CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Diabetes Mellitus and Heart Failure

Michael Lehrke, MD, Nikolaus Marx, MD

Department of Internal Medicine I, University Hospital Aachen, Germany.

ABSTRACT

Epidemiologic and clinical data from the last 2 decades have shown that the prevalence of heart failure in diabetes is very high, and the prognosis for patients with heart failure is worse in those with diabetes than in those without diabetes. Experimental data suggest that various mechanisms contribute to the impairment in systolic and diastolic function in patients with diabetes, and there is an increased recognition that these patients develop heart failure independent of the presence of coronary artery disease or its associated risk factors. In addition, current clinical data demonstrated that treatment with the sodium glucose cotransporter 2 inhibitor empagliflozin reduced hospitalization for heart failure in patients with type 2 diabetes mellitus and high cardiovascular risk. This review article summarizes recent data on the prevalence, prognosis, pathophysiology, and therapeutic strategies to treat patients with diabetes and heart failure.

 • The American Journal of Medicine (2017) 130, S40-S50

KEYWORDS: Cardiac function; Ejection fraction; Heart failure; Sodium glucose cotransporter 2; Type 2 diabetes mellitus

Epidemiologic and clinical data from the last 2 decades have led to the recognition that, in addition to myocardial infarction and other atherosclerosis-related cardiovascular events, heart failure is a major contributor to cardiovascular morbidity and mortality in patients with diabetes. In certain patients with diabetes, the observation that myocardial dysfunction is present in the absence of coronary artery disease, valvular disease, and the sequelae of associated cardiovascular risk factors[1] has led to the use of the poorly understood term "diabetic cardiomyopathy." This term was first used in 1972 by Rubler et al,[2] describing myocardial dysfunction in patients with diabetes in the absence of coronary artery disease, hypertrophy, or valvular heart disease. There is ongoing discussion whether diabetic cardiomyopathy exists as a specific entity or not, as considered by Ernande and Derumeaux in their review from 2012, "Diabetic cardiomyopathy: myth or reality?"[3]

This ongoing discussion reflects the fact that little is known about the pathophysiology and the underlying molecular mechanisms of heart failure in patients with diabetes. Only recently have clinical and epidemiologic data demonstrated the incidence, prevalence, and prognosis of heart failure in patients with diabetes. To date, heart failure has been described as *heart failure with preserved ejection fraction* (HFpEF) or *heart failure with reduced ejection fraction* (HFrEF), according to left ventricular function. To dichotomize heart failure into these 2 entities has certain

Funding: This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. The authors received no direct compensation related to the development of the manuscript. Manuscript editorial support was provided by Marissa Buttaro, MPH, RPh, of Envision Scientific Solutions, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc.

Conflict of Interest: ML has received speaker fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Novo Nordisk, Roche, Sanofi-Aventis, and Servier; is an advisory board member for Amgen, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, and Roche; and has received research support from Boehringer Ingelheim. NM has received speaker fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Novartis, Novo Nordisk, Roche, and Sanofi-Aventis; is a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Genfit, Merck Sharp & Dohme, Novo Nordisk, and Sanofi-Aventis; has received research support from Boehringer Ingelheim; and is an investigator for clinical trials sponsored by Boehringer Ingelheim and Sanofi-Aventis.

Authorship: The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version that reflects the authors' interpretation and conclusions. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Requests for reprints should be addressed to Nikolaus Marx, MD, Department of Internal Medicine I, University Hospital Aachen, Pauwelsstraße 30, D-52074 Aachen, Germany.

E-mail address: nmarx@ukaachen.de

http://dx.doi.org/10.1016/j.amjmed.2017.04.010

limitations and probably does not cover an intermediate stage that the most recent guidelines of the European Society of Cardiology (ESC) termed *heart failure with a mid-range ejection fraction* (HFmrEF; ejection fraction 40%-49%).[4] This extended definition is a first step to better phenotyping and an improved taxonomy of heart failure. Nevertheless, clinical and epidemiologic data, as well as experimental data, have only focused on HFrEF and HFpEF. Therefore, we have used these 2 entities as the basis for the overview provided in this article.

