
Concomitant Diabetes Mellitus and Heart Failure

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Abstract: The prevalence of patients with concomitant diabetes mellitus (DM) and heart failure (HF) is growing exponentially. Patients with HF and DM show specific metabolic, neurohormonal, and structural heart abnormalities, which potentially contribute to worse HF outcomes than seen in patients without comorbid DM. Subgroup analysis of recent trials suggest that patients with HF and DM may respond differently to standard therapy, and 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, pointing to the need of developing specific medications to be tested in dedicated future studies to address the unique metabolic and hemodynamic alterations seen in these patients. (Curr Probl Cardiol 2015;40:7–43.)

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 DM¹ with an important epidemiologic, clinical, and economic influence. Patients with

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HF and DM show specific metabolic, neurohormonal, and structural heart abnormalities, which potentially contribute to worse outcomes than seen in patients without comorbid DM.^{2,3}

Notably, subgroup analyses of recent trials conducted in hospitalized patients with HF who had DM showed a different response to standard medication, with these patients being more prone to develop side effects than 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, 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.

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, increasing 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%-2% of individuals older than 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 effect as they do not adequately account for undiagnosed HF in patients with preserved EF or impaired fasting glucose.^{8,13}

Gary S. Francis: There are now emerging data that HF with preserved EF (HFpEF) also presents with multiple phenotypes, including metabolic abnormalities and coronary microvascular inflammation (Paulus WJ, Tschöpe C. *JACC* 2013; 62:263-271). Likewise, HFpEF, similarly to HF with reduced EF, is strongly associated with DM. Compared to nondiabetic 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 (LV) hypertrophy, a trend toward higher LV 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 DM,

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

HF is one of the most common reasons for hospital admission in those older than 65 years 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 a 1-year mortality rate of 30% and 5-year mortality rate up to 50%. One of the major reasons for this poor prognosis relates to the comorbid diseases including DM that adversely affect 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%-47%, depending on the specific characteristics of the cohort studied (eg, age, country, and severity of HF).¹⁷⁻²⁰ HF and DM association is particularly relevant in patients hospitalized for HF, as approximately 40% of patients with reduced EF have DM²¹ and DM is one of the noncardiac comorbidities associated with notably higher risks for both all-cause and HF-related preventable hospitalizations²² and rehospitalization.²³

In patients with DM, the prevalence of HF is between 9% and 22%, which is 4 times higher than that seen in the general population,²⁴ and DM is a risk factor for HF development especially in women (5-fold) than in 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 when compared with normal individuals or patients with coronary artery disease (CAD).

Pathophysiology

The pathophysiological basis of the relationship between HF and DM may involve several possible scenarios that further potentiate each other (Fig). DM may increase the risk of HF through increased risk for CAD and subsequent progression to postischemic 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.

Postischemic HF in Diabetes

Patients with DM show an increase of 2-4-folds in the relative risk of cardiovascular (CV) morbidity and mortality when compared with

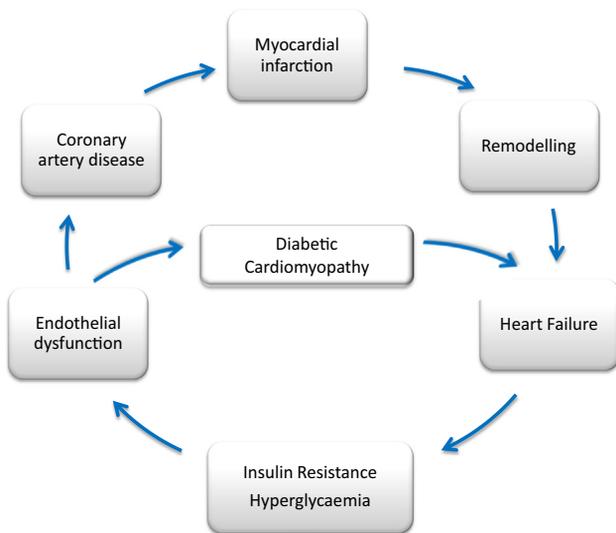


Fig. Pathophysiological links between diabetes and heart failure. (Color version of figure is available online.)

nondiabetic subjects.^{28,29} In a Finnish population-based study, the risk of acute myocardial infarction was 7-fold greater in patients with DM compared with patients without, with a similar risk to that of a nondiabetic 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 10-20 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.

Epidemiologic 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 DM³³ 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 in 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 with nondiabetic patients.²⁵ Other studies have consistently demonstrated that DM is a powerful risk factor for and accelerates the development of postmyocardial infarction HF,³⁵ likely because of a more limited capacity of LV remodeling.

Gary S. Francis: DM is arteriopathic through a number of mechanisms. These include reduced vascular nitric oxide, reduced prostacycline production, and enhanced endothelin, angiotensin II, tissue factor, 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.

HF-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, which in turn triggers HF in a vicious cycle.

