Heart failure: an underestimated therapeutic target in diabetes

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Heart failure (HF) is a frequent finding in patients with diabetes and is associated with an impaired prognosis with respect to the need for hospitalization as well as mortality. The following article presents an overview of the incidence and prognosis of HF in patients with type 2 diabetes and discusses the effects of various antidiabetic drugs on HF. *Cardiovasc Endocrinol Metab* 7:10–12 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Various epidemiological and clinical data published over the last few years have led to the recognition that heart failure (HF), in addition to myocardial infarction, stroke, and other atherosclerosis-associated events, is an important contributor to cardiovascular (CV) morbidity and mortality in patients with diabetes. The term diabetic cardiomyopathy stems from Rubler *et al.* [1], describing already in 1972 the presence of myocardial dysfunction in patients with diabetes in the absence of coronary heart disease, hypertrophy, or valve disease. Since then, there has been considerable controversy on whether diabetic cardiomyopathy is a separate entity in heart disease [2], reflecting the fact that little is known about the pathophysiology and the underlying molecular mechanisms leading to cardiac changes in diabetes. Various studies showed that diabetes is associated with an increased risk for incident HGF ranging from an incidence rate of 10–12% over 3 years depending on the population examined [3,4]. Still, none of these studies distinguished between HF with reduced ejection fraction (HFREF) or HF with preserved ejection fraction (HFPEF). As about 50% of all patients hospitalized for HF in an emergency setting show a preserved ejection fraction, this has been a major limitation in this context. In contrast, in HF patients, there is a high prevalence of prediabetes or diabetes, with a suggested prevalence between 25 and 40% in various studies [5].

Prognosis of patients with diabetes and established heart failure

Mortality and hospitalization for heart failure are clinically meaningful endpoints with respect to the prognosis of patients with HF and as such used in clinical and epidemiological studies. Patients with diabetes have a significantly higher risk for these endpoints compared with nondiabetic HF patients. As such, various population-based studies show an increase in mortality in diabetic patients

with HF. The Danish Investigations of Arrhythmia and Mortality on Dofetilide study examined in 5499 patients hospitalized because of congestive HF the mortality rate depending on the presence of diabetes. This study could show that 31% of all patients with HF and diabetes died within 1 and 50% after 3 years, suggesting a markedly increased mortality in patients with diabetes and HF [6]. Additional data on the prognosis of diabetes and established HF came from the large HF trials SAFE, VALIANT, and CHARM. All of these studies confirmed an increased mortality risk in patients with diabetes. For example, data from the CHARM trial suggest that 40% of all patients with diabetes reached the CV endpoint of CV death or rehospitalization for HF within 3 years. Among these patients, patients with reduced left-ventricular ejection fraction (LVEF) showed the highest risk, followed by patients with diabetes and preserved ejection fraction. The risk of non-diabetic patients both with preserved as well as reduced ejection fraction were significantly lower compared with diabetic patients. A similar trend has been shown for the overall mortality [7]. These data underscore that patients with diabetes and HF have a worse prognosis and that the risk for hospitalization of HF or CV death ranges from 12 to 15% within 1 year.

Therapy of heart failure in patients with diabetes

Current guidelines, neither from the European [8] nor from the American cardiology societies, elude on specific therapeutic approaches in HF patients with diabetes compared with patients without diabetes.

