Glycemia Lowering and Risk for Heart Failure
Recent Evidence from Studies of Dipeptidyl Peptidase Inhibition

Jixin Zhong, MD, PhD*; Aditya Goud, MD*; Sanjay Rajagopalan, MD

The global epidemic of type 2 diabetes mellitus (T2DM) has substantial implications for cardiovascular disease–related morbidity and mortality.1 The prevalence of T2DM in patients with heart failure (HF) is high, with strong and independent association between T2DM and incident HF observed in multiple prospective studies and in randomized-controlled clinical trials. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which enrolled subject’s 255 years of age with hypertension and ≥1 risk factor, patients with T2DM had a 2-fold risk for HF hospitalization or death after adjustment for other risk factors (RR, 1.95). The association with T2DM was independent of coronary artery disease and at least equivalent in magnitude and greater than that for electrocardiographic left ventricular (LV) hypertrophy.2 All measures of glycemia including fasting, postprandial, measures of insulin resistance, and hemoglobin A1c (HbA1c) have been associated with risk of developing HF, with the association extending to both HF with preserved ejection fraction and to HF with reduced ejection fraction.3,4 A substantial body of evidence from preclinical studies, endomycocardial biopsies in humans and more recently with cardiac MRI, support increased myocardial stiffness in T2DM related to alteration in extracellular matrix. There are multiple proximate mediators that have been hypothesized to play a role including advanced glycation end product deposition and reactive oxygen species that may increase myocardial stiffness during diastole, by cross-linking collagen or by enhancing collagen formation.5,6 Another pernicious proximal mediator is the elevation in postprandial lipids, such as remnant lipoproteins, characteristic of atherogenic dyslipidemia, a highly prevalent abnormality in T2DM, that may result in direct myocardial deposition of lipid, leading to microcirculatory dysfunction, alteration in substrate use and mitochondrial dysfunction.7,8 Indeed, positron emission tomography studies show reduced myocardial glucose uptake in favor of fatty acid uptake in a majority of the studies.9 Over the past decade, glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP4) inhibitor-based therapies (incretin agents) have revolutionized the management of T2DM, as these address abnormalities in postprandial glucose and lipoproteins and reduce fasting glycemia without causing hypoglycemia. Moreover, incretin agents seem to exert pleiotropic effects on the cardiovascular system including favorable effects on myocardial and vascular function leading to the anticipation that these agents may successfully address cardiovascular risk in T2DM, including susceptibility to HF.

HF Signals With Glycemia-Lowering Therapies
Although hyperglycemia in T2DM has been shown to be associated with excess risk of HF, the converse of lowering glucose pharmacologically may not always result in reduced propensity for HF. Thus, before we can satisfactorily address the issues related to incretin-based therapies, and whether these agents alter susceptibility to HF, the evidence (if any) supporting glycemia lowering and HF susceptibility needs to be understood.

The United Kingdom Prospective Diabetes Study (UKPDS) was one of the first trials to describe a hypothetical beneficial relationship between glycemia lowering and HF risk.10 UKPDS was a randomized-controlled trial of diet alone (n=411) versus intensive blood-glucose control with metformin, aiming for normoglycemia [<6 mmol/L; n=342]. A secondary analysis compared patients allocated to metformin (n=342) with overweight patients allocated to chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409). The primary outcome measure was an aggregate of any diabetes mellitus–related clinical end point, diabetes mellitus–related death, and all-cause mortality. The results of UKPDS suggested an important benefit for glycemia lowering and a linear relationship between glycemia lowering and reduction of the primary end point.10 In a secondary analysis of UKPDS, the adjusted rate of HF was reduced to 2.3 events/100 person-years in those with HbA1c levels <6%, from 11.9 in those whose HbA1c levels were >10%, with a near linear relationship between lowering of HbA1c and risk for HF, that extended to levels <6% with no apparent lower threshold of risk.11 From a pathophysiologic standpoint, glycemia lowering is associated with a correction of several pathophysiologic core principles at play and may indeed be expected to lower risk, provided the agent(s) under consideration worked by lowering glucose alone. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which involved patients with recent onset T2DM, impaired fasting glucose and impaired glucose tolerance in addition to other
cardiovascular risk factors, tested a strategy of insulin glargine versus standard care, to a target fasting blood-glucose level of ≤95 mg/dL (5.3 mmol/L) or standard care. Despite normalization of fasting plasma glucose over a median follow-up duration of 6.2 years, cardiovascular outcomes were similar in the 2 groups (2.94 and 2.85/100 person-years respectively, for the first coprimary outcome of CV death, nonfatal myocardial infarction [MI], or nonfatal stroke [hazard ratio [HR], 1.02; confidence interval [CI], 0.94–1.11; P=0.63]). The secondary end point was a composite of any of these events, revascularization or hospitalization for HF and was no different (HR, 1.04; CI, 0.97–1.11; P=0.27). When examined individually, hospitalization for HF occurred in 4.9% (n=310) in the glargine arm, compared with 5.5% (n=343) in the standard care arm (HR, 0.90; CI, 0.77–1.05; P=0.27) suggesting a reduction in risk, albeit without statistical significance. Thus, a nearly pure glucose-lowering strategy via supplementation of glargine in a large population did not demonstrate excess risk for HF but neither was it associated with lowering of HF.