Diabetic HF

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

Table 1. Connection between alterations, underlying mechanisms, and consequent functional and structural changes associated with diabetic cardiomyopathy

Alteration	Underlying mechanisms	Effects	Structural features	Functional features
↑ FFA concentration	↑ FFA uptake ↓ GLUT4 and glucose uptake ↑ PPAR α activation Accumulation of TG and DAG	↑ FFA oxidation ↓ Glucose oxidation Cardiolipotoxicity	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
↓ Ca ²⁺ homeostasis	↓ Release of Ca ²⁺ from the SR ↓ SERCA activity by oxidative stress ↓ Myofilament Ca ²⁺ sensitivity	↓ Cardiac contractility	Substructural changes in myocytes	Diastolic dysfunction
↑ PKC activation	↓ NO availability ↑ ET-1 production Stimulates CTGF expression	↑ Endothelial dysfunction ↑ Cell permeability ↑ Cardiac fibrosis	Myocellular hypertrophy and fibrosis	Diastolic dysfunction and normal or slightly decreased EF
↑ AGE formation	Cross-link formation between AGEs and proteins AGE/RAGE binding stimulates ↑ TGF β production ↑ ROS production	Fibrosis ↑ Myocardial stiffness ↓ Myocardial relaxation Oxidative stress Inflammation	Myocellular hypertrophy and fibrosis Slightly increased 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

AngII, angiotensin II; Ca²⁺, calcium; CTGF, connective tissue growth factor; DAG, diacylglycerol; ET-1, endothelin-1; NO, nitric oxide; PKC, protein kinase C; PPAR α proliferator-activated receptor α ; RAGE, AGE receptor; RAS, renin-angiotensin system; ROS, reactive oxygen species; SERCA, sarco-(endo-)plasmic reticulum Ca²⁺ ATPase; SR, sarcoplasmic reticulum; TG, triglycerides; TGF β , transforming growth factor- β .

synergistic pathologic 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](#).

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 long-standing, 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 β -oxidation produces more adenosine triphosphate (ATP) than glucose oxidation, it is less favorable owing to the significantly higher oxygen consumption and cardiac efficiency is reduced.⁴⁰ FFA myocardial uptake may exceed FFA β -oxidation capacity, leading to accumulation of triglycerides 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 (eg, 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 types 1 and 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: There are some data to suggest that the risk of HF could be lessened by tight control of HBA1c. Lind et al demonstrated that patients with a HA1c of at least 10.5% had a 4-fold greater risk of HF than those with a HA1c of less than 6.5% did (Lind M, Bounais I, Olsson M et al. *Lancet* published online June 25, 2011). However, strict glycemc control has not uniformly been demonstrated to reduce the onset of HF ([Section Treatment of Diabetes in Patients With HF](#)).

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)⁴⁹ and the predominance of the fetal β myosin heavy chain expression with respect to the α myosin heavy chain,⁵⁰ leading to depressed adenosine triphosphatase (ATPase) activity of myofibrils and reduced contractile force. In addition, alterations in sarco-(endo-)plasmic reticulum Ca^{2+} ATPase 2 activity, inefficient sequestration of Ca^{2+} in the sarcoplasmic reticulum resulting in Ca^{2+} 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 Ca^{2+} ATPase in the transgenic models has been shown to protect the heart against severe contractile dysfunction in diabetic patients.⁵¹ In addition, a perturbation in the function of the endoplasmic reticulum, a central organelle entrusted with Ca^{2+} homeostasis and protein folding and maturation, has been suggested to be involved in myocyte apoptosis.⁵²

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 end products (AGEs) resulting from the nonenzymatic glycation and oxidation of proteins and lipids, the activation of the protein kinase C-diacylglycerol signaling pathway, and increased levels of poly-(adenosine diphosphate [ADP]-ribose)polymerase enzymes that are involved in cellular processes including DNA repair and programmed cell death.⁵³

AGE accumulation in DM is known to induce myocardial alterations primarily by forming 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.⁵⁴ Secondly, soluble extracellular AGEs bind to their receptors, stimulating the upregulation of transforming growth factor- β an important prosclerotic factor⁵⁵ that has 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 resulted in improved diastolic function and reduced, myocyte hypertrophy, despite the persistence of hyperglycemia in a rodent model of diabetic diastolic dysfunction, suggesting that protein kinase C inhibition may represent a novel therapeutic strategy for the prevention of DM-associated cardiac dysfunction.⁵⁸ The activation of all the aforementioned hyperglycemic-induced pathways characterizes the middle stage of diabetic cardiomyopathy associated with myocellular hypertrophy and myocardial fibrosis that contribute to abnormal diastolic dysfunction and normal or slightly decreased EF.

RAAS 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 or proliferation, vascular inflammation, and oxidative damage.⁵⁹⁻⁶¹

Oxidative, Nitrosative, and Nitrate Stress. Hyperglycemia-induced pathway activation eventually results in the production of oxygen-derived oxidants from both mitochondrial and nonmitochondrial 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 that 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-1, which in turn induces the poly (ADP-ribosyl)ation of glyceraldehyde-3-phosphate dehydrogenase, resulting in nuclear factor- κ B, aldose reductase, and polyol pathway activation.⁶³ These effects are relevant in all stages of HF including LV hypertrophy, interstitial fibrosis, adverse remodeling after myocardial infarction, and myocyte apoptosis.⁵³

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

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 with a depressed baroreflex function leading to impaired regulation of heart rate variability, stroke volume, and blood pressure, which have been associated with both systolic and diastolic dysfunction. Patients with severe cardiac autonomic neuropathy may have distal sympathetic denervation associated with proximal ventricular islands of hyperinnervation that result in myocardial regions that are electrically unstable. 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 most deaths being related to macrovascular diseases and being sudden and unexpected.⁷² These results have also been confirmed in the Action to Control Cardiovascular Risk in Diabetes 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 nondiabetic patients with HF, sympathetic activation occurs in the later HF stages and leads to insulin resistance. On the contrary, 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.

