

Play of Chance Versus Concerns Regarding Dipeptidyl Peptidase-4 Inhibitors: Heart Failure and Diabetes

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The delicate balance of disease management versus off-target effects of treatment continues to be a vital concern to both patients and physicians. This article offers a brief overview of heart failure in diabetes and comments on the recent outcome trials of dipeptidyl peptidase-4 (DPP-4) inhibitors, with a closer look at a few pathobiological concerns.

The importance of safe antidiabetic treatments becomes apparent when one considers the increasing obesity and diabetes pandemics. Approximately 150,000 patients with moderate-high cardiovascular (CV) risk factor profiles are currently enrolled in trials of antidiabetic agents. Establishing the CV safety of newer antidiabetic agents, especially with respect to heart failure, remains crucial.

Heart failure syndrome is a symptom complex composed of worsening shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and the well-known manifestation of ankle edema. The syndrome is characterized by physical findings of fluid retention (dependent edema), a third heart sound, rales sounds, and distension of the neck veins. In addition, heart failure is associated with chronic inflammation and a prothrombotic state. Endothelial dysfunction and proteomic and neurohormonal activation occur many months before development of the syndrome complex.^{1,2}

Newer areas of basic science research have identified potential prognostic indicators in chronic heart failure (miR126 and miR508-5p) that might be used as novel markers leading to earlier diagnosis and treatment of heart failure.^{3,4} Heart failure has several etiologies ranging from mechanical and electrical dysfunction to structural and valvular abnormalities. Moreover, the consequences of heart failure are multi-systemic and adversely affect the liver, kidneys, bone marrow, and muscle.

Recent data from the Olmstead County population study⁵ showed that patients with diabetes had equal amounts of systolic and diastolic dysfunction. Patients with diabetes frequently have preserved left-ventricular function (a normal

ejection fraction) but with a poorly compliant left ventricle that is very sensitive to volume changes. For example, people with type 2 diabetes who are exposed to an extra salt and fluid load could experience enough of an increase in circulating blood volume to place them into symptomatic heart failure. Autonomic dysfunction, glucose toxicity, and oxidative stress are believed to play a role in the development of heart failure in people with diabetes (Figure 1).

The occurrence of CV events and mortality in patients with diabetes is frequently underestimated when considering heart failure in diabetes. Notably, myocardial infarction (MI), non-ST elevation MI, and stroke are the leading primary endpoints of most current antidiabetic drug trials. However, heart failure may

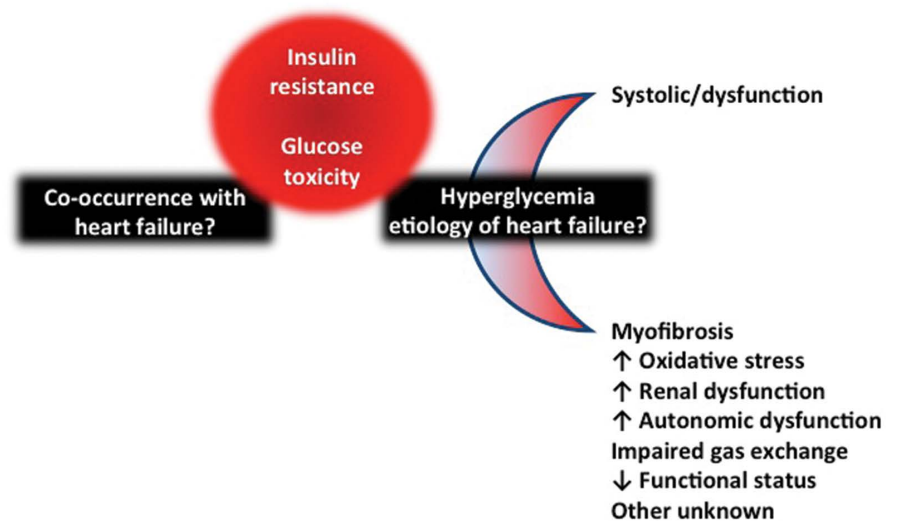


Figure 1. Diabetes and heart failure: a complex pathophysiological association.