Metformin use is endorsed by multiple guidelines as the initial therapy of choice in T2DM. Although its use in patients with HF is discouraged, this is primarily because of the risk of lactic acidosis that may be accentuated in HF. Indeed, there is still a black box warning for the cautious use of metformin in this population, primarily related to lactic acidosis risk.12 Key observational studies to analyze the safety of metformin use in patients with chronic HF seem to suggest a reduction in mortality with no excess risk in this patient population.13 A recently concluded randomized-controlled clinical trial in a high-risk ST-segment-elevation MI population did not demonstrate any adverse effect of metformin on LV function.15 In contrast, sulfonylurea use is associated with excess risk for HF. After adjusting for sex and duration of diabetes mellitus, first as standard care, to a target fasting blood-glucose level of ≤95 mg/dL (5.3 mmol/L) or standard care. Despite normalization of fasting plasma glucose over a median follow-up duration of 6.2 years, cardiovascular outcomes were similar in the 2 groups (2.94 and 2.85/100 person-years respectively, for the first coprimary outcome of CV death, nonfatal myocardial infarction [MI], or nonfatal stroke [hazard ratio [HR], 1.02; confidence interval [CI], 0.94–1.11; P=0.63]). The secondary end point was a composite of any of these events, revascularization or hospitalization for HF and was no different (HR, 1.04; CI, 0.97–1.11; P=0.27). When examined individually, hospitalization for HF occurred in 4.9% (n=310) in the glargine arm, compared with 5.5% (n=343) in the standard care arm (HR, 0.90; CI, 0.77–1.05; P=0.27) suggesting a reduction in risk, albeit without statistical significance. Thus, a nearly pure glucose-lowering strategy via supplementation of glargine in a large population did not demonstrate excess risk for HF but neither was it associated with lowering of HF.

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Collectively, these findings suggest that there is an association with antiglycemic agents and HF, particularly between PPARγ agonists and sulfonylureas with minimal to no association between metformin and insulin use. Further it is likely that drugs that specifically target a single step rather than broad pathways including molecular master switches (eg, thiazolidinediones) may open the door to unpredicted off-target side effects. In the case of PPARγ and combined PPARα/γ agonists, the role of these agents in increasing sodium retention must be acknowledged.19,20 These include activation of epithelial Na+ channel (ENaC), either directly or through serum and glucocorticoid-regulated kinase-1. Alternative mechanisms in the collecting duct may include stimulation of non-ENaC sodium channel or inhibition of chloride secretion to the tubular lumen. In addition, thiazolidinediones may augment sodium reabsorption in the proximal tubule by stimulating the expression and activity of apical Na+/H(+)-exchanger-3 and basolateral Na+–HCO3 (−) cotransporter as well as of Na+, K+–ATPase.21 Finally, it may be hypothesized that glycemia lowering in patients accustomed to years of hyperglycemia may exacerbate cardiac dysfunction at least in the short term, by favoring less efficient bioenergetic pathways (for instance by unfavorably altering the balance of free fatty acid oxidation and glycolysis).22

Pharmacological Inhibition of DPP4 and Relevance to HF

The development of DPP4 inhibitors (DPP4i) as a class of antidiabetic medications was predicated on the notion that these drugs would raise GLP-1/gastric inhibitory polypeptide levels resulting in enhancement of insulinotropic effects of glucose. This rather simple construct has been replaced with a much more nuanced understanding of this protein as an important post-translational modifier of a number of substrates (reducing or enhancing their function via N-terminal degradation), besides playing a role independent of this function. DPP4 (CD26) is a transmembrane glycoprotein with exopeptidase activity that cleaves dipeptides from the N-terminal of proproteins such as adenosine deaminase may also influence immune function. The catalytic function of DPP4 is involved in catalytic inactivation of >25 proteins many of which are involved in regulation of cardiovascular function.23 DPP4 is expressed ubiquitously in the cardiovascular system and on immune cells (T cells, NK cells, macrophages, and dendritic cells). DPP4 also circulates as a soluble form that has preserved catalytic function, which could exert independent effects, in addition to its membrane bound function. The noncatalytic function of DPP4 has been described previously and its role as a T cell and dendritic activation protein is well recognized.24 Furthermore, the binding to proteins such as adenosine deaminase may also influence immune function. The catalytic function of DPP4 is involved in catalytic inactivation of >25 proteins many of which are involved in regulation of cardiovascular function.23

