JACC: HEART FAILURE
VOL. 3, NO. 2, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2014.08.004

STATE-OF-THE-ART PAPER

Impact of Diabetes on Epidemiology, Treatment, and Outcomes of Patients With Heart Failure

Alessandra Dei Cas, MD, PhD,* Sadiya S. Khan, MD,† Javed Butler, MD, MPH,‡ Robert J. Mentz, MD,§ Robert O. Bonow, MD, MS,‖ Angelo Avogaro, MD, PhD,¶ Diethelm Tschoepe, MD,# Wolfram Doehner, MD, PhD,** Stephen J. Greene, MD,‖ Michele Senni, MD,†† Mihai Gheorghiade, MD,‖ Gregg C. Fonarow, MD‡‡

ABSTRACT

The prevalence of patients with concomitant heart failure (HF) and diabetes mellitus (DM) continues to increase with the general aging of the population. In patients with chronic HF, prevalence of DM is 24% compared with 40% in those hospitalized with worsening HF. Patients with concomitant HF and DM have diverse pathophysiologic, metabolic, and neurohormonal abnormalities that potentially contribute to worse outcomes than those without comorbid DM. In addition, although stable HF outpatients with DM show responses that are similar to those of patients without DM undergoing evidence-based therapies, it is unclear whether hospitalized HF patients with DM will respond similarly to novel investigational therapies. These data support the need to re-evaluate the epidemiology, pathophysiology, and therapy of HF patients with concomitant DM. This paper discusses the role of DM in HF patients and underscores the potential need for the development of targeted therapies. (J Am Coll Cardiol HF 2015;3:136–45) © 2015 by the American College of Cardiology Foundation.

Heart failure (HF) is a clinical manifestation of diverse cardiac and noncardiac abnormalities and represents a heterogeneous group of patients ranging from stable outpatients with chronic HF to those with worsening symptoms requiring hospitalization for HF. In hospitalized patients with HF, post-discharge readmission and mortality rates approach 15% and 30%, respectively, at 60 to 90 days, but no specific therapy has been shown definitively to improve post-discharge readmission and mortality rates. Furthermore, HF with concomitant diabetes mellitus (DM) may have further increase risk through different pathophysiologic, hemodynamic, and neurohormonal abnormalities. This is especially critical as approximately 24% of HF patients overall and 40% of hospitalized HF

From the *Unit of Diabetes and Prevention of Associated Diseases, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy; †Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ‡Cardiology Division, Stony Brook University, Stony Brook, New York; §Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina; ‖Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ¶Department of Medicine, University of Padova, Padova, Italy; #Heart and Diabetes Center North Rhine Westfalia, University Clinic of the Ruhr University, Bochum, Germany; **Center for Stroke Research, Charite Universitätsmedizin, Berlin, Germany; ††Cardiovascular Department, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; and the ‡‡Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan-University of California Medical Center Los Angeles, Los Angeles, California. Dr. Butler is a consultant for Amgen, Bayer, Celladon, GE Healthcare, Medtronic, Takeda, and Trevena. Dr. Mentz has consulting relationships with Bristol-Myers Squibb, GlaxoSmithKline, and Novartis. Dr. Gheorghiade is a consultant for Bayer, Novartis, Takeda, Cardiocell, and Johnson & Johnson. Dr. Fonarow has consulting relationships with Novartis, Medtronic, Amgen, Bayer, Boston Scientific, Johnson & Johnson, and The Medicines Co.; and is a consultant for Agency for Healthcare Research and Quality and National Institutes of Health. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 25, 2014; revised manuscript received August 18, 2014, accepted August 22, 2014.

patients have DM, and these figures are expected to grow exponentially in the next decades with the growth of an aging population. HF patients with DM may represent a different pathophysiologic population than those without DM, which affects intracellular calcium release, myocardial lipid metabolism, and impaired endothelial cell function. Hospitalized HF patients with DM show an even worse prognosis with increased rates of cardiovascular (CV) mortality and HF hospitalization post-discharge (1).