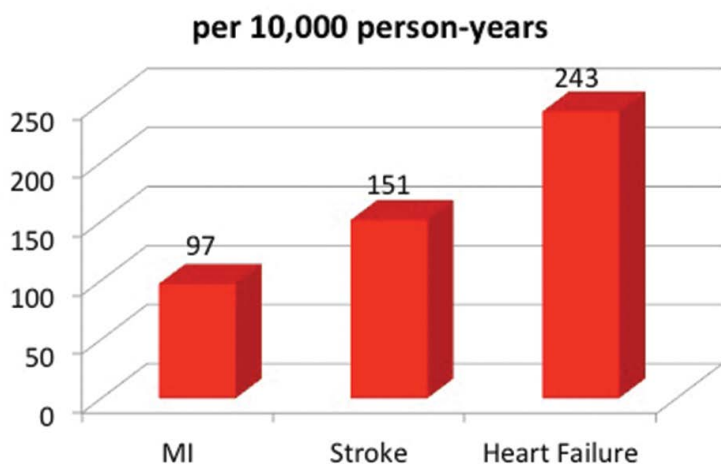


Figure 2. This figure illustrates the importance of heart failure consideration in primary endpoint trials with hypoglycemic agents. A retrospective cohort study⁶ with nearly 50 million lives found a high incidence of heart failure compared to the classic primary endpoints in most diabetes trials. Adapted from Ref. 6.

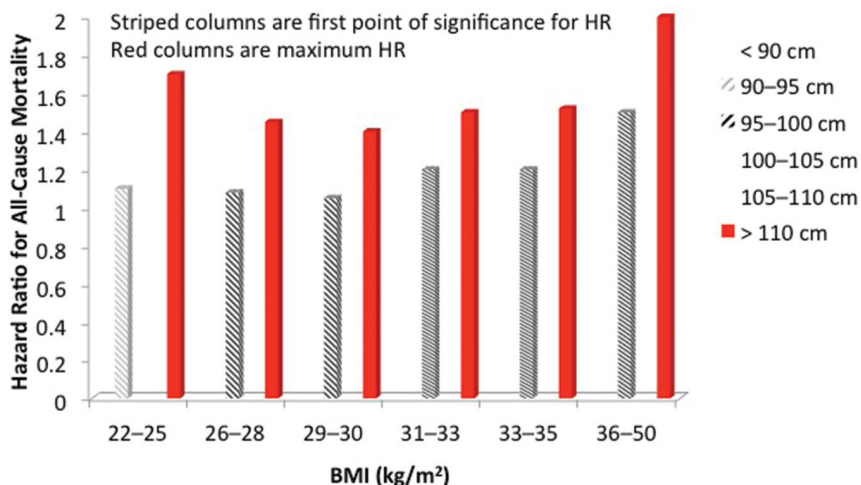


Figure 3. This pooled data from 11 prospective cohort studies with 650,386 white adults found a significant correlation in all-cause mortality when waist circumference was combined with BMI. Note that even at a low BMI, there is an increased risk for all-cause mortality with a waist circumference > 90 cm (36 inches). Adapted from Ref. 8.

need to be added or considered as a principal secondary endpoint. Recently, Juhaeri et al.⁶ reported in a retrospective study encompassing > 50 million lives from Medicaid, Medicare, and 60 health maintenance organizations the incidence of heart failure, MI, and stroke in type 2 diabetes patients on insulin. The highest incidence was for heart fail-

ure (Figure 2). In addition, Bertoni et al.⁷ evaluated 151,738 Medicare beneficiaries with diabetes with practically a 10-fold increase in heart failure mortality versus patients with diabetes who were free of heart failure at 60 months.

In summary, the heart failure syndrome in diabetes carries an ominous outlook, and, with an

increasing number of antidiabetic drugs to reduce blood glucose levels, newer trials should consider heart failure as one of the major clinical endpoints. In addition to an increasing BMI, which is frequently associated with diabetes, waist circumference should also be evaluated, even for patients with a normal weight (Figure 3).⁸

Despite advances in medical and surgical therapy for the management of patients with diabetes, lifestyle modification leading to weight loss alone affords improvement in the CV risk profile, as shown in Table 1. It is possible that interventional procedures such as endobarrier or gastric bypass surgery may carry less risk for markedly obese patients who are at high risk for diabetes or who have diabetes, but these procedures also carry some degree of surgical risk.