Although most of the experimental evidence on DPP4 inhibition attributes effects to the inhibition of breakdown of active GLP-1 (7–36) to inactive GLP-1 (9–36) and ligation of GLP-1
receptor, the magnitude of elevation in circulating GLP-1 is small with DPP4 inhibition, with many studies failing to demonstrate any effect fasting GLP-1 levels.\textsuperscript{25} Although it is certainly conceivable that increase in GLP-1 postprandially or in tissue niches in response to DPP4 inhibition may drive GLP-1–mediated effects, the elevation of GLP-1 seen with pharmacological doses of GLP-1 (60–90 pmol/L) may provide for distinct GLP-1–mediated effects independent of DPP4. The other proteins of interest modulated by DPP4 include stromal cell–derived factor-1 (SDF-1, also known as CXCL12), granulocyte–macrophage colony–stimulating factor (GM-CSF), granulocyte CSF (G-CSF), interleukin-3 (IL-3), eotaxin, regulated on activation normal T cell expressed and secreted (also known as CCL22), macrophage-derived chemokine (also known as CCL22), eotaxin (also known as CCL11), monokine-induced by interferon-γ (also known as CXCL9), interferon-γ–induced protein-10 (also known as CXCL10), and interferon-inducible T-cell α chemoattractant (also known as CXCL11), etc. The SDF-1/CXCR4 axis is of particular interest, as this protein may play a physiological role in the recruitment of CXCR4 positive progenitor cells to promote tissue repair.\textsuperscript{26} Cleaveage of the N-terminal end of SDF-1 results in its inactivation and loss of chemotactic inactivity SDF-1\textsuperscript{-17}. DPP4 inhibition in experimental models improves homing and engraftment of hematopoietic stem cells.\textsuperscript{27} Sipeglitatin treatment in patients with T2DM increases circulating endothelial progenitor cell and plasma SDF-1.\textsuperscript{29} DPP4 may also regulate stem cell function via its effects on GM-CSF, G-CSF, IL-3, and eotaxin.\textsuperscript{30} DPP4 deficiency or catalytic inhibition promoted hematopoiesis and bone marrow engraftment in mice after radiation or chemotherapy.\textsuperscript{31} DPP4-truncated CSFs blunted the activity of their respective full-length CSF, both in vitro and in vivo with the truncated GM-CSF, demonstrating a higher affinity to GM-CSF receptor compared with full-length GM-CSF. DPP4 converts brain natriuretic peptide (BNP) to produce BNP (3–32), which has reduced vasodilation and natriuretic effects.\textsuperscript{31} In humans, however, acute inhibition of DPP4 with sitagliptin does not potentiate BNP-mediated forearm blood flow.\textsuperscript{32} Removal of N-terminal dipeptides from neuropeptide Y, peptide YY, and substance P by DPP4, is believed to alter the receptor subtype specificity of neuropeptide Y and peptide YY, while reducing activity of substance P. Whether these effects of DPP4 contribute to alterations in hemodynamics is intriguing, although the lack of DPP4 inhibition on blood pressure argues against a significant net effect on this axis.\textsuperscript{33–35} In summary, current evidence seems to support an important role for DPP4, in regulation of a range of peptides of relevance to the cardiovascular system, and in particular may be relevant to potential effects on HF in the patient with T2DM.

