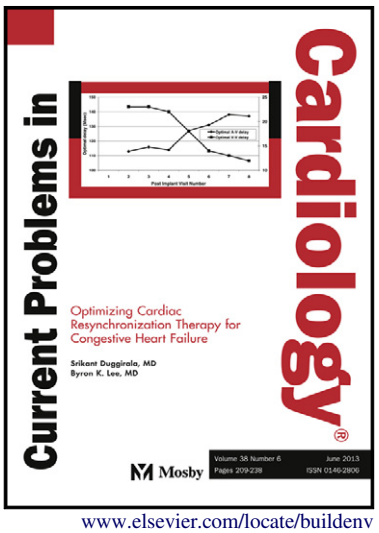

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Concomitant Diabetes Mellitus and Heart Failure

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Abstract

The prevalence of patients with concomitant diabetes mellitus and heart failure is growing exponentially. Patients with heart failure and diabetes mellitus show specific metabolic, neurohormonal and structural heart abnormalities, which potentially contribute to worse heart failure outcomes compared to those patients without comorbid diabetes mellitus. Sub-group analysis of recent trials suggest that patients with heart failure and diabetes mellitus may respond differently to standard therapy, and data are emerging on the possible increase in the risk of hospitalizations for heart failure in patients with diabetes mellitus treated with specific class of anti-diabetic agents, pointing to the need of developing specific medications to be tested in dedicated future studies in order to address the unique metabolic and hemodynamic alterations seen in these patients.

Keywords: diabetes mellitus, heart failure, diabetic cardiomyopathy, therapy

Abbreviations:

ACE= Angiotensin converting enzyme inhibitor

ARB=AT1- receptor blocker

CAD= coronary artery disease

CV=cardiovascular

DM= diabetes mellitus

EF= ejection fraction

FFA=free fatty acid

HF=heart failure

LV=left ventricular

RAAS=renin-angiotensin-aldosterone system

1.INTRODUCTION

The prevalence of patients with concomitant heart failure (HF) and diabetes mellitus (DM) is growing exponentially with the aging of the general population. Approximately 40% of patients hospitalized with HF and reduced ejection fraction (EF) have DM [1] with an important epidemiologic, clinical, and economic impact. Patients with HF and DM show specific metabolic, neurohormonal and structural heart abnormalities which potentially contribute to worse outcomes compared to those without comorbid DM [2,3].

Notably, sub-group analyses of recent trials conducted in hospitalized HF patients with DM showed a different response to standard medication being more prone to develop side effects compared to patients with the same degree of HF but without DM [4] and a bidirectional effect of therapy in patients with or without DM [5]. Conversely, data are emerging on the possible increase in the risk of hospitalizations for HF in patients with DM treated with specific class of antidiabetic agents [6,7]. These data, though cautiously interpreted in the context of post-hoc analyses, suggest the need to identify or develop a targeted therapy to be tested in dedicated future studies, particularly in patients hospitalized for acute HF with concomitant DM.

2. EPIDEMIOLOGY

The prevalence of patients with both HF and DM in the general population is estimated at 0.5% in men and 0.4% in women [8]. The public health burden of HF and DM is substantial: HF afflicts 1-2% of the general population rising to >5-10% in subjects aged >65 years [9], whereas the prevalence of DM worldwide is estimated at 5-6% [10] and it is predicted to increase to >8 % of the adult population by 2030 [11]. The prevalence of both diseases is increasing worldwide with the aging of the general population: 1.5 to 2% of individuals over the age of 65 have both HF and DM and the prevalence is expected to grow exponentially in the next decades [12]. In addition, these prevalence figures tend to underestimate the true impact as they do not adequately account for undiagnosed HF in patients with preserved ejection fraction (EF) or impaired fasting glucose [8,13].

Gary S. Francis, MD: There are now emerging data that heart failure with preserved ejection fraction (HFpEF) also presents with multiple phenotypes, including metabolic abnormalities and coronary microvascular inflammation [Paulus WJ, Tschö pe C.JACC 213;62:263-71]. Likewise, HFpEF similar to heart failure with reduced ejection fraction, is strongly associated with diabetes mellitus. Compared to non-diabetic HFpEF patients, diabetic HFpEF patients tend to be younger, more obese, more likely hypertensive, have more renal function impairment, and more vascular disease. HFpEF patients with diabetes have more left ventricular hypertrophy, a trend toward higher left ventricular filling pressures, less exercise tolerance and more need for hospitalization. [Lindman BR, Dávila-Román VG, Mann DL, et.al. Cardiovascular Phenotypes in HFpEF Patients with and without Diabetes. JACC 2014; 64:541-549]. About 30-40% of patients with HFpEF have diabetes mellitus,

and diabetes in patients with HFpEF is associated with a 70% to 80% increase in mortality and hospitalization rate.

HF is one of the most common reasons for hospital admission in those aged 65 and over with consequent high costs for the healthcare system [14]. Despite improvements in the treatment of patients with chronic HF with reduced EF, the survival of the patients hospitalized for HF remains poor, with one-year mortality of 30% and 5-year mortality up to 50%. One of the major reasons for this poor prognosis relates to the co-morbid diseases including DM that adversely impact survival in patients with HF [15,16]. HF and DM often occur concomitantly as demonstrated in HF studies in which the prevalence of DM ranges from 10% to 47% depending on the specific characteristics of the cohort studied (e.g. age, country, severity of HF) [17,18,19,20]. HF and DM association is particularly relevant in patients hospitalized for HF as approximately 40% of these patients with reduced EF have DM [21] and DM is one of the non-cardiac comorbidities associated with notably higher risks for both all-cause and HF-related preventable hospitalizations [22] and re-hospitalization [23].

In patients with DM the prevalence of HF is between 9-22%, which is 4 times higher than the general population [24] and DM is a risk factor for HF development especially in women (5-fold) compared to men (2.4-fold) [25]. The relationship between DM and HF is bidirectional, with each disease independently increasing the risk for the other [8, 26]. Patients with advanced HF show marked insulin resistance, a condition associated with an increased risk of developing type 2 DM, compared to normal individuals or patients with coronary artery disease (CAD).

3. PATHOPHYSIOLOGY

The pathophysiological basis of the relationship between HF and DM may involve several possible scenarios, that further potentiate each other (figure 1). DM may increase the risk of HF through increased risk for CAD and subsequent progression to post-ischemic HF. In addition, DM may induce myocardial alterations directly altering cardiac structure and function (diabetic cardiomyopathy) [27]. Finally, HF may induce insulin resistance and the subsequent progression to DM.

3.1. Post-ischemic Heart Failure in Diabetes

Patients with DM show a 2 to 4 fold increase in the relative risk of cardiovascular (CV) morbidity and mortality compared to non-diabetic subjects [28,29]. In a Finnish population-based study, the risk of acute myocardial infarction was 7-fold greater in patients with DM compared to patients without with a similar risk to that of a non-diabetic with a history of previous myocardial infarction [28], suggesting that DM is a CV risk equivalent. DM is the most important predictor of myocardial infarction and death in subjects with unstable coronary syndromes even after consideration of the extent of CAD and benefits of revascularization [30].