Moreover, data for possible differential effects of drugs in HF patients with or without DM are emerging from the aliskiren drug study in the subgroup analysis of the ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) trial in patients admitted to the hospital with reduced ejection fraction (EF) (2) and from possible increased risk of HF for antidiabetic drugs, as in the SAVOR-TIMI (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus-Thrombolysis In Myocardial Infarction) trial for the dipeptidyl peptidase (DPP)-4 saxagliptin (3). Although these results should be interpreted with caution and viewed in the context of a subgroup analysis of a secondary endpoint with corresponding statistical limitations, the epidemiology, pathophysiology, prognosis, and management of HF patients with DM should be carefully evaluated in an effort to improve their prognosis and outcomes. This paper discusses the role of DM in HF patients and underscores the need for development of targeted therapies.

EPIDEMIOLOGY

HF is the primary cause of more than 1 million hospitalizations in the United States annually (4). Hospitalization for HF is associated with unacceptably high post-discharge mortality and re-hospitalization rates (5), with figures that have remained largely unchanged over the last 2 decades. CV mortality and readmission rates for clinically stable patients recently discharged following a HF hospitalization are approximately 25% at 6 months, and all-cause mortality exceeds 30% at 1 year. Hospitalized HF patients show heterogeneous clinical profiles in terms of HF cause and pathophysiology and both CV and non-CV comorbidities (6).

Approximately 40% of hospitalized HF patients with low EF have DM (1). Notably, DM in hospitalized patients is associated with worse prognosis (1), increased risk for combined CV mortality and HF-related hospitalization (7), and longer hospital stay (8), despite receiving care that is similar to that for patients without DM (1,9) although this paradigm is not a consistent finding (10), particularly in women (11).

In a pre-specified subgroup analysis of the ASTRONAUT study, patients hospitalized for HF with DM were older and had higher systolic blood pressure, more frequent ischemic HF etiology, renal impairment, and greater likelihood of receiving treatment with an angiotensin II receptor blocker (ARB) drug (2).

In patients with DM, the prevalence of HF is greater than that of the general population (12), and a 1% increase in glycosylated hemoglobin in DM patients is associated with an 8% increased risk of HF (13). Patients with HF show marked insulin resistance (14), which increases their risk of developing type 2 DM compared to that of normal individuals or patients with coronary artery disease. Similarly, insulin resistance in HF patients, even in the absence of overt DM, is an independent predictor of worse prognosis, suggesting a pathophysiologic involvement of insulin resistance in HF progression (14). Thus, the relationship between DM and HF is bidirectional, with each disease independently increasing the risk for the other.

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin II receptor blocker

ATP = adenosine triphosphate

CV = cardiovascular

DM = diabetes mellitus

EF = ejection fraction

FFA = free fatty acid

HF = heart failure

LV = left ventricular

RAAS = renin-angiotensin-aldosterone system

PATHOPHYSIOLOGY OF HF IN DIABETES

Insulin resistance and hyperglycemia are the central metabolic perturbations that accompany type 2 DM, driving several adaptive and maladaptive cellular responses that lead to specific changes in myocardial structure and function (diabetic cardiomyopathy) (**Figure 1**). Longstanding metabolic and functional alterations ultimately lead to irreversible structural changes. At this later stage, comorbidities seen commonly in patients with DM, such as hypertension, dyslipidemia, microvascular dysfunction, autonomic dysfunction, and renal impairment may accelerate the progression of cardiac dysfunction toward advanced disease (6).

METABOLIC ALTERATIONS. One consequence of insulin resistance is enhanced release of free fatty acid (FFA) and reduction in myocardial glucose transporter expression and glucose uptake. This change in substrate availability leads to an imbalance of glucose and FFA uptake and use in the heart. As these metabolic alterations become longstanding, high FFA levels activate myocyte expression of peroxisome proliferator-activated receptor-α that stimulates transcription of multiple genes responsible for an increase in mitochondrial FFA transport and oxidation (15). FFA β-oxidation is less favorable