin 50 mg b.i.d. (or 50 mg q.d. if taking a sulfonylurea) (n = 128) or placebo (n = 126). The proportion of NYHA classes I, II, and III was 9.8, 52.8, and 37.4%, respectively. The primary end point, the mean increase in the ejection fraction by 52 weeks, was 4.1 in the vildagliptin group versus 3.5 in the placebo group (P = 0.670), confirming noninferiority. Remarkably, patients taking vildagliptin, in comparison with those taking placebo, showed increases in left ventricular end-diastolic volume (P = 0.007), left ventricular end-systolic volume (LVESV) (P = 0.06), and stroke volume (P = 0.002). BNP had fallen at 52 weeks relative to baseline by 14% in the placebo group versus 28% in the vildagliptin group. Worsening of HF occurred in 22 patients in the placebo versus 23 in the vildagliptin group, but death from any cause occurred in 4 patients in the placebo group versus 11 in the vildagliptin group. Increases in left ventricular end-diastolic volume and LVESV are usually considered to be unfavorable, reflecting decreased systolic function. However, the primary end point showed that vildagliptin did not have an unfavorable effect on LVESV. Furthermore, the decrease in BNP in the vildagliptin group suggests that the increased left ventricular volumes observed did not result in increased left ventricular wall stress (31).

Differential Effect Observed in the Different Drugs in the Class

The differential effect observed with regard to hospitalization for HF with the different DPP-4 inhibitors is yet unclear. The molecules differ significantly with respect to their chemical structure, metabolism (saxagliptin is metabolized to an active metabolite), mode of interaction with the enzyme (sitagliptin and alogliptin form noncovalent interactions, and saxagliptin and vildagliptin form a reversible covalent enzyme-inhibitor complex), and route of elimination (48). Whether any of these pharmacological differences is the cause of the different biological phenomena has yet to be shown.

Conclusion

The issue of the relationship of DPP-4 inhibitors with increased risk for hospitalization for HF has not yet been resolved. In the SAVOR-TIMI 53 trial, increased hospitalization for HF was an unexpected finding, while in the same study the primary and secondary end points were balanced in the general and baseline HF populations. A possible mechanism to explain these findings has not yet been found, and further studies are presently being conducted to better understand this observation. The EXAMINE post hoc analysis for hospitalization for HF demonstrated a nonsignificant trend, while in TECOS, the risk for hospitalization for HF was balanced between sitagliptin and placebo groups. Population differences in these trials limit our ability to directly compare the three studies and therefore to come to a definite conclusion. Other observational studies and meta-analyses are also in disagreement with respect to a possible relationship between DPP-4 inhibitors and increased risk for hospitalization for HF.

Further studies investigating a possible pathophysiological relationship of these drugs to increased risk of hospitalization for HF, as well as head-to-head studies with other antidiabetes drugs (from the same or other classes), might resolve the question of the possible association of these drugs with hospitalization for HF and explain the differential effects observed within this class.

ADDENDUM

After submission of our review in 2015, a number of relevant articles focusing on the potential relationship between the use of DPP-4 inhibitors and hospitalization for HF were published.

Filion et al. (49) reported data from a very large cohort using health care data from four Canadian provinces, the U.S., and the U.K., including a total of 1,499,650 patients, with 29,741 hospitalized for HF (incidence rate 9.2 events per 1,000 person-year). The rate of hospitalization for HF did not increase with the use of incretin-based drugs as compared with oral antidiabetes drug combinations among patients with a history of HF (HR 0.86 [95% CI 0.62–1.19]) or among those without a history of HF (0.82 [0.67–1.00]). The results were similar for DPP-4 inhibitors and GLP-1 analogues. Mean duration of treated diabetes in this analysis was 0.8 years in patients without HF and 1.8 years in those with HF at baseline.

Toh et al. (50) examined the associations of hospitalization for HF with saxagliptin and sitagliptin in a large, population-based, retrospective, new-user cohort study, wherein 78,553 saxagliptin users and 298,124 sitagliptin users contributed an average of 7–9 months of follow-up data to one or more pairwise comparisons. The risk for hospitalization for HF was not higher with DPP-4 inhibitors than with the other study drugs. The HRs were 0.83 (95% CI 0.70–0.99) for saxagliptin versus sitagliptin, 0.63 (0.47–0.85) for saxagliptin versus pioglitazone, 0.69 (0.54–0.87) for saxagliptin versus sulfonylureas, 0.61 (0.50–0.73) for saxagliptin versus insulin, 0.74 (0.64–0.85) for sitagliptin versus pioglitazone, 0.86 (0.77–0.95) for sitagliptin versus sulfonylureas, and 0.71 (0.64–0.78) for sitagliptin versus insulin. Results from the 1:1 propensity score–matched analyses were similar as well as were results in subgroups of patients with and without prior CVD.