The pathophysiological basis for these adverse outcomes involves the hyperglycemic milieu that exacerbates concomitant CV risk factors such as hypertension, dyslipidemia and activation of neurohormonal and inflammatory mechanisms resulting in accelerated and more extensive CAD. Insulin-resistance and consequent compensatory hyperinsulinemia is an early and central defect in the natural history of type 2 DM that may precede its diagnosis by 10 to 20 years [31]. This defect in insulin action, is associated with a cluster of abnormalities referred to as the insulin resistance syndrome (or metabolic syndrome) that contributes to endothelial dysfunction and progression toward advanced atherosclerosis.

Epidemiological studies show that subjects with insulin-resistance have an increased risk of incident CAD, even in the absence of overt DM [32]. When overt DM occurs, hyperglycemia-induced oxidative stress may lead to a prothrombotic and proinflammatory state favoring the propensity to plaque complications. Coronary tissue from patients with DM exhibits a larger content of lipid-rich atheroma and macrophage infiltration than tissue from patients without DM [33] and impaired platelet aggregation and adhesion with consequent higher risk of thrombosis. Angiographic examination of patients with DM and unstable angina has shown a higher incidence of plaque ulceration and intracoronary thrombus formation than subjects without DM [34]. Importantly, results from the Framingham Heart Study demonstrated that patients with DM are at increased risk of developing HF following myocardial infarction with worse outcome compared to non-diabetic patients.[25] Other studies have consistently demonstrated that DM is a powerful risk factor for and accelerates the development of post-myocardial infarction HF [35], likely due to a more limited capacity of left ventricle remodeling.

Gary S. Francis, MD: Diabetes mellitus is arteriopathic through a number of mechanisms. These include reduced vascular nitric oxide, reduced prostacycline production, and enhanced endothelin, angiotensin II, tissue factor activity, and platelet activity. There seems to be a clear benefit from coronary artery bypass graft surgery in patients with diabetes and 3-vessel disease, irrespective of coronary vascular disease severity scoring systems.

3.2. Heart Failure Induced Type 2 Diabetes

There is evidence showing that advanced HF (New York Heart Association) functional class III-IV is also associated with a greater incidence of DM [26]. The mechanisms underlying this association are not fully understood. Sympathetic nervous system overactivity and consequent lipolysis, activation of the renin-angiotensin-aldosterone system (RAAS) and increased cytokine production in HF might play a role in the development of insulin-resistance and consequent progression to type 2 DM. HF may induce insulin resistance that in turn triggers HF in a vicious cycle.

3.3. Diabetic Heart Failure

Patients with DM may develop a unique form of cardiac alterations termed diabetic cardiomyopathy, defined as a defect in ventricular contractile function that is independent of CAD and hypertension [27]. The term diabetic cardiomyopathy describes myocardial changes induced by diabetes-associated defects: insulin-resistance and hyperglycemia which are central drivers in several adaptive and maladaptive responses ultimately inducing specific detrimental myocyte abnormalities [36]. Several synergistic pathological mechanisms have been investigated as determinants of diabetic cardiomyopathy [37]. Connection between alterations, underlying mechanisms and consequent functional and structural changes associated with diabetic cardiomyopathy are shown in table 1.

3.3.1. Metabolic Alterations

One of the consequences of insulin-resistance is the impaired hormone capacity to inhibit adipose tissue lipolysis with consequent enhanced free fatty acid (FFA) release particularly in subjects with visceral adiposity, and the reduction in myocardial glucose transporter GLUT4 expression and glucose uptake. These metabolic alterations may be firstly related to changes in substrate availability (higher availability in FFA and insulin resistance-mediated impairment in myocyte glucose metabolism) and lead to a shift from glucose to FFA uptake and utilization in the heart [27,38]. As metabolic alterations become longstanding, high FFA levels activate myocyte expression of peroxisome proliferator-activated receptor α that stimulates the transcription of multiple genes responsible for an increase in mitochondrial FFA transport and oxidation [39]. Although FFA □-oxidation produces more adenosine triphosphate (ATP) than glucose oxidation, it is less favourable due to the significantly higher oxygen consumption and cardiac efficiency is reduced [40]. FFA myocardial uptake may exceed FFA □-oxidation capacity leading to triglycerides accumulation in the myocytes (lipotoxicity) [41] and production of toxic lipid intermediates such as diacylglycerol and ceramides [42], both promoting oxidative stress and cardiomyocyte apoptosis with consequent mechanical dysfunction and organ failure.

These metabolic substrate changes lead to dysfunction of myocardial mitochondria [43] with increased generation of reactive oxygen species promoting mitochondrial uncoupling and leading to increased oxygen consumption and reduced myocardial efficiency [44]. Reduced ATP synthesis contributes to diminished myocardial high-energy phosphate reserves and potentially to contractile dysfunction [45]. Diabetic mitochondrial dysfunction is sustained by ultrastructural changes (e.g., hyperplasia, reduced organelle size, loss of membranes and cristae) and reduced expression of genes involved in oxidative phosphorylation [46]. The phosphocreatine/ATP ratio, a surrogate marker of mitochondrial function and cardiac energetics, is significantly reduced in patients with type 1 and type 2 DM without a known history of CAD, and correlates with the degree of diastolic dysfunction [47]. Myocardial mitochondria in patients with DM have specific impairments in maximal capacity to oxidize FFA and glutamate in parallel with an increased mitochondrial H_2O_2 emission, providing

insight into the role of mitochondrial dysfunction and oxidative stress in the pathogenesis of HF in diabetic patients [48]. These metabolic alterations characterize the early stages of diabetic cardiomyopathy without overt functional alterations.

Gary S. Francis, MD: There are some data to suggest that the risk of heart failure could be lessened by tight control of HBA1c. Lind and colleagues demonstrated that patients with a HA1c of at least 10.5% had a four-fold greater risk of heart failure than did those with a HA1c of less than 6.5% [Lind M, Bounais I, Olsson M et.al. Lancet published online June 25, 2011]. However, strict glycemic control has not uniformly been demonstrated to reduce the onset of heart failure (see page 19, section 8).

3.3.2. Impaired calcium homeostasis

DM is associated with abnormalities in calcium handling. Major changes in DM include a shift in myosin isoenzyme composition (from V1 to V3 isoforms) [50] and the predominance of the fetal β myosin heavy chain expression with respect to the α myosin heavy chain [51], leading to depressed ATPase activity of myofibrils and reduced contractile force. In addition, alterations in sarco-(endo-) plasmic reticulum $Ca2^{+}$ ATPase (SERCA) 2 activity, inefficient sequestration of $Ca2^{+}$ in the sarcoplasmatic reticulum resulting in $Ca2^{+}$ overload in the cytosol and defects in ryanodine receptors activity have been proposed as major determinants of impaired relaxation and contractile dysfunction. Accordingly, overexpression of sarco-(endo-) plasmic reticulum $Ca2^{+}$ ATPase in the transgenic models has been shown to protect the diabetic heart against severe contractile dysfunction [52]. Recently, a perturbation in the function of the endoplasmic reticulum, a central organelle entrusted with $Ca2^{+}$ homeostasis and protein folding and maturation, has been suggested as the leading cause of myocytes apoptosis [53].

3.3.3. Hyperglycemia-induced alterations

Hyperglycemia is one of the main pathogenic mechanisms leading to diabetic structural alterations in HF. Important consequences of hyperglycemia-induced cellular injury are the formation of advanced glycation endproducts resulting from the nonenzymatic glycation and oxidation of proteins and lipids , the activation of the protein kinase C / diacylglycerol signaling pathway and increase levels of Poly-(ADP-ribose) polymerase enzymes that are involved in cellular processes including DNA repair and programmed cell death [49].