Clinical Phenotypes of Diabetic HF

Diastolic Dysfunction

The most frequent and earliest functional abnormality seen in the heart of diabetic patients 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-thirds had impaired relaxation and one-third pseudonormalization of mitral inflow on Doppler echocardiography.⁷⁶ It is of note that patients with diastolic dysfunction were young (mean age 43 years), 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 these conditions were present.⁷⁶

Subjects with type 2 DM are more susceptible to preclinical diastolic and systolic dysfunction than patients with type 1 disease,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 they receive exogenous insulin, making them metabolically similar to patients with type 2 DM.

Gary S. Francis: Both stiff cardiac myocytes and fibrosis contribute to LV 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 HF and HFpEF, is clearly complex and multifactorial. Clearly, diastolic dysfunction is a primary feature of diabetic HF.

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 2-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

Response to Stress Tests

Latent LV dysfunction in the heart of diabetic patients, 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 with 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.

HF Progression and Prognosis

Long-standing 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 toward significantly increased LV size and 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 with DM who were older than 65 years of age, HF was associated with a mortality rate of 32.7 per 100 person-years compared with 3.7 per 100 person-years among those with DM who remained free of HF.⁸³ Among hospitalized patients with HF, 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 postdischarge mortality and rehospitalizations compared with 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 in which each 1% increase in glycosylated hemoglobin was associated with an 8% increased risk of HF.⁸⁷

HF Screening in the Population With DM

The higher morbidity and mortality observed in patients with HF and DM mandate its early identification to initiate adequate treatments and delay disease progression. Currently, there is no single imaging, biomarker, or histologic finding that is pathognomonic for diabetic cardiomyopathy. In the Studies of Left Ventricular Dysfunction 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. Using 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 to select patients for echocardiographic evaluation, but it is not sensitive enough for early detection of preclinical myocardial dysfunction.⁹⁰ Furthermore, plasma brain natriuretic peptide levels have been found to be significantly higher in patients with HF who had DM than in the nondiabetic patients at the same HF score⁹¹; 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 patients with HF who have DM is not clear; proposed mechanisms include an increase in brain natriuretic peptide formation or a decrease in degradation due to hyperglycemia, cardiac autonomic dysfunction,⁹² or higher RAAS activation compared with nondiabetic patients.

Other biomarkers of interest are those related to the synthesis or degradation of types I and III fibrillar collagens (serum aminoterminal

propeptide of types I and 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 been 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 stages A through D.⁹⁷ Patients with DM who do not yet demonstrate LV dysfunction would be considered under stage A. As patients move through stages B-D, they develop structural changes, symptoms, and then refractory end-stage disease.

Importantly, patients with HF 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 and IV.

Treatment of HF in Patients With Diabetes

Results from subgroup analyses of recent trials suggest that patients with HF who have DM might not respond equally to standard treatment being more prone to develop drug side effects⁴ or having divergent trends in response to some drugs compared with patients with HF who do not have 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 patients with HF, and similarly patients with HF who have reduced EF must be differentiated from those with preserved EF. These distinctions are important and underlay different degree of hemodynamic and neuro-hormonal abnormalities, distinct clinical characteristics, varying risks for adverse outcomes, and dissimilar efficacy of existing therapies. Similarly, patients with DM are heterogeneous in 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 targets and therapeutic strategies.⁹⁸ Finally, drug interactions might blunt clinical efficacy and favor side-effect occurrence or HF precipitation.

RAAS Inhibition

The RAAS is overactivated 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 and myocardial and renal fibrosis and predispose to oxidative stress, inflammation, thrombosis, and sudden cardiac death.⁹⁹⁻¹⁰¹

Angiotensin-converting enzyme inhibitors (ACE-Is) show similar effects in patients with HF with or without DM¹⁰²⁻¹⁰⁵ and long-term high dose of lisinopril was as effective and well-tolerated in patients with HF who have DM.¹⁰⁶ These effects were also confirmed 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 to be useful in preventing the development of HF in patients with DM¹⁰⁸ and substantial clinical evidence points to a positive effect 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 morbidity¹¹⁰ and Valsartan Heart Failure Trial¹¹¹ studies, ARB use was not as effective in the DM subgroup.

Guidelines recommend that treatment with ACE-I/ARBs in patients with DM 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.¹¹² Data suggest that patients with HF who have DM may also receive great benefit from mineral receptor antagonist therapy.¹¹³ The rationale for mineral receptor antagonist use in addition to ACE-I/ARBs is the synergistic increase in plasma renin activity and the aldosterone escape phenomenon that could reduce the expected ACE-I/ARB therapy benefits. In addition, DM¹¹⁴ and HF¹¹⁵ are characterized by a maladaptive mineralocorticoid 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.¹¹⁶ In post-myocardial infarction patients with reduced LVEF, eplerenone added to standard therapy reduced the mean length and total days of HF hospitalizations when compared with placebo in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study with no significant mortality differences between patients with and without DM.¹¹⁷ Although mineral receptor antagonists have been demonstrated to be highly effective in patients with HF, their use in combination with ACE-I or ARBs in patients with HF who have concomitant DM has been constrained by the concern of renal function worsening, elevation in creatinine, and risk of hyperkalemia.¹¹² 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 ACE-Is, 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 in comparison with the use of a 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 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 rehospitalizations.⁵ A potential explanation for the possible negative effects of aliskiren in patients with DM is increased adverse events, including severe hyperkalemia (serum potassium ≥ 6.0 mmol/L, 9.7% vs 4.7% in DM with aliskiren vs placebo) with concomitant ACE-I/ARB

(85%) and mineralocorticoid receptor antagonist (55%) therapy. A second possible mechanism is the differential effect on neurohormonal profiles in patients with DM with differential effects in the RAAS cascade. It should be noted that these results should be interpreted with caution and viewed in the context of a subgroup analysis on a secondary end point, highlighting the need of further dedicated trials in patients with DM and HF.

