The Impact of Diabetes on HF

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Type 2 diabetes mellitus (T2DM) has been described as a possible risk factor for heart failure (HF), according to Heiko Bugger, MD, Freiburg University Heart Center, Freiburg, Germany. Several different pathways may contribute to the increased risk for HF in patients with T2DM, including the increased prevalence of coronary artery disease or other risk factors for HF, because traditional risk factors for HF are more prevalent in patients with T2DM. In addition, animal models of T2DM have demonstrated the existence of a diabetic cardiomyopathy that has similar pathologic findings as seen in human diabetic hearts.

The prevalence of T2DM in patients with HF is 15% to 25%, and the United Kingdom Prospective Diabetes Study showed a 16% decrease in HF with each 1% reduction in glycated hemoglobin [Stratton IM et al. *BMJ* 2000]. In a large retrospective cohort analysis, the incidence of HF was 30.9 versus 12.4 cases per 1000 person-years in patients with diabetes compared with those without [Nichols GA et al. *Diabetes Care* 2004]. Risk factors for HF identified in this study are shown in Table 1.

Table 1. Risk Factors for Heart Failure in Type 2 Diabetes Mellitus

Risk Factor	HR	95% CI	p
Age at baseline (per 5 years)	1.40	1.35–1.45	0.001
Ischemic heart disease[a]	2.36	2.06–2.69	0.001
BMI (per 2.5 kg/m^2)	1.12	1.09–1.15	0.001
Mean HbA_{1c} (per percentage point)	1.32	1.23–1.41	0.001
Duration of diabetes (per year)	1.05	1.03–1.07	0.001
Microalbuminuria[a]	0.78	0.65–0.93	0.006
Gross proteinuria[a]	1.25	1.08–1.46	0.004
ESRD[a]	1.54	1.04–2.30	0.032
Mean diastolic blood pressure (per 5 mm Hg)	1.10	1.04–1.16	0.001
Use of insulin[a]	1.25	1.06–1.48	0.007
Use of sulfonylurea[a]	0.99	0.85–1.17	0.892
Use of metformin[a]	1.02	0.86–1.22	0.849
Female sex[a]	0.97	0.85–1.10	0.656

BMI=body mass index; ESRD=end-stage renal disease; HbA_{1c}=glycated hemoglobin.

[a]Dichotomous variables, where hazard ratio represents risk if the variable is present.

THE EFFECT OF HEART FAILURE DRUGS IN DIABETES

The effect of HF drugs in patients with diabetes differs from the effect in patients with HF who do not have diabetes, said Adriaan A. Voors, MD, University Medical Center Groningen, Groningen, the Netherlands, who reviewed the evidence. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may prevent new-onset T2DM, according to data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial, with valsartan showing a 14% relative risk reduction [McMurray JJ et al. *N Engl J Med* 2010].

Mineralocorticoid receptor antagonists may be more efficacious in patients with HF and T2DM. A greater absolute risk reduction in HF hospitalization and cardiovascular (CV) death was found in patients with systolic HF and T2DM compared with the overall group (13.7% vs 7.6%) in an analysis of data from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure with eplerenone [Eschalier R et al. *J Am Coll Cardiol* 2013]. Prof. Voors stated that the use of mineralocorticoid receptor antagonists should be considered in patients with systolic HF and T2DM.

Ivabradine, compared with atenolol and amlodipine, did not have a deleterious effect on glycated hemoglobin or induce a change in fasting glucose in a retrospective analysis of patients with chronic stable angina and T2DM [Borer JS, Tardif JC. *Am J Cardiol* 2010]. In the Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial, the effect of ivabradine was the same in patients with and without T2DM in a subgroup analysis [Swedberg K et al. *Lancet* 2010].

The use of β-blockers in patients with diabetes has shown mixed results with regard to efficacy. In the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure, nebivolol had no effect on the primary end point of mortality or CV hospital admission in patients with diabetes. A subgroup analysis of this trial suggested that β-blockers may be less beneficial in patients with T2DM and HF [Flather MD et al. *Eur Heart J* 2005]. The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure also showed that a β-blocker, metoprolol, was not effective in T2DM [Deedwania PC et al. *Am Heart J* 2005]. Prof. Voors noted that these data should be interpreted with caution. Beta-blockers have been shown to be effective in patients with HF, and until a prospective trial specifically in patients with diabetes suggests otherwise, the use of β-blockers in patients with diabetes continues to be warranted.

Aliskiren is probably not safe in patients with HF and T2DM, as shown by a subgroup analysis of the Aliskiren Trial on Acute Heart Failure Outcomes, with an increased risk for all-cause death (HR, 1.64 for patients with vs 0.69 for patients without diabetes; p<0.01) [Maggioni AP et al. *Eur Heart J* 2013].