AGE accumulation in DM is known to induce myocardial alterations primarily via two mechanisms. Advanced glycation endproducts form cross-links within or between proteins such as myocardial collagen, laminin and elastin, thereby impairing the ability of collagen to be degraded, leading to collagen accumulation and fibrosis with increased myocardial stiffness and impaired cardiac relaxation [54]. Secondly, soluble extra-cellular advanced glycation endproducts bind to their receptors,

stimulating the upregulation of transforming growth factor– an important pro-sclerotic factor [55] that have also been implicated in inflammatory signaling pathways [56].

Hyperglycemic-induced protein kinase C activation also contributes to cardiac fibrosis by stimulating connective tissue growth factor expression [57]. Protein kinase C inhibition attenuates diastolic dysfunction, myocyte hypertrophy, and collagen deposition despite preserved cardiac contractility in a rodent model of diabetic diastolic representing a novel therapeutic strategy for the prevention of DM-associated cardiac dysfunction [58]. The activation of all the above hyperglycaemic-induced pathways characterise the middle stage of diabetic cardiomyopathy associated with myocellular hypertrophy and myocardial fibrosis which contribute to abnormal diastolic dysfunction and normal or slightly decreased EF.

3.3.4. Renin Angiotensin Aldosterone System Activation

DM is associated with the activation of the RAAS with consequent overproduction of angiotensin II, which contributes to heart fibrosis by stimulating extracellular matrix component synthesis, apoptosis/proliferation, vascular inflammation and oxidative damage [59,60,61].

3.3.5. Oxidative, nitrosative and nitrative stress

Hyperglycaemia-induced pathway activation eventually results in the production of oxygen-derived oxidants from both mitochondrial and non-mitochondrial sources. A chronic increase in oxidative stress has several harmful effects on the CV system by directly damaging proteins and DNA, by interfering with nitric oxide production and by the modulation of intracellular signaling pathways and proteins involved in the stimulated production of reactive oxygen species. Mitochondrial derived-reactive oxygen species appear to play the most crucial role as they can interact with nitric oxide to form peroxynitrite species which attack various biomolecules leading (among other processes) to the production of a modified amino acid, nitrotyrosine, that can disrupt endothelial nitric oxide synthase activity ultimately reducing nitric oxide bioavailability and resulting in endothelial dysfunction [62]. Peroxynitrite induces DNA strand breaks and activates the nuclear enzyme poly(ADP-ribose) polymerase (PARP)-1 PARP which, in turn, induces the poly(ADP-ribosyl)ation of glyceraldehyde- 3-phosphate dehydrogenase resulting in NF-κB, aldose reductase and the polyol pathway activation [63]. These effects are relevant in all stages of HF from LV hypertrophy to interstitial fibrosis, adverse remodeling after myocardial infarction and myocyte apoptosis [49].

3.3.6. Disease of Small Cardiac Vessels

Hyperglycemia is known to induce microangiopathy, mainly through AGE formation, characterized by thickening of the capillary basement membrane and formation of microaneurysms [64]. These structural alterations cause functional modification such as impaired nitric oxide production and permeability of the endothelium with consequent endothelial dysfunction and decreased vessel density

[65]. The consequent deficiency in coronary blood flow reserve contributes to loss of contractile proteins and myocyte necrosis with reactive focal perivascular and interstitial fibrosis, collagen deposition and hypertrophy of myocardial cells [66].

3.3.7. Cardiac Autonomic Neuropathy

Cardiac autonomic neuropathy is a common microvascular complication of DM affecting almost 17% of the patients with type 1 and 22% of those with type 2 DM [67]. The severity of hyperglycemia and DM duration are major determinants of cardiac autonomic neuropathy, which leads to impaired regulation of CV function [68]. An early manifestation of cardiac autonomic neuropathy is parasympathetic denervation with an imbalance toward higher relative sympathetic drive [69]. Increased cardiac sympathetic activity, as already discussed, increases lipolysis, FFA overflow influencing myocardial substrate utilization [70], mitochondrial uncoupling [71] and oxidative stress with consequent cardiac dysfunction. Cardiac autonomic neuropathy is also associated to a depressed baroreflex function leading to impaired regulation of heart rate variability, stroke volume and blood pressure that have been associated with both systolic and diastolic dysfunction. Patients with severe cardiac autonomic neuropathy may have distal sympathetic denervation associate with proximal ventricular islands of hyperinnervation that result in myocardial regions that are unstable electrically. In support of this concept, the estimated 8-year survival rate in patients with cardiac autonomic neuropathy was 77% compared with 97% in those with normal autonomic function, with the majority of deaths related to macrovascular diseases and sudden unexpected deaths [72]. These results have been confirmed also in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which cardiac autonomic neuropathy was strongly associated with all-cause and CV disease mortality independent of baseline CVD, DM duration, multiple traditional CV risk factors and medications [73].

Sympathetic overactivity is a common feature in DM and HF with different causal chains. In non-diabetic HF, sympathetic activation occurs in the later HF stages leading to insulin-resistance, whereas cardiac autonomic neuropathy is a central determinant of the diabetes-induced microvascular complication worsening metabolic and functional alterations in diabetic cardiomyopathy, The subsequent progression to HF, in turn, increases sympathetic activity.

4. CLINICAL PHENOTYPES OF DIABETIC HEART FAILURE

4.1. Diastolic dysfunction

The most frequent and earliest functional abnormality in the diabetic heart is impaired diastolic compliance, setting the stage for HF with normal EF [74]. Although this alteration is not unique to DM, it has been detected in up to 75% of asymptomatic patients with DM [75]. A small study provided insight into the phenotypic characteristics of patients with DM with LV diastolic dysfunction: 40% had diastolic dysfunction, of which two third had impaired relaxation and one third pseudo-normalization

of mitral inflow on Doppler echocardiography [76] Of note, patients with diastolic dysfunction were young (mean age 43 yrs), normotensive, and under good diabetic control, supporting the hypothesis that diastolic dysfunction is an early feature in DM [77]. The abnormalities were more evident in the diabetic-hypertensive group, showing an additive effect on LV relaxation when both of these conditions were present [76].

Subjects with type 2 DM are more susceptible to preclinical diastolic and systolic dysfunction compared to type 1 patients [78], supporting a role of insulin resistance-mediated alterations in the determination of early cardiac dysfunction and a possible protective role for insulin therapy. Diastolic dysfunction was associated with the presence of mild complications of DM whereas systolic dysfunction was found in the presence of more severe diabetic complications, suggesting that the extent of systolic dysfunction may depend more on the magnitude and duration of hyperglycemia [79].However, in patients with DM, the clear phenotypic distinctions noted in experimental animal models (marked hyperinsulinemia without hyperglycemia leading to LV hypertrophy and diastolic dysfunction and hyperglycemia without hyperinsulinemia leading to systolic dysfunction) have not been confirmed. In patients with type 1 DM, systolic dysfunction is less evident than in animal models because these patients receive exogenous insulin, making them metabolically similar to patients with type 2 DM.