β-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 system, which is characteristically overactivated in both conditions. Therefore, therapy with β-blockers should be prescribed also in HF patients with DM,¹¹² unless specifically contraindicated. Subgroup analyses of trials conducted in patients with advanced HF have shown that β-blockers are as effective in reducing all-cause mortality¹²¹⁻¹²³ and hospitalization rates for HF in patients with and without DM.^{124,125} These results were also confirmed by a recent meta-analysis.¹²⁶

Administration of the β-blocker carvedilol 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 DM¹²⁷ and an identical reduction of morbidity and mortality in the subgroup of patients with DM, even in the condition of severe symptomatic HF.¹²⁸

In relation to which β-blocker should be used in patients with HF who have 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 suggested that the combined alpha and β blocker carvedilol was more beneficial compared with the selective beta 1 antagonist metoprolol in reducing mortality in patients with HF, 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

Diuretics

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

Treatment of Diabetes in Patients With HF

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 been shown to enhance myocardial contractility parameters likely because of 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 trial, strict glycemic control was not associated with a reduced onset of HF,¹³¹ and in the Diabetes Mellitus and Diastolic Dysfunction study, neither insulin nor oral agent therapy was associated with an improvement in diastolic function, despite a reduction in the level of 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 populations such as those with HF. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, plasma glucose concentration ≤ 4.5 mmol/L (hypoglycemia) proved to be a strong predictor of all-cause death (hazard ratio = 1.38, 95% CI: 0.06-1.81) in patients with HF following acute myocardial infarction during long-term follow-up.¹³⁴ Combination therapy with several antidiabetic agents 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.

Metformin

Metformin is recognized as the first-line agent in type 2 DM.¹¹² It improves insulin sensitivity by reducing hepatic glucose production and enhancing peripheral glucose uptake. There is robust evidence that metformin use improves outcome in patients with HF compared with 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 patients with HF.^{136,137} Recently, it has been suggested that beneficial CV effects of

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

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 PPAR γ activation	↑ Fluid retention and edema ↓ Angiotensin II levels ↓ Blood pressure, ↑ Endothelial function ↓ Inflammation ↑ HDL and ↓ TG and LDLox
Sulfonylureas	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 proinflammatory 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
SGLT-2 inhibitors	Kidney SGLT-2 inhibition	↓ Fluid retention and edema ↓ Blood pressure

BNP, brain natriuretic peptide; cAMP, cyclic adenosine monophosphate; DPP-4, dipeptidyl-peptidase 4; GLP-1, glucagonlike peptide-1; HDL, high-density lipoprotein; KATP, adenosine triphosphate-sensitive potassium; LDLox, oxidized low-density lipoprotein; MAPK, mitogen-activated protein kinase; PI-3K, phosphatidylinositol kinase; PPAR γ , peroxisome proliferator-activated receptor γ ; SGLT-2, sodium-glucose cotransporter-2; TG, triglyceride; VSMCs, coronary vascular smooth muscle cells.

metformin might be mediated by adenosine monophosphate (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 Food and Drug Administration has recently withdrawal this

contraindication and now metformin can be used in patients with HF 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 rehospitalization rate compared to insulin or sulphonylureas.¹⁴¹

Thiazolidinediones

Thiazolidinediones (TZDs) are synthetic ligands of the nuclear peroxisome proliferator-activated receptor γ that modulate the expression of genes involved in insulin sensitivity. They exert an 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 been shown to improve diastolic function and LV compliance.¹⁴³ A systematic review and meta-analysis of controlled trials demonstrated a reduced all cause mortality but an increased risk of hospital admission for HF in patients treated with pioglitazone as compared with those treated with metformin, sulphonylureas, and insulin.¹³⁶ The clinical use of TZDs 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 in 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 TZDs be used with caution in patients under New York Heart Association functional Classes I and II but generally avoided in patients with symptomatic HF.¹⁴¹

Sulphonylureas

Sulphonylureas stimulate β -cell insulin release by binding to the pancreatic Sulphonylurea receptor 1 and closing the ATP-sensitive

potassium channels. It has been suggested that Sulphonylureas that show considerable affinity for cardiac subtypes of sulfonylurea 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, although¹⁴⁶ this topic is still a matter of debate. In the United Kingdom Prospective Diabetes study, the use of sulphonylureas was not associated with an increased risk of HF,¹⁴⁷ and a recent study conducted in diabetic patients with HF showed no considerable difference in mortality risk with different sulphonylureas.¹⁴⁸ In contrast, results from a retrospective cohort study showed a 18%-30% excess risk for HF of second generation sulphonylureas compared with metformin,¹⁴⁹ and these results were also confirmed in a large retrospective cohort study of adults without HF.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 CV outcomes in patients with HF.¹⁴⁸

Insulin

Whether the use of insulin in patients with HF and type 2 DM is associated with an increased risk of HF is still controversial. Insulin-treated patients showed a significantly worse prognosis compared to non-insulin treated and paradoxically tight glycemic control was associated with improved survival in diabetic patients with advanced HF^{151,152} However, it should be emphasized that insulin therapy may just be a surrogate marker of patients with a longer disease duration or greater microvascular and macrovascular disease in type 2 DM. In the Outcome Reduction with an Initial Glargine Intervention trial, insulin glargine treatment did not increase the risk of HF vs standard care at 6 years follow-up.¹⁵³