A Role for DPP4 in HF: Experimental Evidence
DPP4 levels correlate with the severity of HF in animal models and humans.\textsuperscript{36} Although DPP4–/– mice are normal with no obvious morphological change or alteration in systolic/diastolic functional changes, they demonstrate improved survival after left anterior descending artery occlusion with increase in Akt1, Gsk3β, Ppara, P13K, and Hemooxygenase 1 transcripts.\textsuperscript{37} These effects are similar to those obtained with sitagliptin administration in murine models, where upregulation of cardioprotective pathways and favorable effects on LV remodeling are observed.\textsuperscript{38} Indeed, in open label studies conducted in non-diabetic and diabetic humans with coronary artery disease and normal LV function undergoing dobutamine stress echocardiography, with blinded assessment of segmental function, sitagliptin treatment (both acutely and short term) improved recovery of ischemic segments after stress.\textsuperscript{39,40} In nonischemic models of HF, there is evidence to support a protective effect of DPP4 inhibition (Table). Both pharmacological and genetic DPP4 inhibition seems to reverse diabetic diastolic LV dysfunction.\textsuperscript{41} The effects of DPP4 inhibition seem to be specific to diabetic HF at least in 1 study, as evidenced by an increase in myocardial DPP4, which through a reduction in SDF-1 levels attenuates HIF-1α–mediated angiogenesis (Figure).\textsuperscript{41} To what extent DPP4 mediated increase in SDF-1 or other factor that regulate stem cell homing and angiogenesis contribute to postinfarct remodeling remains an open question and will require further mechanistic studies.\textsuperscript{29}

Because activation of the GLP-1 receptor (GLP-1R) also upregulates cardioprotective pathways, it has been reasonably hypothesized that increase in GLP-1 after DPP4 inhibition could mediate its effects via this pathway (Figure). Several uncontrolled studies in humans have suggested that GLP-1 administration may improve myocardial function and indices of HF.\textsuperscript{47} This has led to the widespread belief that DPP4 inhibition may also mediate its favorable effects via increase in GLP-1. It is important to note that almost all preclinical studies that attribute cardiovascular effects of DPP4 to GLP-1–mediated effects on myocardial function, do so only by association between improvements in functional indices and elevation in GLP-1 levels.\textsuperscript{48} Recent evidence, however, seems to rule out a significant involvement of GLP-1 by demonstrating lack of expression in myocardial GLP-1R, ruling out a direct effect of GLP-1/GLP-1R on myocardial function.\textsuperscript{49} In these experiments, selective deletion of cardiomyocyte GLP-1R in mice, produced no differences in survival or adverse LV remodeling after left anterior descending artery occlusion or in response to adriamycin-induced LV dysfunction.\textsuperscript{49} Collectively, these data would argue against a significant effect of GLP-1 directly on the myocardium at least in response to DPP4 inhibition. These experiments do not rule out an indirect effect of exogenous GLP-1–based therapy via other mechanisms including natriuretic pathways as has been postulated.\textsuperscript{50}

DPP4 is highly expressed in the kidney and has been implicated in sodium retention through both renal mechanisms as well as through degradation of natriuretic peptides. DPP4 forms a complex with Nα/H+ exchanger-3 at the level of the brush membrane of the proximal convoluted tubule.\textsuperscript{51} DPP4 inhibition may thus interfere with Na+ reabsorption increasing natriuresis.\textsuperscript{52,53} The preservation of GLP-1 levels by DPP4i may additional result in the elevation of natriuretic peptides, such as ANP. Indeed, GLP-1 has been shown to increase ANP synthesis from the atria and this may also contribute to a natriuretic response.\textsuperscript{50}