Gary S. Francis, MD: Both stiff cardiac myocytes and fibrosis contribute to left ventricular chamber dysfunction. There may be hypophosphorylation of titin, altering the giant molecule's distensibility. The profibrotic action of growth promoting hormones such as endothelin – 1, angiotensin II, and aldosterone are unopposed due to reduced nitric oxide bioavailability. Microvascular inflammation may lead to further proliferation of fibroblasts and myofibroblasts. So the development of diastolic dysfunction, found in both systolic heart failure and HFpEF, is clearly complex and multifactorial. Clearly, diastolic dysfunction is a primary feature of diabetic heart failure.

4.2. Systolic Dysfunction

In the diabetic heart, systolic dysfunction is believed to be a later manifestation of disease, usually occurring after the development of diastolic dysfunction. Recently, the use of two-dimensional speckle tracking echocardiography has shown the presence of subclinical LV systolic dysfunction, measured as a decrease in LV longitudinal shortening, in asymptomatic diabetic patients with normal EF and assumed to have "isolated" diastolic dysfunction [80].

4.3. Response to Stress Tests

Latent LV dysfunction in diabetic heart, even in asymptomatic subjects with normal resting LV dimension and function, can be unmasked during exercise. Patients with type 2 DM with normal myocardial function at rest but an abnormal response to exercise stress had significantly reduced

longitudinal diastolic functional reserve index compared to those with a normal stress response, highlighting the important role of myocardial diastolic relaxation in maintaining normal myocardial function and exercise capacity [81].These findings suggest that impaired cardiac performance after exercise could be a potential tool to detect early contractile dysfunction in DM.

5. HEART FAILURE PROGRESSION AND PROGNOSIS

Longstanding metabolic and functional alterations ultimately lead to irreversible structural changes. In this later stage of diabetic cardiomyopathy, diabetic comorbidities such as hypertension, dyslipidemia, microvascular dysfunction, autonomic dysfunction, and renal impairment may accelerate the progression of cardiac dysfunction [82]. This heterogeneity results in clinical phenotypic variability and progression towards significantly increased LV size, mass and wall thickness with overt abnormal diastolic and systolic dysfunction.

Cardiac dysfunction in patients with DM portends worse prognosis. In a cohort of 151,738 adults >65 of age with DM, HF was associated with 32.7 per 100 person-years mortality rate compared to 3.7 per 100 person-years among those with DM who remained free of HF [83]. Among hospitalized HF patients, those with DM tended to more frequently present with acute pulmonary edema or acute coronary syndrome [84]. HF and renal impairment were the main determinants of outcome in patients with DM and CAD [85] and conversely, DM is a potent independent risk factor for mortality in patients hospitalized with HF, particularly in women [86]. Most sources suggest that patients with HF and DM are at higher risk for post-discharge mortality and re-hospitalizations compared to their peers without DM [3,15], although some studies have shown them to be at similar risk [23]. Glycemic control is an important prognostic factor as shown in a large cohort of diabetic patients (25,958 men and 22,900 women), in which each 1% increase in glycosylated hemoglobin was associated with an 8% increased risk of HF [87].

6. HEART FAILURE SCREENING IN THE POPULATION WITH DIABETES MELLITUS

The higher morbidity and mortality observed in patients with HF and DM mandates its early identification in order to initiate adequate treatments and delay disease progression. Currently, there is no single imaging, biomarker or histological finding pathognomonic for diabetic cardiomyopathy. In the Studies of Left Ventricular Dysfunction (SOLVD) Registry only approximately half of the patients with an EF <45% had HF symptoms [88], making it difficult to screen only based on clinical grounds. Known independent risk factors for HF in diabetic patients are older age, longer DM duration, visceral obesity, higher glycosylated hemoglobin and albuminuria [88], making the use of clinical characteristics to screen HF in diabetic patients also difficult. Brain natriuretic peptide as a screening tool, showed a sensitivity of 92% and specificity of 72% for LV systolic dysfunction and it has been shown to be prognostically significant [89]. Brain natriuretic peptide levels might therefore be considered a cost-effective test with which to select patients for echocardiographic evaluation, but not sensitive enough

for early detection of pre-clinical myocardial dysfunction [90]. Furthermore, plasma brain natriuretic peptide levels have been found significantly higher in HF patients with DM than in the non-diabetic patients at the same HF score [91]; this needs to be taken into account when interpreting brain natriuretic peptide levels in patients with DM. The underlying mechanism for the higher brain natriuretic peptide level in HF patients with DM is not clear; proposed mechanisms include an increase in brain natriuretic peptide formation and/or a decrease in degradation due to hyperglycemia, cardiac autonomic dysfunction [92] or higher RAAS activation compared to non-diabetic patients.

Other biomarkers are of interest class of biomarkers related to the synthesis and/or degradation of types I and III fibrillar collagens (serum aminoterminal propeptide of type I and type III), the most abundant collagens in the myocardium and associated with cardiac remodeling [93]. Serum concentrations of the carboxy-terminal propeptide of procollagen type I were related to changes of LV filling dynamics in patients with early type 2 DM [94]. Upregulation of matrix metalloproteinase activities or downregulation of their inhibitors (tissue inhibitors of matrix metalloproteinases) lead to degeneration of the extracellular matrix and replacement fibrosis. Assays of these markers remain experimental and need to be further validated in large trials [95].

Conventional echocardiographic techniques for assessing LV hypertrophy are not specific for diabetic cardiomyopathy. The development of new ultrasound techniques such as echo strain imaging and the use of magnetic resonance imaging for the evaluation of strain and strain rate have shown to be effective in the identification of subclinical LV systolic and diastolic dysfunction in asymptomatic patients with DM and normal EF [80]. Recently, the European Society of Cardiology has suggested criteria for the diagnosis of diastolic dysfunction [96], but there are no specific guidelines for HF screening in the asymptomatic population with DM, and recommendations for HF screening are warranted. A combination of clinical characteristics, potential symptoms, biomarkers of cardiac function and new diagnostic techniques may provide potential tools to identify diabetic subjects at increased risk of developing HF. The current approach to the classification of HF emphasizes the development and progression of the disease from Stage A through D [97]. Patients with DM who do not yet demonstrate LV dysfunction would be considered Stage A. As patients move through stages B-D, they develop structural changes, symptoms and then refractory end-stage disease.

Importantly, HF patients who have not been diagnosed with DM should be screened for early detection of glucose intolerance or DM to start preventive and therapeutic strategies and improve prognosis, especially in those with advanced NHYA functional classes III/IV.

7. TREATMENT OF HEART FAILURE IN PATIENTS WITH DIABETES

Results from sub-group analyses of recent trials suggest that HF patients with DM might not respond equally to standard treatment being more prone to develop drug side effects [4] or having divergent trends in response to some drugs compared to HF patients without DM [5]. Data on the efficacy and tolerability of drugs used in the treatment of chronic or hospitalized HF in patients with DM are

limited to subgroup analyses of randomized clinical trials with possible problems of inadequate statistical power. Outpatients with HF differ from hospitalized HF patients, and similarly HF patients with reduced EF must be differentiated from those with preserved EF. These distinctions are important and underlay different degree of hemodynamic and neurohormonal abnormalities, distinct clinical characteristics, varying risks for adverse outcomes, and dissimilar efficacy of existing therapies. Similarly, DM patients are heterogeneous in terms of disease duration, severity of microvascular and end-organ complications, comorbidities, degree of neurohormonal activation and event rate; indeed the newly introduced guidelines recommend a patient-centered therapeutic approach with individualized target s and therapeutic strategies [98]. Finally, drug interactions might blunt clinical efficacy and favor side effect occurrence or HF precipitation.