Glucagon-like Peptide-1 Agonists

The incretin hormone glucagon-like peptide-1 is released by intestinal L-cells in response to a meal and is rapidly degraded by the enzyme dipeptidyl-peptidase 4. It exerts its hypoglycemic effects by stimulating β -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 AMP production.¹⁵⁴ These effects have been implicated in the beneficial action

of Glucagon-like peptide-1 on preischemic 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.¹⁵⁸⁻¹⁶⁰ Continuous administration of glucagonlike peptide-1 for 5 weeks in HF patients without DM significantly improved LVEF and quality of life.¹⁶¹ Furthermore, a retrospective analysis of a large database¹⁶² and a meta-analysis of randomized studies¹⁶³ have suggested no substantial CV risk increase in patients treated with the Glucagon-like peptide-1 agonist exenatide as compared with those treated with other antidiabetic drugs. Studies are underway to investigate glucagonlike peptide-1 agonists to improve HF (Functional Impact of Glucagon-like peptide-1 for Heart Failure Treatment ClinicalTrials.gov Identifier: [NCT01800968](https://clinicaltrials.gov/ct2/show/study/NCT01800968)).

Dipeptidyl-Peptidase 4 Inhibitors

Dipeptidyl-peptidase 4 inhibitors are becoming important oral anti-hyperglycemic agents, a recommended therapeutic option when glycemic control cannot be achieved with metformin or first-line therapy where metformin is contraindicated.⁹⁸ Recently, the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus Thrombolysis in Myocardial Infarction-53 trial reported a significant increase in the risk of hospitalizations for HF in patients treated with saxagliptin compared with those given 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 trial showed no significant excess of HF in the HF arm given the dipeptidyl-peptidase 4 inhibitor alogliptin.¹⁶⁴ A recent meta-analysis conducted to assess the effect of this class of agents on the incidence of acute HF that 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 or active comparators (odds ratio = 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 end points in DM trials. Ongoing trials including Exenatide Study of Cardiovascular Event Lowering and Sitagliptin Cardiovascular Outcome Study trials,

which include prespecified end points of HF hospitalization and will add knowledge to these previous findings.

Sodium-Glucose Cotransporter-2 Inhibitors

Inhibition of sodium-glucose cotransporter-2 in the proximal kidney tubule represents a novel strategy that 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 Although a benefit is expected from blood pressure and weight reduction, long-term studies are required to demonstrate the effect 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.

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 utilization¹⁶⁸ 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 nondiabetics with HF. Etomoxir 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 etomoxir in patients with HF was stopped prematurely owing to an elevation in the levels of 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 patients with HF.¹⁷⁰ The anti-ischemic agent trimetazidine has been shown to improve EF in patients with HF likely owing to a stimulation of glucose oxidation secondary to inhibition of long-chain 3-ketoacyl coenzyme A thiolase, the last enzyme involved in mitochondrial FFA oxidation.^{171,172} A recent meta-analysis has shown that additional use of trimetazidine in patients with HF 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 trial showed a greater antianginal effect of ranolazine in patients with CAD and stable angina and DM.¹⁷⁶ The mechanisms behind the antidiabetic effects of ranolazine are unclear, but 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 exercise¹⁷⁹ to increase energy production. Dysregulated AMP-activated protein kinase activation has been hypothesized as a possible underlying mechanism 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 pharmacologic manipulations for patients.

Conclusions

DM and HF are interrelated 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 pathologic 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 patients with HF and DM 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 as many contemporary therapies used for DM are contraindicated or limited by comorbidities such as renal dysfunction. Subgroup analyses of recent trials conducted in hospitalized patients with HF who have DM showed a different response to standard medication being more prone to develop side effects compared with 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 a specific class of antidiabetic agents. These data should be cautiously interpreted in the context of post hoc analyses; however, they 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 patients with DM.

Gary S. Francis: This excellent review of DM and HF by Dei Cas and colleagues has much updated information for the clinician about the interaction of these 2 epidemics. It is now reasonably clear that DM is associated with both systolic and diastolic HF, independent of associated CAD. Multiple complex mechanisms are operative, and there is no highly specific therapy. Some of the newer drugs used for the treatment of DM, especially the thiazolidines, may actually cause excessive fluid retention, thus mimicking or even causing the syndrome of HF. Whether these newer antidiabetic drugs may actually worsen the contractile performance of the heart is not yet particularly clear. One thing that is clear, the comorbid condition of DM complicates the management of these patients with HF and is likely responsible for some of the very high readmission rates being reported. The growing 2-way coassociation between HF and DM requires that cardiologists and others caring for patients with HF must be increasingly familiar with the management of DM.

REFERENCES

1. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;27:2725-36.
2. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699-703.
3. Sarma S, Mentz RJ, Kwasny MJ, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. *Eur J Heart Fail* 2013;15:194-202.
4. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of alicikiren for type 2 diabetes. *N Engl J Med* 2012;367:2204-13.