SAVOR and EXAMINE Trials

Two recent DPP-4 inhibitor trials have increased discussion about hospitalizations for heart failure even though basic science studies have not noted significant heart failure concerns.

The SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus [TIMI-53]) trial⁹ evaluated the safety and efficacy of saxagliptin on CV outcomes in patients with diabetes who are at risk for CV events. The trial was designed as a superiority trial. However, a closed testing hierarchy prespecified that a test for noninferiority of the primary composite endpoint should be completed first to preserve the alpha level, followed by a test for superiority. A total of 16,492 diabetes patients were prospectively randomized to saxagliptin 5 mg daily (2.5 mg if glomerular filtration rate [GFR] was < 50 ml/min/1.73 m²) or placebo, with a mean follow-up of 2.1 years. Demographic data are shown in Table 2. The primary end-

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Table 1. Effects of Diabetes Management Strategies on Known Classic CV Risk Factors

Management Strategy	CRP	LDL	BP	PPG	Weight Loss	Decrease in CV Events?	Side Effects?
SGLT-2 inhibitor	↓	↑	↓↓↓	↓↓	↓↓	?	Yes
Statin	↓	↓↓↓↓	0	?	0	Yes (ARR 3–4%)	Yes
TZD	↓	++/-	↓↓	↓↓	↑	+/-	Yes
DPP-4 inhibitor	↓	+/-	+/-	↓↓	0	No (HF?)	Yes
Weight loss of 10%	↓↓	↓	↓↓	↓	↓↓↓	Yes (ARR 1–2%)	Hunger
Endobarrier	?	?	+/-?	↓↓	↓↓↓	?	Yes
Gastric bypass	↓↓	↓	↓	↓↓	↓↓↓	Yes/SOS	Yes

ARR, absolute risk reduction; BP, blood pressure; CRP, C-reactive protein; LDL, LDL cholesterol; PPG, postprandial glucose; SGLT-2, sodium glucose co-transporter 2; SOS, Swedish Obese Subjects study; TZD, thiazolidinedione.

Table 2. Comparison of Baseline Demographics from the SAVOR⁹ and EXAMINE¹⁰ Trials

	SAVOR (Stable CAD)		EXAMINE (ACS)	
	Saxagliptin	Control	Alogliptin	Control
BMI (kg/m ²)	31	31	28	28
Duration of diabetes (years)	10.3	10.3	7.1	7.3
Hypertension (%)	81	82	82	83
Prior heart failure (%)	12.8	12.8	28	27
Prior MI (%)	38	37	77	77
Prior revascularization (%)	43	43	74	74
Mean A1C (%)	8.0	8.0	8.0	8.0
GFR > 60 ml/min/1.73 m ² (%)	84	84	71	70
Aspirin therapy (%)	75	76	91	91
Statin therapy (%)	78	78	90	90
ACE inhibitor therapy (%)	82	82	82	82

ACS, acute coronary syndrome; CAD, coronary artery disease.

point was a composite of CV death, MI, or ischemic stroke.

The primary endpoint occurred in 613 patients in the saxagliptin group and 609 patients in the placebo group (7.3 and 7.2%, NS). The 2-year Kaplan-Meier estimate for superiority was not achieved (hazard ratio [HR] with saxagliptin 1.00, 95% CI 0.89–1.12, *P* = 0.99). However,

noninferiority was significant at *P* < 0.001. The major composite secondary endpoints of CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization, and heart failure was 12.8% in the treatment arm and 12.4% in the placebo arm (2-year Kaplan-Meier estimate HR 1.02, 95% CI 0.94–1.11, *P* = 0.66, NS). Unfortunately,