7.1. RAAS inhibition

The RAAS is over-activated both in HF and DM and its inhibition represents an important therapeutic goal in both conditions. Angiotensin II and aldosterone are the final effectors underlying the cardio-renal continuum in DM. Both angiotensin II and aldosterone have receptors and activities that are widespread throughout the body, including tissues in the brain, heart and blood vessels. They both stimulate smooth muscle hypertrophy in the vascular system, myocardial and renal fibrosis and predispose to oxidative stress, inflammation, thrombosis and sudden cardiac death [99,100,101].

ACE-Is show similar effects in HF patients with or without DM [102,103,104,105] and long-term high-dose of lisinopril was as effective and well-tolerated in HF patients with DM [106]. These effects were confirmed also with AT1- receptor blockers (ARBs) therapy in reducing the incidence of first hospitalization for HF in type 2 DM [107]. ACE-I/ARB blockade has been shown useful in preventing the development of HF in DM patients [108] and substantial clinical evidence points to a positive impact of RAAS blockade on the incidence of new-onset type 2 DM [109]. In relation to which RAAS inhibitor might be more effective in patients with HF and DM, in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) [110] and Valsartan Heart Failure Trial (ValHeFT) [111] studies, ARB use was not as effective in the DM subgroup.

Guidelines recommend that Treatment with ACE-I/ARBs in DM patients should be initiated at low doses, with gradual uptitration to the doses used in clinical trials (or the maximally tolerated doses) with frequent monitoring of renal function and electrolytes [117]. Data suggest that HF patients with DM may also receive great benefit from mineral receptor antagonist therapy [112]. The rational for mineral receptor antagonist use in addition to ACE-I/ARBs is due to the synergistic increase in plasma renin activity and to the aldosterone escape phenomenon that could reduce the expected ACE-I/ARB therapy benefits. In addition, DM [113] and HF [114] are characterized by a maladaptive mineralcorticoid receptor activation that contributes to hypertension, fibrosis, apoptosis, or inflammation potentiating cardiac and renal damage.

The addition of the mineral receptor antagonist eplerenone to traditional HF therapy has been shown to reduce morbidity and mortality in patients who develop LV dysfunction after myocardial infarction [115]. In post-myocardial infarction patients with reduced LVEF, eplerenone added to standard therapy reduced the mean length and total days of HF hospitalizations compared to placebo in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) with no significant mortality differences between patients with and without DM [116]. Although mineral receptor antagonists have been demonstrated to be highly effective in patients with HF, their use in combination with ACE-I and/or ARBs in HF patients with concomitant DM, has been constrained by the concern of renal function worsening, elevation in creatinine, and risk of hyperkalemia [117]. Importantly, eplerenone seems to have no effect on new-onset DM in patients with HF [118], suggesting a neutral metabolic profile.

The newly introduced direct renin inhibitor aliskiren inhibits the renin–angiotensin axis at the most proximal step, offering the theoretical advantage of preventing the compensatory rise in plasma renin activity, when combined with ACEIs, ARBs or diuretics. However, the use of aliskiren to treat CV and renal complications in patients with type 2 DM, resulted in a higher frequency of adverse events including renal dysfunction, hyperkalemia (8.8% vs. 5.6%), hypotension (12.1% vs. 8.0%), and stroke than placebo resulting in the addition of aliskiren to standard therapy with RAAS blockade in patients with type 2 DM being actively not recommended.[4] Subgroup analyses from the ASTRONAUT trial (AliSkiren TRial ON Acute heart failure oUTcomes) conducted in hospitalized HF patients with DM showed a statistically significant interaction between aliskiren treatment and DM status at 12 months for CV death or HF re-hospitalizations [5]. One potential explanation for the possible negative effects of aliskiren in DM patients include increased adverse events including severe hyperkalemia (serum potassium≥6.0mmol/L, 9.7 vs. 4.7% in DM with aliskiren vs. placebo) with concomitant ACE inhibitor/ARB (85%) and MRA (55%) therapy. A second possible mechanism is the differential effect on neurohormonal profiles in patients with BM with differential effects in the RAAS cascade. Of note, these results should be interpreted with caution and viewed in the context of a subgroup analysis on a secondary endpoint highlighting the need of further dedicated trials in patients with DM and HF.

7.2. Beta-blockers

The administration of β-blockers to patients with concomitant DM has been traditionally regarded as relatively contraindicated because of fears that these drugs may blunt symptoms of hypoglycemia or may exacerbate insulin resistance [119,120]. There is now clear evidence of the importance of blocking the sympathetic nervous systems which is characteristically overactivated in both conditions. Therapy with β-blockers should be therefore prescribed also in HF patients with DM [117], unless specifically contraindicated. Sub-group analyses of trials conducted in patients with advanced HF have shown that β-blockers are as effective in reducing all-cause mortality [121,122,123] and hospitalization rates for HF

similarly in patients with and without DM [124,125].These results were confirmed also by a recent meta-analysis [126].

The β-blocker carvedilol administration showed similar beneficial effects on LV function, resting and exercise hemodynamics and clinical conditions, with a similar good tolerability in HF patients with and without concomitant DM [127] and a reduction of morbidity and mortality identical in the subgroup of patients with DM, also in condition of severe symptomatic HF [128].

In relation to which β-blocker should be used in HF patients with DM, there are theoretical benefit with carvedilol as it may increase skeletal muscle blood flow and improve glucose uptake. The Carvedilol or Metoprolol European Trial (COMET), suggested that the combined β ? carvedilol was more beneficial compared to the selective ?-1 antagonist metoprolol in reducing mortality in HF patients, with similar results in those with concomitant DM [129].However, guidelines do not support the use of one evidence-based β-blocker over another in this population [97].

7.3. Diuretics

Diurectics are mandatory for the treatment of decompensated HF and no data are available to indicate a possible different efficacy in patients with or without DM.

8. TREATMENT OF DIABETES IN PATIENTS WITH HEART FAILURE

It is assumed that an improvement in glycemic control is beneficial to delay the progression and improve myocardial dysfunction especially in the early stages. Metabolic control has shown to enhance myocardial contractility parameters likely due to a more efficient myocardial energy substrate use and improved microvascular perfusion [130]. However, results from recent trials have challenged this assumption. In the Action in Diabetes and Vascular Disease (ADVANCE) trial, strict glycemic control was not associated with a reduced onset of HF [131] and in the Diabetes Mellitus and Diastolic Dysfunction (DADD) study neither insulin or oral agent therapy were associated with an improvement in diastolic function despite a reduction in glycosylated hemoglobin [132].

Hypoglycemia induced by DM medications is recognized as a major limiting factor in the attainment of glycemic goals. Frequent hypoglycemic events in patients with compromised defenses against hypoglycemia (such as type 1 or advance type 2 DM) attenuate hormonal and autonomic responses to subsequent hypoglycemic events increasing the risk of hypoglycemia unawareness and of recurrent severe hypoglycemic episodes by a factor of 25 or more [133]. Hypoglycemia may promote a reduced threshold for malignant arrhythmias and subsequent sudden cardiac death especially in vulnerable population such as those with HF. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) plasma glucose concentration ≤4.5 mmol/L (hypoglycemia) proved to be strong predictors of all-cause death (HR 1.38, 95% CI1.06-1.81) in HF after acute myocardial infarction patients during long-term follow-up [134]. Combination therapy with several antidiabetic agents in order to achieve glucose targets further increases the risk of

hypoglycemic events. Table 2 describes Cellular mechanisms and possible cellular effects in HF of the commercially available antidiabetic agents.