5. Gheorghiadu M, Böhm M, Greene SJ, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *J Am Med Assoc* 2013;309:1125-35.
6. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317-26.
7. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis* 2014;24:689-97.
8. Thrainsdottir IS, Aspelund T, Thorgeirsson G, et al. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care* 2005;28:612-6.
9. *National Heart Lung and Blood Institute*. People Science Health. What is heart failure? (<http://www.nhlbi.nih.gov/health/health-topics/topics/hf/>); Accessed February 2012.
10. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414-31.
11. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047-53.
12. Bonow RO, Gheorghiadu M. The diabetes epidemic: a national and global crisis. *Am J Med* 2004;116(suppl 5A):2S-10S.
13. Davies M, Hobbs F, Davis R, et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001;358:439-44.
14. Hall MJ, DeFrances CJ, Williams SN, Golosinskiy A, Schwartzman A. National Hospital Discharge Survey: 2007 summary. National health statistics reports; no 29. Hyattsville, MD: National Center for Health Statistics. (<http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf>); 2010.
15. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377-85.
16. De Groote P, Lamblin N, Mouquet F, et al. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. *Eur Heart J* 2004;25:656-62.
17. The CONSENSUS trial study group. Effect of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316:1429-35.
18. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, et al. Diabetes in heart failure: prevalence and impact on outcome in the population. *Am J Med* 2006;119:591-9.
19. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 1996;77:1017-20.
20. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme —a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;24:442-6.

21. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149:209-16.
22. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003;42:1226-33.
23. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2007;154:277.e1-e8.
24. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879-84.
25. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29-34.
26. Amato L, Paolisso G, Cacciatore F, et al. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. The Osservatorio Geriatrico Regione Campania Group. *Diabetes Metab* 1997;23:213-8.
27. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007;115:3213-23.
28. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-34.
29. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-44.
30. Norhammar A, Malmberg K, Diderholm E, et al. Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. *J Am Coll Cardiol* 2004;43:585-91.
31. UK Prospective Diabetes Study Group. UK prospective diabetes study 16: overview of 6 years of therapy of type II diabetes: a progressive disease. *Diabetes* 1995;44:1249-58.
32. Zavaroni I, Bonini L, Gasparini P, et al. Hyperinsulinemia in a normal population as a predictor of non-insulin-dependent diabetes mellitus, hypertension, and coronary heart disease: the Barilla factory revisited. *Metab Clin Exp* 1994;48:989-94.
33. Moreno PR, Murcia AM, Palacios IF, et al. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation* 2000;102:2180-4.
34. Silva JA, Escobar A, Collins TJ, Ramee SR, White CJ. Unstable angina: a comparison of angioscopic findings between diabetic and nondiabetic patients. *Circulation* 1995;92:1731-6.

35. Murcia AM, Hennekens CH, Lamas GA, et al. Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. *Arch Intern Med* 2004;164:2273-9.
36. Karason K, Sjöström L, Wallentin I, Peltonen M. Impact of blood pressure and insulin on the relationship between body fat and left ventricular structure. *Eur Heart J* 2003;24:1500-5.
37. Dei Cas A, Spigoni V, Ridolfi V, Metra M. Diabetes and chronic heart failure: from diabetic cardiomyopathy to therapeutic approach. *Endocr Metab Immune Disord Drug Targets* 2013;13:38-50.
38. Herrero P, Peterson LR, McGill JB, Matthew S, Lesniak D, Dence C. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. *J Am Coll Cardiol* 2006;47:598-604.
39. Buchanan J, Mazumder PK, Hu P, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology* 2005;146:5341-9.
40. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation* 2004;109:2191-6.
41. Sharma S, Adroque JV, Golfman L, et al. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. *FASEB J* 2004;18:1692-700.
42. Wang CN, O'Brien L, Brindley DN. Effects of cell-permeable ceramides and tumor necrosis factor- α on insulin signaling and glucose uptake in 3T3-L1 adipocytes. *Diabetes* 1998;47:24-31.
43. Marcovina SM, Sirtori C, Peracino A, et al. Translating the basic knowledge of mitochondrial functions to metabolic therapy: role of L-carnitine. *Transl Res* 2013;161:73-84.
44. Boudina S, Abel ED. Mitochondrial uncoupling: a key contributor to reduced cardiac efficiency in diabetes. *Physiology (Bethesda)* 2006;21:250-8.
45. Boudina S, Sena S, O'Neill BT, Tathireddy P, Young ME, Abel ED. Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity. *Circulation* 2005;112:2686-95.
46. Shen X, Zheng S, Thongboonkerd V, et al. Cardiac mitochondrial damage and biogenesis in a chronic model of type 1 diabetes. *Am J Physiol Endocrinol Metab* 2004;287:E896-905.
47. Metzler B, Schocke MF, Steinboeck P, et al. Decreased high-energy phosphate ratios in the myocardium of men with diabetes mellitus type I. *J Cardiovasc Magn Reson* 2002;4:493-502.
48. Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ, Neuffer PD. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. *J Am Coll Cardiol* 2009;54:1891-8.
49. Rupp H, Elimban V, Dhalla NS. Modification of myosin isozymes and SR Ca(2+)-pump ATPase of the diabetic rat heart by lipid-lowering interventions. *Mol Cell Biochem* 1994;132:69-80.