hospitalization for heart failure was significantly increased in the saxagliptin arm by 27% (HR 1.27, 95% CI 1.07–1.51, *P* < 0.007). The risk for primary and secondary endpoints among patients who received saxagliptin was comparable to that among patients without a history of heart failure (primary endpoint HR in the saxagliptin group 1.13, 95% CI 0.89–1.43, vs. 0.97, 95% CI 0.85–1.10, in the comparison group; secondary endpoint HR in the saxagliptin group 1.06, 95% CI 0.89–1.27, vs. 1.01, 95% CI 0.91–1.11, in the comparison group). The rate of acute and chronic pancreatitis was similar in the saxagliptin and placebo groups: 0.3 vs. 0.2% for acute pancreatitis and < 0.1 vs. 0.1% for chronic pancreatitis.

The absolute risk for hospitalization for heart failure was highest among patients with a history of heart failure. However, the relative risk among patients assigned to saxagliptin was similar regardless of baseline history of heart failure (HR 1.21, 95% CI 0.93–1.58, vs. 1.32, 95% CI 1.04–1.65). In summary, the DPP-4 inhibitor saxagliptin did not reduce CV events in diabetes

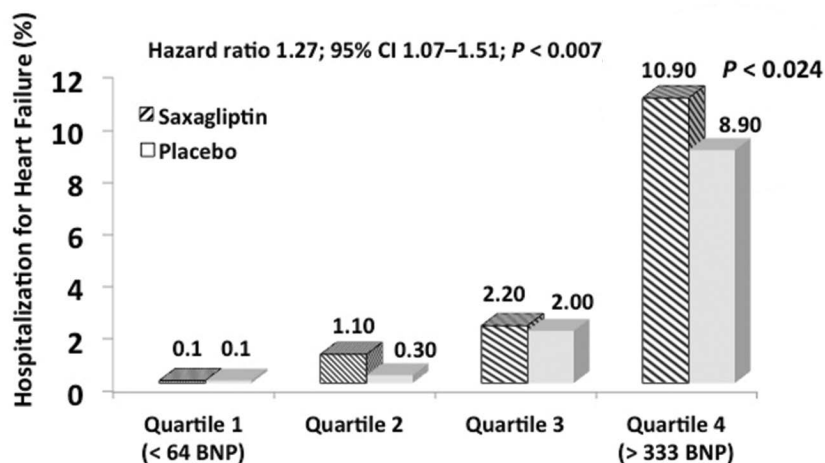
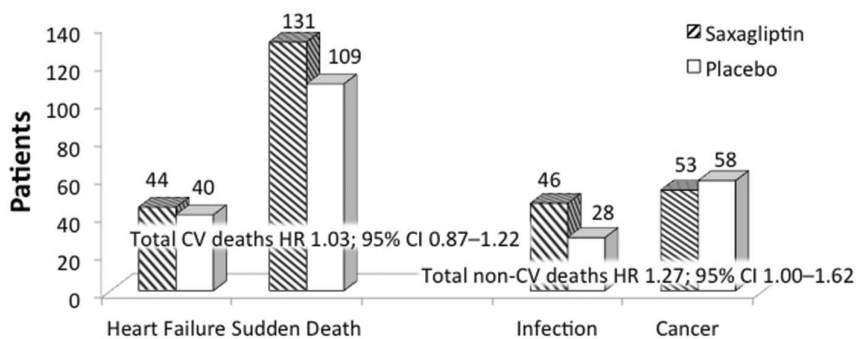


Figure 4. The possible off-target effect of increased heart failure hospitalizations from saxagliptin in the SAVOR trial. Higher N-terminal pro-B-type natriuretic peptide levels predicted increased risk for heart failure hospitalizations. The highest levels significantly increased this risk, but did not increase mortality. Most of the patients had a history of heart failure. Adapted from References 9 and 11.



	Saxagliptin	Placebo	HR
Total deaths (2-year Kaplan-Meier estimate [%])	420 (4.9)	378 (4.2)	1.11; 95% CI 0.96–1.27

Figure 5. Patient deaths in the SAVOR trial. There was no increase in total deaths or deaths from heart failure. More patients suffered sudden cardiac death than death from heart failure. The reassuring finding of no difference in cancer deaths was supportive of safety with regard to malignancy. Adapted from Ref. 9.

patients. The apparent off-target effect of increased risk for hospitalization for heart failure (best predicted by history of heart failure) will remain a question for future trials to answer in patients with stable CV disease and diabetes (Figures 4 and 5).

The EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) trial¹⁰ was a double-blinded noninferiority trial comparing placebo to

alogliptin and evaluating the impact of treatment on major CV events in patients with type 2 diabetes and acute coronary syndrome within 15–90 days before randomization. Demographic data are shown in Table 2. The primary CV endpoint was a composite of death from CV causes, nonfatal MI, and nonfatal stroke. A total of 5,380 patients underwent randomization with a follow-up of up to 40 months (median 18 months).

The primary endpoint occurred in 305 patients (11.3%) assigned to alogliptin and in 316 patients (11.8%) assigned to placebo (HR 0.96, upper boundary of the one-sided repeated confidence interval 1.16, $P < 0.001$ for noninferiority, $P = 0.32$ for superiority) at 36 months of follow-up. Table 3 shows the components of the primary endpoint and additional exploratory adjudicated components. The EXAMINE trial did not find significantly increased hospitalizations for heart failure. However, there were more patient hospitalizations for heart failure in the alogliptin arm than in the placebo arm. The principal secondary endpoints of death from CV causes, nonfatal MI, nonfatal stroke, and urgent revascularization because of unstable angina were not significant between placebo and alogliptin (13.4% [$n = 359$] vs. 12.7% [$n = 344$], $P < 0.26$). Hospitalization for heart failure in the alogliptin treatment arm was 106 of 2,701 events compared to 89 of 2,679 events in the placebo arm (odds ratio 1.19, 95% CI 0.89–1.58).

Figure 6 provides a comparison of the rates of hospitalization for heart failure between the SAVOR and EXAMINE trials. However, comparing these two trials in terms of heart failure may be misleading. The first concern is whether the patients in these studies had preserved left-ventricular function (low or high ejection fractions). Many patients with type 2 diabetes have preserved left-ventricular function but diastolic dysfunction. Other patients have ischemic heart disease with reduced left-ventricular function or a combination of both conditions. Understanding of heart failure in these two studies remains obscure; more data are required to fully understand the relationship between DPP-4 inhibitor therapy and heart failure.

Conclusion

Both of the SAVOR⁹ and EXAMINE¹⁰ trials failed to find CV event reduction in patients with diabetes using DPP-4 inhibitor therapy. Moreover, there was a

significant increase in hospitalizations for heart failure with saxagliptin, but not with alogliptin. The reason for increased heart failure admissions with saxagliptin remains unclear, and it is possible this finding could be by

play of chance rather than the result of other unknown off-target effects. Resolution of this issue awaits future studies to determine whether this is a problem with the DPP-4 inhibitor class, the characteristics of the specific drug within the class, or play of chance.

Pending large trials such as TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) and CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes)^{12,13} will help to answer some questions related to the possible link between hospitalization for heart failure and DPP-4 inhibitor therapy. Unfortunately, these trials have not included heart failure as a primary or principal secondary endpoint (Table 4).

Potential beneficial pleiotropic effects of DPP-4 inhibitors on the CV system are outlined in Figure 7. Translational consideration findings have ranged from improvement in cardiac function to increased circulating blood volume caused by neuropeptide Y-mediated vasoconstriction of the microcirculation.¹⁴ The optimal management of patients with diabetes who remain at risk for heart failure in addition to a plethora of other CV problems deserves due attention. Additional research will be

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Table 3. Components of the Primary Endpoint and Additional Exploratory Adjudicated Components in the EXAMINE Trial

	Alogliptin	Placebo	HR
Primary endpoint: death from CV causes, non-fatal MI, and nonfatal stroke (%)	11.3	11.8	NS
CV death (%)	3.3	4.1	NS
Non-fatal MI (%)	6.39	6.5	NS
Non-fatal stroke (%)	1.1	1.2	NS
Exploratory adjudicated components:			
All-cause death (%)	3.9	4.9	NS
Heart failure hospitalization [% (n)]	3.1 (106)	2.9 (89)	NS
History of heart failure (%)	18.1	22.3	NS