8.1. Metformin

Metformin is recognized as the first-line agent in type 2 DM [117]. It improves insulin sensitivity by reducing hepatic glucose production and enhancing peripheral glucose uptake. There is robust evidence that metformin use improves outcome in HF patients compared to other hypoglycemic agents [135]. These data have been confirmed in a recent meta-analysis and in a nested case control study in which metformin was associated with reduced all-cause mortality in diabetic HF patients [136,137]. Recently it has been suggested that beneficial CV effects of metformin might be mediated by AMP-activated protein kinase signaling [138]. AMP-activated protein kinase activation ultimately inhibits carnitine palmitoyltransferase-1, a key regulator of the FFA uptake in the mitochondria, and stimulates glucose uptake and glycolysis [139], thereby blunting the metabolic shift characteristic of diabetic cardiomyopathy.

Metformin use in HF is limited by concerns regarding the risk of lactic acidosis. The FDA has recently withdrawal this contraindication and now metformin can be used in HF patients in whom LV dysfunction is not severe, hemodynamics are stable, and renal function is normal. A retrospective cohort study has shown that metformin therapy is safe also in diabetic patients with advanced HF [140]. In hospitalized patients with HF, metformin was associated to lower 1-year mortality and re-hospitalization rate compared to insulin or sulphonylureas [141].

8.2. Thiazolidinediones

Thiazolidinediones are synthetic ligands of the nuclear peroxisome proliferator-activated receptor γ (PPARγ) that modulate the expression of genes involved in insulin sensitivity. They exert and insulin sensitizer action by increasing skeletal glucose uptake and oxidation, decreasing FFA concentrations and reducing hepatic glucose production. Pioglitazone, the current commercially available TZD, has been shown to display additional potential beneficial effects on the CV system, such as decreases in angiotensin II levels, blood pressure reduction, improvement in endothelial function and anti-inflammatory properties [142] Pioglitazone therapy has also shown to improve diastolic function and LV compliance [143] and cohort studies demonstrated no increase in the risk of HF in patients treated with pioglitazone as compared with metformin, sulfonylureas and insulin [136]. However, the clinical use of thiazolidinediones in patients with CV disease has been limited by the risk of fluid retention and peripheral edema, that could potentially lead to development of HF in patients with or without pre-existing LV systolic or diastolic dysfunction or to induce HF decompensation in those with established HF. A meta-analysis of 19 randomized controlled trials enrolling 16,390 patients demonstrated an increased risk of HF with pioglitazone compared with placebo or active control [144]. Pioglitazone treatment in diabetic patients with advanced HF was associated with an earlier time to onset and

significant increase peripheral edema, HF progression and hospitalizations, although there was no increase in mortality [145]. In consideration of these side effects, it is currently recommended that thiazolidinediones be used with caution in patients in New York Heart Association functional class I and II but generally avoided in patients with symptomatic HF [141]

8.3. Sulphonylureas

Sulphonylureas stimulate □-cell insulin release by binding to the pancreatic sulphonylurea receptor 1 and closing the ATP-sensitive potassium channels. It has been suggested that sulphonylureas which show a considerable affinity for cardiac subtypes of sulphonylurea receptors such as glimepiride and glyburide, may abrogate the adaptive cardiac responses to systolic overload (ischemic preconditioning) in failing hearts by inducing a closure of cardiac potassium sensitive ATP channels [146]. This topic is still matter of debate and studies are inconclusive regarding an increased risk of HF with sulphonylurea treatment. In the United Kingdom Prospective Diabetes (UKPDS 33) study the use of sulphonylureas was not associated with an increased risk of development of HF [147] and a recent study conducted in diabetic patients with HF failed to demonstrate any considerable difference in mortality risk with different sulphonylureas [148]. In contrast, results from a retrospective cohort study showed that monotherapy with second generation sulphonylureas was associated with a significant 18% to 30% excess risk for congestive HF compared with metformin [149], and these results were confirmed also in a large retrospective cohort study of adults without HF newly treated with sulphonylureas [150]. With respect to possible differences among different types of sulphonylureas, results from a large cohort suggest that it is unlikely that there are important differences in mortality associated with individual sulfonylureas in patients with HF [148].

8.4. Insulin

Whether the use of insulin in HF patients with type 2 DM is associated with an increased risk of HF is still controversial. A substantial number of reports has shown higher mortality rates in association with tight glycemic control in patients with DM and HF, mainly under insulin treatment [151,152]. Diabetic patients with advanced HF receiving insulin had a markedly increased risk of death as compared without DM and those with DM and HF who were not treated with insulin [151]. However, it should be emphasized that insulin therapy may just be a surrogate marker of patients with a longer disease duration or greater micro and macrovascular disease in type 2 DM. In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, insulin glargine treatment did not increased the risk of HF vs standard care in a 6 year follow-up [153].

8.5. Glucagon-like peptide 1agonists

The incretin hormone glucagon-like peptide-1 is released by intestinal L-cells in response to meal and rapidly degraded by the ubiquitously expressed enzyme dipeptidyl peptidase 4. It exerts its

hypoglycemic effects by stimulating □-cell glucose-dependent insulin secretion. Commercially available drugs are either exogenous glucagon-like peptide-1 analogues (resistant to cleavage) or dipeptidyl peptidase 4 inhibitors. Glucagon-like peptide-1 receptors are almost ubiquitous and are expressed throughout the CV system and the myocardium. Glucagon-like peptide-1 binding to myocardial receptors has a positive inotropic effect and stimulates glucose uptake via cyclic adenosine monophosphate (cAMP) production [154]. These effects have been implicated in GLP-1 beneficial action on pre-ischemic conditioning and limiting infarct size, which have been demonstrated in animal models [155,156]. Incretin-based therapy has been shown to improve cardiac function, cardiac remodeling and survival in animal models [157], suggesting a potential benefit in HF. Small clinical studies have shown that glucagon-like peptide-1 infusion leads to an improvement of EF, reduction in brain natriuretic peptide levels and enhanced functional capacity in patients with chronic HF [158,159,160]. Continuous 5 weeks glucagon-like peptide-1 administration in HF patients without DM significantly improved LVEF and quality of life [161]. Furthermore, a retrospective analysis of a large database [162] and a meta-analysis of randomized studies [163] have suggested no substantial CV risk increase in patients treated with the GLP-1 agonist exenatide, as compared with other antidiabetic drugs. Studies are underway to investigate glucagon-like peptide-1 agonists to improve HF (Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) ClinicalTrials.gov Identifier: NCT01800968).