Treatment of patients with diabetes and heart failure with reduced ejection fraction

In patients with symptomatic New York Heart Association class II–IV HF and reduced ejection fraction (LVEF < 40%), treatment with angiotensin-converting

enzyme (ACE) inhibitors [alternative: angiotensin receptor blockers (ARBs)] and β -blockers is recommended, with titration to the maximum tolerated evidence-based dose (class IA recommendation) [8]. If patients are still symptomatic and have an LVEF of up to 35%, the addition of mineralocorticoid receptor antagonists is recommended. If still symptomatic, various therapeutic options exist for patients with New York Heart Association II–IV HF. In patients who are able to tolerate ACE inhibitors or ARBs, angiotensin receptor neprilysin inhibitors should be used to replace ACE inhibitors or ARBs. In patients with sinus rhythm and a QRS duration of at least 130 ms, implantation of a cardiac resynchronization therapy device is recommended. Finally, patients with sinus rhythm and a heart rate of at least 70 bpm should receive ivabradine; patients with symptoms and signs of congestion should receive diuretics. Moreover, patients with an LVEF of up to 35% despite optimal medical therapy or a history of symptomatic ventricular tachycardia or ventricular fibrillation should receive an implantable cardioverter defibrillator.

Treatment of patients with diabetes and heart failure with preserved ejection fraction

At present, treatment for HFPEF has not been shown to reduce mortality or morbidity; therefore, the guidelines recommend treatment of any comorbidities (e.g. hypertension, chronic kidney disease, chronic obstructive pulmonary disease) [8]. In addition, symptomatic therapy usually includes diuretics, especially in patients with congestion. The effect of various agents, including empagliflozin, on CV morbidity and mortality in patients with HFPEF will be determined by future trials in HF; however, thus far, symptom control is the major therapeutic goal.

Effects of antidiabetic drugs on heart failure endpoints in diabetes

Despite the alarming prognostic data lined out above, neither clinicians nor physician-scientists had paid attention to the problem of HF in diabetes. Only recent cardiovascular outcome trials on patients with type 2 diabetic patients treated with novel antidiabetic drugs have led to the recognition that HF in diabetes is an underestimated problem that deserves further investigation and development of diagnostic and therapeutic strategies. Early cardiovascular outcome trials with thiazolidinediones (such as pioglitazone or rosiglitazone) showed an increased risk of treated patients for heart failure hospitalization in trials such as PROactive [9] or RECORD [10]. Recently, data from the SAVOR-TIMI 53 trial surprisingly showed that treatment with saxagliptin compared with placebo leads to an unexpected increase in HF hospitalization [11], whereas no such an effect was observed with other DPP4-inhibitors [12]. Finally, the results of the EMPA-REG outcome trial surprisingly showed a significant reduction in CV endpoints along with a reduction in CV death and hospitalization for HF. In this study, examining the effect of empagliflozin on

CV endpoints compared with placebo in patients with type 2 diabetes and prevalent CV disease, empagliflozin led to a significant reduction of the primary endpoint of CV death, nonfatal myocardial infarction, and nonfatal stroke as well as a significant reduction in overall mortality. As a secondary endpoint, empagliflozin led to a significant 35% reduction of hospitalization for HF independent of the presence of HF at baseline [13]. These data on HF hospitalization have been confirmed recently in the CANVAS trial program with a reduction of HF hospitalization by the SGLT2-inhibitor canagliflozin [14]. These data shifted our attention away from the classical atherosclerotic endpoints myocardial infarction and stroke toward the clinically similar meaningful endpoints of hospitalization for HF and HF death. The implementation of platelet-inhibition, ACE inhibitors, and statins in patients with diabetes has led to a marked reduction in coronary endpoints such as myocardial infarction and hospitalization for unstable angina over the last decades, but we have been less successful in the improvement of HF endpoints in patients with diabetes. This is in particular true for patients with diabetes and HF with preserved ejection fraction in which, as of yet, we have options only to control symptoms.

A call for action

The lack of clear diagnostic of therapeutic strategies in HF patients with diabetes should be a call for action to better phenotype these patients to improve the taxonomy of HF and diabetes. We have to use big data approaches, bioinformatics, and/or cluster analysis to better understand the different phenotypes of HF patients with diabetes to gain a better understanding of the pathophysiology of HFREF and HFPEF in these patients. Such data could provide us with further mechanistic insights and as such pave the way for the development of individualized and tailored therapies for this high-risk population.

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Conflicts of interest

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