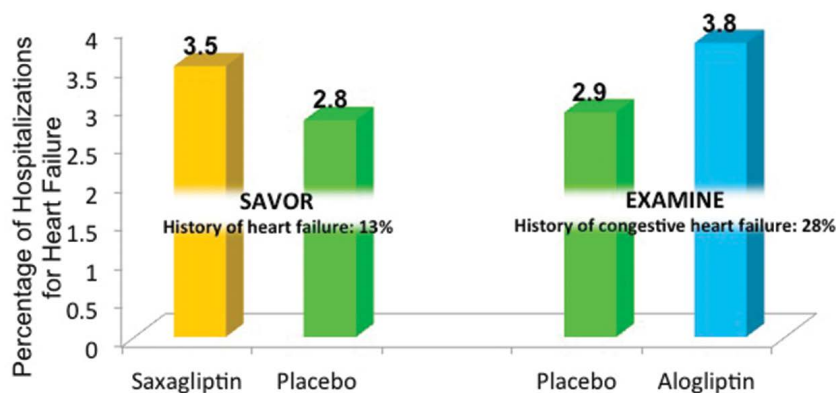


Figure 6. Comparison of rates of hospitalization for heart failure in the SAVOR⁹ and EXAMINE¹⁰ trials.

Table 4. Ongoing, Prospective Clinical Trials of DPP-4 Inhibitors With CV Outcomes

DPP-4 Inhibitor	Trial	Design	Patient Characteristics	Primary Endpoint
Linagliptin	CAROLINA	<ul style="list-style-type: none"> n = 6,000 5 mg glimepiride vs. 1–4 mg linagliptin Noninferiority and superiority trial 	A1C 6.5–8.5%, high CV risk	Time to first occurrence of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or CV death
Sitagliptin	TECOS	<ul style="list-style-type: none"> n = 14,000 50 or 100 mg sitagliptin vs. placebo Noninferiority trial 	A1C 6.5–8.0%, history of cardiovascular disease	Time to first confirmed CV event (nonfatal MI, nonfatal stroke, or hospitalization for unstable angina)

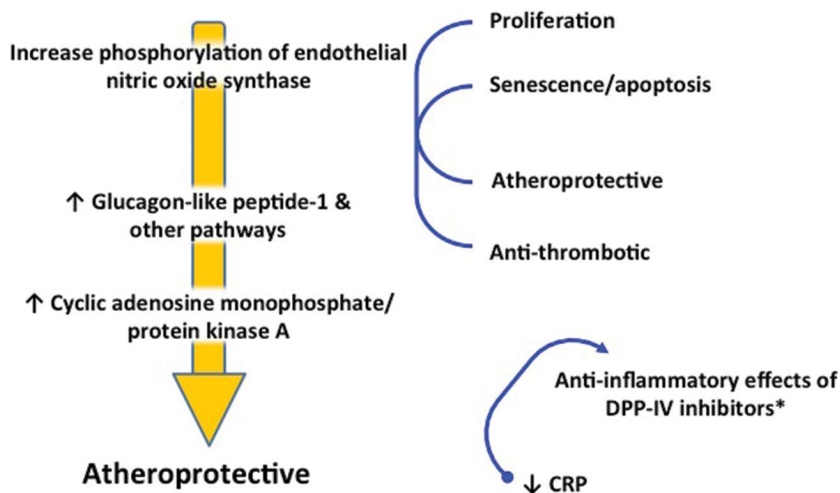


Figure 7. Potential beneficial cellular pleotropic effects of DPP-4 inhibitors. Antithrombotic, anti-inflammatory, and atheroprotective effects are key players in the CV arena. *Makdissi A, Ghanim H, Vora M, Green K, Abuaysheh S, Chaudhuri A, Dhindsa S, Dandona P: Sitagliptin exerts an antiinflammatory action. *J Clin Endocrinol Metab* 97:3333–3341, 2012.

required to clarify the role of novel agents such as DPP-4 inhibitors.

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