8.6. Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 inhibitors are becoming important oral antihyperglycemic agents , a recommended therapeutic option when glycemic control cannot be achieved with metformin or first-line therapy where metformin is contraindicated [98]. Recently, the SAVOR TIMI-53 (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus e Thrombolysis in Myocardial Infarction-53) reported a significant increase in the risk of hospitalizations for HF in patients treated with saxagliptin compared to placebo, despite significantly improved glycemic control and reduction in development and progression of microalbuminuria [6]. On the contrary, the Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes (EXAMINE) trial showed no significant excess of HF in the dipeptidyl peptidase 4inhibitor alogliptin arm [164]. A recent meta-analysis conducted to assess the effect of this class of agents on the incidence of acute HF which examined a total of 84 eligible trials showed that the overall risk of acute HF was higher in patients treated with dipeptidyl peptidase 4 inhibitors in comparison with those treated with placebo/active comparators (OR: 1.19[1.03; 1.37];$p < 0.015$), without any clear evidence of differences among drugs of the class.[7] The possible mechanisms are unclear but it is important to note that brain natriuretic peptide is a substrate for dipeptidyl peptidase 4 inhibitors [165]. The finding of an increased risk of HF with DM therapies highlights the need to include HF and HF hospitalizations as endpoints in DM trials. Ongoing trials including Exenatide Study of Cardiovascular Event Lowering (EXSCEL) and

Sitagliptin Cardiovascular Outcome Study (TECOS) trials, which included prespecified endpoints of HF hospitalization will add knowledge to these previous findings.

8.7. Sodium-glucose cotransporter-2 inhibitors

Inhibition of sodium-glucose cotransporter-2 in the proximal kidney tubule represents a novel strategy which reduces hyperglycemia independent of insulin secretion or action [166]. Inhibition of glucose reabsorption in the kidney induces mild osmotic diuresis, which drives diuresis with blood pressure reduction and caloric loss. In patients with type 2 diabetes inadequately controlled on pioglitazone, the addition of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, further reduced HbA1c levels and mitigated the pioglitazone-related weight gain without increasing hypoglycemia risk [167]. While a benefit is expected from blood pressure and weight reduction, long-term studies are required to demonstrate the impact of sodium-glucose cotransporter-2 inhibitors on CV outcomes; these trials are now in progress, and are expected to report in the next 4–5 years.

9. AREAS FOR FUTURE RESEARCH

Therapies targeted to address the specific pathophysiological alterations in patients with HF and DM are needed; specific data on this population are lacking currently. An ideal approach would be to modulate myocardial substrate utilization [168] from FFA to glucose oxidation to achieve a more efficient cardiac energy production. Few drugs have been tested in this respect, although in the setting of a non-diabetic HF. Etoxomir has been shown to reduce FFA oxidation by inhibiting carnitine palmitoyltransferase-1, a key regulator of FFA uptake in the mitochondria. However, a randomized study with etoxomir in HF patients was stopped prematurely due to elevation in liver enzymes [169]. Perhexiline, an antianginal drug, is another CPT-1 inhibitor that has been shown to improve symptoms, maximum oxygen consumption, LVEF, resting and peak stress myocardial function, and skeletal muscle energetics in HF patients [170]. The anti-ischemic agent trimetazidine has been shown to improve EF in HF patients likely due to a stimulation of glucose oxidation secondary to inhibition of long-chain 3-ketoacyl coenzyme A thiolase, the last enxyme involved in mithocondrial FFA oxidation [171,172]. A recent meta-analysis has shown that additional use of trimetazidine in HF patients may decrease hospitalization for cardiac causes, improve clinical symptoms and cardiac function, and simultaneously ameliorate LV remodeling [173]. Ranolazine, currently approved as an antianginal agent, reduces the Na-dependent Calcium overload via inhibition of the late sodium current (late INa) channels and thus has been shown to improve diastolic tone and oxygen handling during myocardial ischemia [174]. Recently, ranolazine has been shown to exert beneficial metabolic effects by reducing glucose and insulin levels in patients with DM [175]. The recently published Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) trial showed a greater antianginal effect of ranolazine in patients with CAD and stable angina and DM [176]. The mechanism behind ranolazine anti-diabetic effects are unclear by a recent experimental study showed that these might be

mediated by the inhibition of glucagon release via blockade of Na channels in the pancreatic α-cells [177].

Enhanced AMP-activated protein kinase signaling might target the pathophysiological link between insulin resistance and development of HF. AMP-activated protein kinase improves insulin sensitivity and may prevent whole body insulin resistance, in part by inhibiting pathways that antagonize insulin signaling [178] and may reduce the risk of progression to type 2 DM. AMP-activated protein kinase is found in abundance in the heart where it regulates the cellular response to low energy states such as hypoxia and exercise [179] to increase energy production. Deregulated AMP-activated protein kinase activation has been hypothesized as a possible underlying mechanisms promoting the cardiac metabolic shift from glucose to FFA oxidation [179]. However, to date, there is no sufficient understanding of the precise molecular mechanisms regulating AMP-activated protein kinase activity in cardiac health and disease to guide its pharmacological manipulations for patients.

10. CONCLUSIONS

DM and HF are inter-related conditions. DM can affect cardiac structure and function in the absence of changes in blood pressure or CAD, a condition called diabetic cardiomyopathy. Insulin resistance and hyperglycemia are central drivers of the initially adaptive pathological but ultimately detrimental changes occurring in diabetic cardiomyopathy. Alterations in substrate utilization and mitochondrial dysfunction seem to be early and key alterations in diabetic cardiomyopathy. In later stages, concomitant CV risk factors such as hypertension, dyslipidemia, neurohormonal activation, renal impairment and CAD may further compromise cardiac dysfunction.

Although HF and DM patients show worse outcomes compared to those without comorbid DM, to date, there are no specific strategies to prevent, diagnose or treat HF associated with DM. Early identification of patients at risk for developing structural alterations in latent stages is mandatory to implement preventive and therapeutic strategies. Treatment of concomitant DM and HF is challenging since many contemporaries therapies used for DM are contraindicated or limited by comorbidities such as renal dysfunction. Sub-group analyses of recent trials conducted in hospitalized HF patients with DM showed a different response to standard medication being more prone to develop side effects compared to patients with the same degree of HF but without DM. Conversely, data are emerging on the possible increase in the risk of hospitalizations for HF in patients with DM treated with specific class of antidiabetic agents. These data, although should be cautiously interpreted in the context of post-hoc analyses, suggest the need to identify or develop a targeted therapy to be tested in dedicated future studies, particularly in patients hospitalized for acute HF with concomitant DM. Drugs targeting cardiac metabolism appear to be promising potential therapies for HF in DM patients.

(Final Comment)

Gary S. Francis, MD: This excellent review of diabetes mellitus and heart failure by Dei Cas and colleagues has much updated information for the clinician about the interaction of these two epidemics. It is now reasonably clear that diabetes mellitus is associated with both systolic and diastolic heart failure, independent of associated coronary artery disease. Multiple, complex mechanisms are operative, and there is no highly specific therapy. Some of the newer drugs used for the treatment of diabetes mellitus, especially the thiazolidines, may actually cause excessive fluid retention, thus mimicking or even causing the syndrome of heart failure. Whether these newer anti-diabetic drugs may actually worsen the contractile performance of the heart is not yet particularly clear. One thing that is clear, the co-morbid condition of diabetes mellitus complicates the management of these patients with heart failure, and is likely responsible for some of the very high readmission rates being reported. The growing two-way co-association between heart failure and diabetes mellitus requires that cardiologists and others caring for patients with heart failure must be increasingly familiar with the management of diabetes mellitus.