Fu et al. (51) published an observational study using an U.S. insurance claims database. After matching, the study included 218,556 patients in comparisons of DPP-4 inhibitors and sulfonylureas and 112,888 patients in comparisons of saxagliptin and sitagliptin. The risk of hospitalization for HF for patients with baseline CVD were not higher in patients treated with DPP-4 inhibitors versus those receiving sulfonylureas (HR 0.95 [95% CI 0.78–1.15]; $P = 0.58$). For patients without baseline CVD, risk for hospitalization for HF was even lower when DPP-4 inhibitors were used (0.59 [0.38–0.89]; $P = 0.01$). There

was no difference in risk in patients treated with saxagliptin versus sitagliptin (0.95 [0.70–1.28]; $P = 0.71$) or in patients with versus without baseline CVD (0.99 [0.56–1.75]; $P = 0.97$]).

Fadini et al. (52) performed a retrospective study in 16 Italian regions, accounting for a population of 18 million individuals, to assess the association between HF risk and use of sulfonylureas, DPP-4 inhibitiors, and thiazolidinediones. A total of 127,555 patients were included, of whom 14.3% were on DPP-4 inhibitors, 72.5% on sulfonylureas, and 13.2% on thiazolidinediones, with an average of 71% being on metformin as combination therapy. During an average 2.6-year follow-up, after adjusting for measured confounders, use of DPP-4 inhibitors was associated with a reduced risk of hospitalization for HF compared with use of sulfonylureas (HR 0.78 [95% CI 0.62–0.97]; $P = 0.026$). After propensity matching, the analysis was restricted to 39,465 patients, and the use of DPP-4 inhibitors was still associated with a lower risk of hospitalization for HF (0.70 [0.52–0.94]; $P = 0.018$).

In 2016, two new meta-analyses analyzing a potential relationship between the use of DPP-4 inhibitors and HF were published (53,54). A very recent meta-analysis of randomized and observational studies by Li et al. (53) including 43 trials ($n = 68,775$ participants) and 12 observational studies (9 cohort studies, 3 nested case-control studies; $n = 1,777,358$ participants) found a small increased risk of hospital admission for HF in patients with type 2 diabetes who received DPP-4 inhibitors versus subjects in control groups from randomized controlled trials (HR 1.13 [95% CI 1.00–1.26]). The authors concluded that the relative effect of DPP-4 inhibitors on HF remains uncertain in patients with type 2 diabetes, given the relatively short follow-up and low quality of evidence. A total of 54 studies with 74,737 participants were included in the meta-analysis by Kongwatcharapong et al. (54). Overall, DPP-4 inhibitors were not associated with an increased risk of HF compared to comparators (RR 1.106 [95% CI 0.995–1.228]; $P = 0.062$). When analyzed individually, saxagliptin was significantly associated with the increased risk of HF (1.215 [1.028–1.437]; $P = 0.022$), while other drugs were not. Age ≥65 years, diabetes duration of ≥10 years, and BMI ≥30 kg/m^2 were associated with an increased risk of HF among patients using saxagliptin. The current evidence suggests a small increase in the risk of hospital admission for HF in patients with existing CVD or multiple risk factors for vascular diseases. Additional randomized controlled trials enrolling patients with existing CVD or multiple risk factors for vascular diseases will be required to definitively assess the effect of DPP-4 inhibitors on such patients.

Duality of Interest. G.S. has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Johnson & Johnson, Merck, and Takeda and is a speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi, and Takeda. A.C. has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme (MSD), Novartis, Novo Nordisk, and Sanofi and is a speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Teva. I.R. has served on the advisory board for AstraZeneca/Bristol-Myers Squibb, Eli Lilly, Medscape, MSD, Novo Nordisk, Sanofi, Orgenesis, SmartZyme Innovation, and LabStyle Innovations; has served as a consultant for AstraZeneca/Bristol-Myers Squibb, Insuline Medical, Gili Medical, Kamada, and FuturRx; has served on the speaker's bureau for AstraZeneca/Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, MSD, Novartis Pharma, Novo Nordisk, Sanofi, and Teva; and is a stock/shareholder for Insuline Medical, LabStyle Innovations, SmartZyme Innovation, Orgenesis, and Glucome. No other potential conflicts of interest relevant to this article were reported.

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