ANTIDIABETIC DRUGS IN HEART FAILURE

Insulin may increase the risk for death in patients with HF, based on some circumstantial evidence, said Prof. Voors. A single-center study of 54 patients with advanced HF

showed that survival was worse for patients with T2DM treated with insulin compared with those not treated with insulin or those without T2DM [Smooke S et al. *Am Heart J* 2005]. A multivariate analysis of the Candesartan in Heart Failure: Assessment of Mortality and Morbidity trial, a large scale, randomized controlled study that evaluated the effects of candesartan in patients with HF, found that insulin-treated T2DM was a risk factor for CV death or HF hospitalization. Furthermore, the relative effect of insulin-treated T2DM on the incidence of CV death or HF hospitalization was greater than that of age or left ventricular ejection fraction (Table 2) [Pocock SJ et al. *Eur Heart J* 2006].

Table 2. Multivariate Analysis of Effect of Insulin on Risk for Primary Outcomes

Variable	HR	95% CI	χ^2 Value
Age (per 10 years)	1.46	1.38–1.54	182
Diabetes: insulin treated	2.03	1.80–2.29	135
Diabetes: other	1.58	1.43–1.74	85
LVEF (per 5%)	1.13	1.11–1.16	120

LVEF=left ventricular ejection fraction.

Thiazolidinediones (TZD) are contraindicated in patients with DM and HF. The US Food and Drug Administration (FDA) issued a warning that TZD cause or exacerbate congestive HF, based on data from the Prospective Pioglitazone Clinical Trial in Macrovascular Events, which showed an increased risk compared with placebo [Erdmann E et al. *Diabetes Care* 2007]. The European Medicines Agency issued a similar warning in 2010. A meta-analysis of rosiglitazone and pioglitazone in patients with prediabetes or T2DM showed that TZD use was associated with an increased risk for developing HF (HR, 1.72; 95% CI, 1.21–2.42) [Lago RM et al. *Lancet* 2007]. The mechanism of HF incidence or exacerbation is thought to be excessive fluid retention.

Sulfonylureas also were associated with increased risk for developing HF, compared with metformin, in patients with T2DM [McAlister FA et al. *Eur J Heart Fail* 2008]. Another analysis found that the long-term mortality risk with different types of sulfonylureas was similar [Andersson C et al. *Diabetes Res Clin Pract* 2011].

Metformin was the only antidiabetic drug not associated with harm for patients with HF and T2DM in a meta-analysis, and it was associated with reduced all-cause mortality in 2 of the 3 studies [Eurich DT et al. *BMJ* 2007]. A larger meta-analysis confirmed these findings [Eurich DT et al. *Circ Heart Fail* 2013]. However, it should be noted that there is a black-box warning from the FDA on the use of metformin in patients with HF because of the possibility of an increase in the risk for lactic acidosis.

The glucagon-like peptide-1 agonists may be beneficial, but data are limited. Dipeptidyl peptidase-4 (DPP-4) inhibitors increase the risk for new-onset HF for patients with T2DM and high CV risk, said Prof. Voors.

For instance, glucagon-like peptide-1 agonists showed beneficial effects on left ventricular ejection fraction, 6-minute walk distance, maximal oxygen uptake, and Minnesota Living With Heart Failure Questionnaire quality-of-life score [Sokos GG et al. *J Card Fail* 2006] but had a negligible effect on B-type natriuretic peptide levels [Munaf M et al. *Int J Pept* 2012]. However, although no large randomized clinical trials have been prospectively designed to determine the effect of glucagon-like peptide-1 agonists on HF, ongoing trials studying the CV safety and efficacy of various agents in the class will be informative.

Such an example has been seen to date with the DPP-4 inhibitors. The DPP-4 inhibitor alogliptin compared with placebo had no effect on the primary end point of CV death, nonfatal myocardial infarction, or nonfatal stroke in the Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome (HR, 0.96) [EXAMINE; White WB et al. *N Engl J Med* 2013]. HF was not an end point in EXAMINE, but 28% of patients had HF at baseline. Data from a nonprespecified analysis presented at the American College of Cardiology conference in March 2014 showed no statistically significant increase in the hospitalization for HF in EXAMINE, although there was a numerical excess among patients treated with alogliptin (3.9% vs 3.3%; HR, 1.19; 95% CI, 0.90–1.58) [Zanand F et al. *J Am Coll Cardiol* 2014], said Charalambos Vlachopoulos, MD, Hippokration Hospital, Athens, Greece.

In contrast, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 study [SAVOR-TIMI 53], HF hospitalization, which was a component of a composite secondary CV end pointend point in the trial, was significantly increased with saxagliptin compared with placebo (HR, 1.27; 95% CI, 1.07–1.51) [Scirica BM et al. *N Engl J Med* 2013]. In February 2014, the FDA issued a safety notice that requested clinical trial data on saxagliptin from the manufacturer, stating that the published data are considered preliminary until the FDA review is completed. Finally, a meta-analysis of 84 trials of DPP-4 inhibitors with a total exposure of 90,731 patient-years showed an increased risk of 19% for developing HF (p=0.015) [Monami M et al. *Nutr Metab Cardiovasc Dis* 2014], though the majority of HF events recorded in this review were contributed from the SAVOR-TIMI 53 trial. Ongoing DPP-4 inhibitor trials will hopefully provide further refinement of the risk for HF associated with these medications and the potential mechanism of action, which to date is unknown.