Legends

Figure 1. Pathophysiological links between diabetes and heart failure

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Figure 1

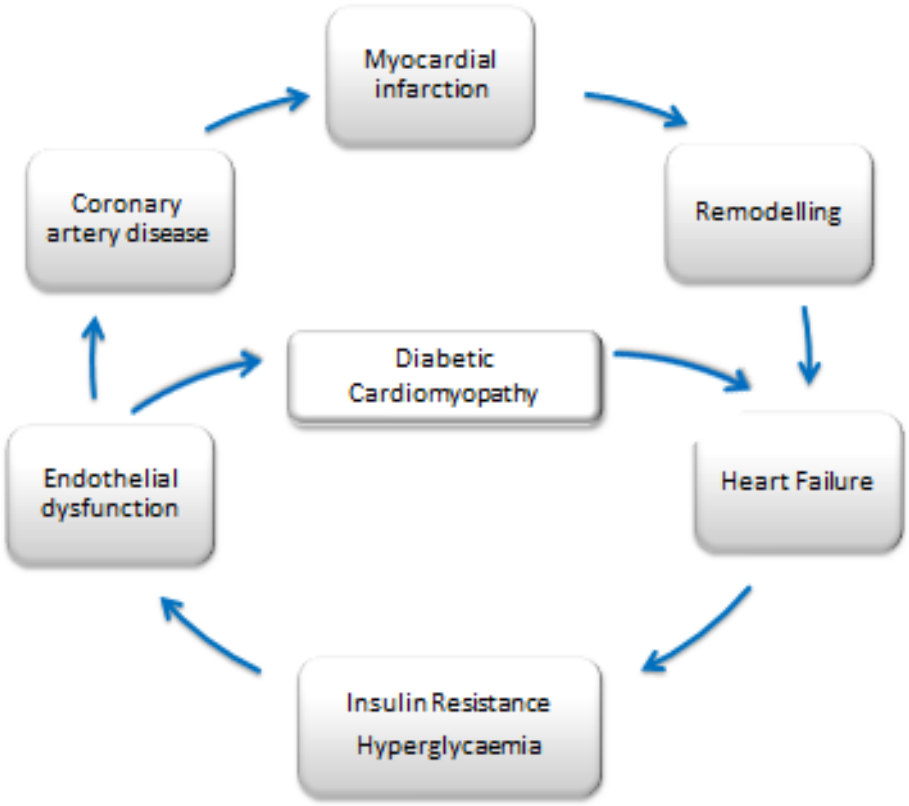

Table 1. Pathophysiologic mechanisms and functional and structural changes associated with diabetic cardiomyopathy

ALTERATION	UNDERLYING MECHANISMS	EFFECTS	STRUCTURAL FEATURES	FUNCTIONAL FEATURES
↑FFA concentration	↑FFA uptake ↓GLUT4 and glucose uptake ↑PPARα activation Accumulation of TG, DAG	↑FFA oxidation ↓ glucose oxidation Cardio-lipotoxicity	Normal LV size, wall thickness and mass	Diastolic dysfunction
↑Mitochondrial dysfunction	Alteration of mitochondrial protein ↓ Mitochondrial oxidative capacity	↓ ATP production ↓ Mitochondrial energetic metabolism	Normal LV size, wall thickness and mass	Diastolic dysfunction
↓$Ca2^{+}$ homeostasis	↓ Release of $Ca2^{+}$ from the SR ↓ SERCA activity by oxidative stress ↓ Myofilament $Ca2^{+}$ sensitivity	↓ Cardiac contractility	Substructural changes of myocytes	Diastolic dysfunction
↑PKC activation	↓NO availability ↑ ET-1 production Stimulates CTGF expression	↑ Endothelial dysfunction and ↑Cell permeability ↑Cardiac fibrosis	Myocellular hypertrophy and fibrosis	Diastolic dysfunction and normal or slightly decreased EF
↑AGE formation	Cross-links formation between AGEs and proteins AGE/RAGE binding stimulates: ↑TGFβ production ↑ ROS production	Fibrosis ↑Myocardial stiffness ↓Myocardial relaxation Oxidative stress Inflammation	Myocellular hypertrophy and fibrosis Slightly increase in LV mass, wall thickness or size	Diastolic dysfunction and normal or slightly decreased EF
↑Activation of RAS	↑ Production of AngII	↑Myocyte apoptosis ↑Interstitial fibrosis Oxidative stress Inflammation	Myocellular hypertrophy and fibrosis	Increase in LV mass, wall thickness or size

FFA, free fatty acids; PPAR proliferator-activated receptor α, ; TG, triglycerides; PKC, Protein kinase C; AGEs, advanced glycation endproducts; RAGE, AGE receptor; TGF, transforming growth factor ; ROS, reactive oxygen species; NO, nitric oxide; ET-1, endothelin-1; CTGF, connective tissue growth factor; LV, left ventricular; Ca2+, calcium; SR, sarcoplasmic reticulum; SERCA, sarco- (endo-) plasmic reticulum Ca2+ ATPase; RAS, rennin-angiotensin system; AngII, angiotensin II; ATP, adenosine triphosphate.

Table 2. Cellular mechanisms and effects of anti-diabetic agents in heart failure.

AGENT	CELLULAR MECHANISM	POSSIBLE CELLULAR EFFECTS IN CAD/HF
Metformin	AMP-kinase activation	↓ activity of carnitine palmitoyltransferase-1, a key regulator of FFA uptake in the mitochondria, ↑ myocardial glucose uptake and glycolysis
Thiazolidinediones	Nuclear transcription factor PPARγ activation	↑ fluid retention and edema ↓ angiotensin II levels ↓ blood pressure, ↑endothelial function ↓inflammation ↑HDL and ↓TG and LDLox
Sulphonylureas	KATP channels closure on β-cell membranes	possible implication of closure of cardiac potassium sensitive ATP channels ↑ body weight
Insulin	Insulin receptor activation	↑ MAPK activation mediating pro-inflammatory and mitogenic effects ↑ PI-3K activation mediating myocardial glucose uptake and glycolysis, NO production and anti-inflammatory effects ↑ body weight
GLP-1 agonists	GLP-1 receptor activation	Possible implication of the binding to cardiomyocytes and VSMCs receptors in the heart ↑glucose myocardial uptake via cAMP production ↓ body weight ↓ blood pressure ↑ inotropic effect
DPP-4 inhibitors	DPP-4 activity inhibition	↑BNP levels
SGLT2 inhibitors	Kidney SGLT2 inhibition	↓ fluid retention and edema ↓ blood pressure

AMP, adenosine monophosphate ; BNP, brain natriuretic peptide; cAMP, cyclic adenosine monophosphate; coronary vascular smooth muscle cells (VSMCs); DPP-4, dipeptidyl peptidase 4; FFA, free fatty acids; GLP-1glucagon-like peptide1; KATP, adenosine triphosphate-sensitive potassium; MAPK, mitogen activated protein kinase; PI-3K, phosphatidylinositol-kinase; PPARγ, peroxisome proliferator-activated receptor γ; SGLT-2, sodium-glucose cotransporter-2

BIOGRAPHICAL SKETCH

Alessandra Dei Cas obtained her medical degree with honors (1998) and Specialty in Endocrinology and Metabolic Diseases with honors (2003) at University of Parma, Italy. She attended for 3 years the Department of Diabetes, Endocrinology and Internal Medicine King's College, London (UK) as Research Associate (2001-2004). In 2007 she obtained her PhD at King's College, London (UK). Since 2006 she is Research Assistant in Endocrinology and Metabolic Diseases at University of Parma, Italy.

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