INCIDENCE AND PREVALENCE OF HEART FAILURE IN DIABETES

Various epidemiologic data have shown that prediabetes is associated with a high risk of heart failure and suggest an age-adjusted hazard ratio (HR) between 1.2 and 1.7 in different populations of patients with impaired fasting glucose,[5,6] although not confirmed in all studies.[7] A large community-based cohort study of 6814 subjects without coronary vascular disease at baseline was followed for 4 years, and the incidence of heart failure, depending on the presence of metabolic syndrome, was analyzed.[8] This study showed that features of metabolic syndrome are associated with an increased risk of heart failure, with two-thirds of patients developing HFrEF. The risk of developing heart failure in subjects with "prediabetes" is lower than in subjects with manifest diabetes.[6]

A retrospective cohort study analyzed data from the Kaiser Permanente Northwest database of 8231 patients with diabetes, none of whom had HF at baseline, and 8845 matched subjects without diabetes; the follow-up period was up to 6 years.[9] Incident heart failure was 30.9 per 1000 person-years in subjects with diabetes and 12.4 per 1000 person-years in subjects without diabetes.[9] Similar results were found in the Heart and Soul study, which showed a doubling of the risk of incident heart failure in patients with diabetes compared with subjects without diabetes in a population of 839 patients with stable coronary artery disease and no signs of heart failure at baseline.[10] However, neither study differentiated between HFrEF and HFpEF.

Prevalence of prediabetes and diabetes is high among patients with heart failure and proves as a relevant predictor of prognosis. Data from Matsue et al[11] suggest that more than one-third of patients who are hospitalized for heart failure without a diagnosis of diabetes exhibit impaired fasting glucose or impaired glucose tolerance. As they discuss, more recent data from various registries show that the prevalence of diabetes in patients with heart failure ranges from approximately 25% to 40%, depending on the population studied.[11] Again, none of these studies differentiated between HFrEF and HFpEF.

PROGNOSIS OF PATIENTS WITH DIABETES AND ESTABLISHED HEART FAILURE

The most meaningful clinical endpoints for prognosis in patients with heart failure are mortality and hospitalization for heart failure. The risk for these endpoints is markedly increased in subjects with diabetes compared with those without diabetes. The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) study assessed the influence of diabetes on the risk of death in 5491 patients hospitalized with congestive heart failure when followed up for 5 to 8 years.[12] In this study population 16% of patients had diabetes at baseline, and approximately 50% had an ejection fraction <35%, suggesting that both HFrEF and HFpEF were present in this subpopulation.[12] Crude mortality analyses suggested a 1-year mortality of 31%, much higher than in subjects without diabetes, and 50% of all heart failure patients with diabetes died after 3 years. Additional data on the prognosis of patients with diabetes and established heart failure came from large heart failure trials, such as the Survival And Ventricular Enlargement (SAVE) trial,[13,14] the Valsartan in Acute Myocardial Infarction Trial (VALIANT),[15] and the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) trial.[16] All of these trials showed an increased risk of death in men and women with diabetes. For example, in CHARM, which analyzed the effect of candesartan versus placebo in a population with HFrEF and HFpEF, it was shown that both men and women with diabetes exhibited a higher risk of cardiovascular death or hospitalization for heart failure compared with subjects without diabetes, with a cumulative incidence rate of approximately 40% over 3 years.[16] Further differentiated analyses in patients with or without diabetes and HFpEF or HFrEF showed that the highest mortality or hospitalization for heart failure risk occurred in patients with diabetes and low ejection fraction (ie, HFrEF), followed by patients with diabetes and HFpEF.[16] The cumulative incidence rate of cardiovascular death and heart failure hospitalization in subjects with diabetes plus HFpEF was similar to that in subjects without diabetes but with HFrEF. A similar trend was true for all-cause mortality. In patients with diabetes, cardiovascular mortality was 58.6 per 1000 patient-years in those with HFpEF and 119.1 per 1000 patient-years in those with a low ejection fraction (ie, HFrEF). Similarly, in patients with diabetes, the risk for first hospital admission for heart failure was 116.6 per 1000 patient-years for those with HFpEF, whereas the rate was 155.4 per 1000 patient-years for those with HFrEF.[16] Compared with subjects without diabetes, the risk of hospitalization for heart failure was almost doubled in patients with diabetes independent of HFpEF or HFrEF.[16] Consequently, among patients with HF, those with diabetes have a higher risk of mortality and hospitalization for HF than those without diabetes.

STRUCTURAL AND FUNCTIONAL CHARACTERISTICS OF CARDIAC DYSFUNCTION IN DIABETES

Structural Changes

Imaging studies have revealed left ventricular concentric remodeling as a relevant characteristic of diabetic