HF Signals With DPP4i
Recently, there were 2 large multicenter randomized-controlled clinical trials that tested the effect of glycemia lowering with DPP4i. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI
to that observed in the overall trial. The number of excess hospitalizations for HF per year if 1000 patients were treated with saxagliptin ranged from 0 in patients with no risk factors to 9 in patients with both risk factors. There was no evidence of direct myocardial toxicity or inflammation with saxagliptin, as reflected by similar change in concentrations of high-sensitivity troponin T and high-sensitivity C-reactive protein between the treatment groups. There was no evidence of a differential effect of saxagliptin on NT-BNP levels at 1 year (BNP but not NT-ProBNP) compared with placebo, a difference that was modest owing to use of glycemia-lowering therapies in the control group, a feature allowed in the trial. After a median follow-up of 18 months, the trial met its noninferiority hypothesis with the primary end point of cardiovascular death, nonfatal MI, and nonfatal stroke occurring in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%; HR, 0.96; upper boundary of the 1-sided repeated CI, 1.16; P=0.001 for non-inferiority). Although HF was not a prespecified end point in EXAMINE, this end point was prospectively defined and collected. In a subsequent prespecified analysis of EXAMINE, the first occurrence of an expanded major adverse cardiovascular events (MACE) end point (all-cause mortality, nonfatal MI, nonfatal stroke, urgent revascularization, and hospitalization for
HF) was assessed. The expanded composite outcome occurred in 443 (16%) and 441 (16.5%) of alogliptin and placebo groups, respectively (HR, 0.98; CI, 0.86–1.12; P = 0.73). First occurrence of hospitalization for HF occurred in 85 (3.1) and 79 (2.9%) of alogliptin and placebo groups, respectively (HR, 1.07; CI, 0.79–1.46; P = 0.68). In an analysis looking at cardiovascular death and HF hospitalization (which included recurrent hospitalization events) there were 201 (7.4%) and 201 (7.5%) events in the alogliptin and placebo groups with HF events occurring in 106 (3.9%) and 89 (3.3%), respectively (HR, 0.98; CI, 0.82–1.21; P = 0.98). In a separate post hoc analysis that stratified patients according to their baseline BNP levels similar to the SAVOR-TIMI 53 analysis, there was no evidence of relationship between BNP levels and occurrence of HF events in the alogliptin groups. In particular, although NT-BNP identified patients at higher risk, the risk did not seem to be elevated in the highest quartile of NT-BNP (HR, 0.90; 95% CI, 0.70–1.16). Concentrations of NT-pro-BNP decreased significantly from baseline to 6 months in the alogliptin group (median value at baseline 423 pg/mL [interquartile range, 156–1103] versus 220 pg/mL [interquartile range, 89–551] at 6 months; P < 0.001). Similar changes were observed in the placebo group (399 pg/mL [interquartile range, 149–982] versus 213 pg/mL [interquartile range, 88–564]; P < 0.001). The difference in change between treatment groups was not significant (P = 0.077).57

Approximately 13% of patients in SAVOR-TIMI 53 had a history of HF. Interestingly, although the use of thiazolidinediones was low in the study, there were numerically more patients using thiazolidinediones in the saxagliptin group (6.2%, 513) than in the placebo group (5.7%, 465) at baseline. Although these differences did not persist at the second and third years, it may be hypothesized to have driven the small difference in HF between the 2 groups. Similarly, insulin and sulfonylurea use although roughly comparable between the 2 groups was numerically higher in the saxagliptin group than in the placebo group (3352, 40.5% and 3281, 40% versus 3448, 41.6% and 3384, 41.2%). Because there was an increase of only 81 cases of HF hospitalizations in the saxagliptin therapy, a possible explanation to the trial’s findings exists in the slight imbalances in baseline treatment (especially thiazolidinediones) and perhaps not to the drug itself. In comparison with SAVOR-TIMI 53, thiazolidinediones use in EXAMINE was infrequent, with only 67 (3%) and 64 (2%) of patients receiving this treatment. Insulin and sulfonylurea use was higher in EXAMINE than in SAVOR-TIMI 53 but nearly identical in the 2 groups (47% using sulfonylureas and 30% using Insulin) both at baseline and during the duration of the trial. Additional reasons for differences between HF outcomes between the trials may relate to structural differences between these small molecules, which may sometimes contribute to differences in outcomes (saxagliptin is a β-amino acid–based DPP4i, whereas alogliptin is a peptidomimetic [modified pyrimidinedione]).

Conclusions
In conclusion, it is important to understand that diabetes mellitus is an incipient HF state. Several previous antidiabetic
agents have been associated with risk for HF, with the risk being the lowest with those that purely regulate glucose. The risk seems to be higher with drugs that are nonselective and target multiple pathways (such as the PPARγ or sulfonylureas). The risk for HF associated with incretin therapies has to be interpreted carefully, with an understanding of their mechanisms of action and in the context of their overall safety and use for the treatment of T2DM. The overall safety profile of these drugs in the treatment of T2DM seems to be exceptional at least in the short term, with minimal risk for hypoglycemia.

In SAVOR-TIMI 53, the excess HF signal noted currently is at odds with what is known about the biology of DPP4 and its effects on substrates, including GLP-1. Although alogliptin seems not to be associated with HF risk, the lack of association must be interpreted in the context of the trial itself. An important message from both EXAMINE and SAVOR-TIMI 53, is that in patients with a history of HF, treatment with a DPP4 inhibitor did not lead to excess risk of developing cardiovascular end points, such as cardiovascular death, nonfatal MI, or nonfatal stroke, in a high risk patient population. In addition, in both EXAMINE and SAVOR-TIMI 53 there did not seem to be an association with mortality. Finally, in both these trials, the presence of HF clearly identified a population of patients at risk for future HF, in whom therapeutic choices may need to be carefully made. Results from other DPP4i trials may address the class effect of these drugs.

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**References**


by sitagliptin improves myocardial response to dobutamine stress. 


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