50. Malhotra A, Sanghi V. Regulation of contractile proteins in diabetic heart. *Cardiovasc Res* 1997;34:34-40.
51. Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH. Over-expression of the sarcoplasmic reticulum Ca(2)-ATPase improves myocardial contractility in diabetic cardiomyopathy. *Diabetes* 2002;51:1166-71.
52. Xu J, Zhou Q, Xu W, Cai L. Endoplasmic reticulum stress and diabetic cardiomyopathy. *Exp Diabetes Res* 2012;2012:827-71.
53. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev* 2004;25:543-67.
54. Hartog JW, Voors AA, Bakker SJ, Smit AJ, van Veldhuisen DJ. Advanced glycation end-products (AGEs) and heart failure: pathophysiology and clinical implications. *Eur J Heart Fail* 2007;9:1146-55.
55. Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. The AGE/RAGE pathway in vascular disease and diabetes mellitus. Part I. The AGE-concept. *Cardiovasc Res* 1998;37:586-600.
56. Bierhaus A, Schiekofer S, Schwaninger M, et al. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* 2001;50:2792-808.
57. Way KJ, Isshiki K, Suzuma K, et al. Expression of connective tissue growth factor is increased in injured myocardium associated with protein kinase C beta2 activation and diabetes. *Diabetes* 2002;51:2709-18.
58. Connelly KA, Kelly DJ, Zhang Y, et al. Inhibition of protein kinase C-beta by ruboxistaurin preserves cardiac function and reduces extracellular matrix production in diabetic cardiomyopathy. *Circ Heart Fail* 2009;2:129-37.
59. He Z, Way KJ, Arikawa E, et al. Differential regulation of angiotensin II-induced expression of connective tissue growth factor by protein kinase C isoforms in the myocardium. *J Biol Chem* 2005;280:15719-26.
60. Fiordaliso F, Cuccovillo I, Bianchi R, et al. Cardiovascular oxidative stress is reduced by an ACE inhibitor in a rat model of streptozotocin-induced diabetes. *Life Sci* 2006;79:121-9.
61. Liu X, Suzuki H, Sethi R, Tappia PS, Takeda N, Dhalla NS. Blockade of the renin-angiotensin system attenuates sarcolemma and sarcoplasmic reticulum remodeling in chronic diabetes. *Ann N Y Acad Sci* 2006;1084:141-54.
62. Pacher P, Szabó C. Role of peroxynitrite in the pathogenesis of cardiovascular complications of diabetes. *Curr Opin Pharmacol* 2006;6:136-41.
63. Pacher P, Liaudet L, Soriano FG, Mabley JG, Szabó É, Szabó. C. The role of poly (ADP-ribose) polymerase in the development of myocardial and endothelial dysfunction in diabetes mellitus. *Diabetes* 2002;51:514-21.
64. Adameova A, Dhalla NS. Role of microangiopathy in diabetic cardiomyopathy. *Heart Fail Rev* 2014;19:25-33.
65. Marti CN, Gheorghiane M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. *J Am Coll Cardiol* 2012;60:1455-69.
66. Strauer BE, Motz W, Vogt M, Schwartzkopff B. Impaired coronary flow reserve in NIDDM: a possible role for diabetic cardiomyopathy in humans. *Diabetes* 1997;46:S119-24.

67. Ziegler D. Diagnosis and treatment of diabetic autonomic neuropathy. *Curr Diab Rep* 2001;1:216-27.
68. DCCT. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998;41:416-23.
69. Axelrod S, Lishner M, Oz O, Bernheim J, Ravid M. Spectral analysis of fluctuations in heart rate: an objective evaluation of autonomic nervous control in chronic renal failure. *Nephron* 1987;45:202-6.
70. Drake-Holland AJ, Van der Vusse GJ, Roemen TH, et al. Chronic catecholamine depletion switches myocardium from carbohydrate to lipid utilisation. *Cardiovasc Drugs Ther* 2001;15:111-7.
71. Schrauwen P, Hoeks J, Hesselink MK. Putative function and physiological relevance of the mitochondrial uncoupling protein-3: involvement in fatty acid metabolism? *Prog Lipid Res* 2006;45:17-41.
72. Rathmann W, Ziegler D, Jahnke M, Haastert B, Gries FA. Mortality in diabetic patients with cardiovascular autonomic neuropathy. *Diabet Med* 1993;10:820-4.
73. Pop-Busui R, Evans GW, Gerstein HC, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010;33:1578-84.
74. Piccini JP, Klein L, Gheorghiane M, Bonow RO. New insights into diastolic heart failure: role of diabetes mellitus. *Am J Med* 2004;116(suppl 5A):64S-75S.
75. Boyer JK, Thanigaraj S, Schechtman KB, Pérez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *Am J Cardiol* 2004;93:870-5.
76. Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA. Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. *Am J Cardiol* 2001;87:320-3.
77. Liu JE, Palmieri V, Roman MJ, et al. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. *J Am Coll Cardiol* 2001;37:1943-9.
78. Astorri E, Fiorina P, Contini GA, et al. Isolated and preclinical impairment of left ventricular filling in insulin-dependent and non-insulin-dependent diabetic patients. *Clin Cardiol* 1997;20:536-40.
79. Raev DC. Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients. *Diabetes Care* 1994;17:633-9.
80. Fonseca CG, Dissanayake AM, Doughty RN, et al. Three-dimensional assessment of left ventricular systolic strain in patients with type 2 diabetes mellitus, diastolic dysfunction, and normal ejection fraction. *Am J Cardiol* 2004;94:1391-5.
81. Jellis CL, Stanton T, Leano R, Martin J, Marwick TH. Usefulness of at rest and exercise hemodynamics to detect subclinical myocardial disease in type 2 diabetes mellitus. *Am J Cardiol* 2011;107:615-21.
82. Metra M, Zacà V, Parati G, et al. Cardiovascular and noncardiovascular comorbidities in patients with chronic heart failure. *J Cardiovasc Med (Hagerstown)* 2011;12:76-84.

83. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699-703.
84. Parissis JT, Rafouli-Stergiou P, Mebazaa A, et al. Acute heart failure in patients with diabetes mellitus: clinical characteristics and predictors of in-hospital mortality. *Int J Cardiol* 2012;157:108-13.
85. Nodari S, Manerba A, Vaccari A, et al. Six-year prognosis of diabetic patients with coronary artery disease. *Eur J Clin Invest* 2012;42:376-83.
86. Gustafsson I, Brendorp B, Seibaek M, et al. Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004;43:771-7.
87. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;103:2668-73.
88. Bourassa MG, Gurné O, Bangdiwala SI, et al. Natural history and patterns of current practice in heart failure. *J Am Coll Cardiol* 1993;22:14A-9A.
89. Bhalla MA, Chiang A, Epshteyn VA, et al. Prognostic role of B-type natriuretic peptide levels in patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 2004;44:1047-52.
90. Fang ZY, Schull-Meade R, Leano R, Mottram PM, Prins JB, Marwick TH. Screening for heart disease in diabetic subjects. *Am Heart J* 2005;149:349-54.
91. Peng Q, Hu W, Su H, Yang Q, Cheng X. Levels of B-type natriuretic peptide in chronic heart failure patients with and without diabetes mellitus. *Exp Ther Med* 2013;5:229-32.
92. Yufu K, Takahashi N, Nakagawa M, Hara M, Saikawa T, Yoshimatsu H. Brain natriuretic peptide and cardiac autonomic function in type 2 diabetic patients. *Diabetes Res Clin Pract* 2006;72:12-9.
93. Maya L, Villarreal FJ. Diagnostic approaches for diabetic cardiomyopathy and myocardial fibrosis. *J Mol Cell Cardiol* 2010;48:524-9.
94. Ihm SH, Youn HJ, Shin DI, et al. Serum carboxy-terminal propeptide of type I procollagen (PIP) is a marker of diastolic dysfunction in patients with early type 2 diabetes mellitus. *Int J Cardiol* 2007;122:e36-8.
95. Ban C, Twigg S. Fibrosis in diabetes complications: pathogenic mechanisms and circulating and urinary markers. *Vasc Health Risk Manag* 2008;4:575-96.
96. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539-50.
97. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*, 53; e1-90.
98. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes

- Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364-79.
99. Brunner HR. Experimental and clinical evidence that angiotensin II is an independent risk factor for cardiovascular disease. *Am J Cardiol* 2001;87:3C-9C.
 100. Rajagopalan S, Duquaine D, King S, Pitt B, Patel P. Mineralocorticoid receptor antagonism in experimental atherosclerosis. *Circulation* 2002;105:2212-6.
 101. Struthers AD. Aldosterone-induced vasculopathy: a new reversible cause of cardiac death. *J Renin Angiotensin Aldosterone Syst* 2001;2:211-4.
 102. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
 103. Moyé LA, Pfeffer MA, Wun CC. Uniformity of captopril benefit in the SAVE Study: subgroup analysis. *Survival and Ventricular Enlargement Study*. *Eur Heart J* 1994;15 (suppl B):2-8. [26-30].
 104. Gustafsson I, Torp-Pedersen C, Køber L, Gustafsson F, Hildebrandt P, Trace Study Group. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. *J Am Coll Cardiol* 1999;34:83-9.
 105. Borghi C, Ambrosioni E, Magnani B, The SMILE Study Investigators. Survival of Myocardial Infarction Long-term Evaluation. Effects of the early administration of zofenopril on onset and progression of congestive heart failure in patients with anterior wall acute myocardial infarction. *Am J Cardiol* 1996;78: 317-22.
 106. Ryden L, Armstrong PW, Cleland JG, et al. Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. *Eur Heart J* 2000;21:1967-78.
 107. Carr AA, Kowey PR, Devereux RB, et al. Hospitalizations for new heart failure among subjects with diabetes mellitus in the RENAAL and LIFE studies. *Am J Cardiol* 2005;96:1530-6.
 108. Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 2003;138:542-9.
 109. Abuissa H, Jones PG, Marso SP, O'Keefe JH Jr. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005;46:821-6.
 110. Young JB, Dunlap ME, Pfeffer MA, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004;110:2618-26.
 111. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
 112. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. *N Engl J Med* 2004;351:543-51.

113. Vardeny O, Wu DH, Desai A, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol* 2012;60:2082-9.
114. Kosugi T, Heinig M, Nakayama T, Matsuo S, Nakagawa T. eNOS knockout mice with advanced diabetic nephropathy have less benefit from reninangiotensin blockade than from aldosterone receptor antagonists. *Am J Pathol* 2010;176:619-29.
115. Ohtani T, Ohta M, Yamamoto K, et al. Elevated cardiac tissue level of aldosterone and mineralocorticoid receptor in diastolic heart failure: beneficial effects of mineralocorticoid receptor blocker. *Am J Physiol Regul Integr Comp Physiol* 2007;292:R946-54.
116. Barnes BJ, Howard PA. Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure. *Ann Pharmacother* 2005;39:68-76.
117. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309-21.
118. Preiss D, van Veldhuisen DJ, Sattar N, et al. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Eur J Heart Fail* 2012;14:909-15.
119. Jacob S, Rett K, Henriksen EJ. Antihypertensive therapy and insulin sensitivity: do we have to redefine the role of beta-blocking agents? *Am J Hypertens* 1998;11:1258-65.
120. Gheorghide M, Goldstein S. Beta-blockers in the post-myocardial infarction patient. *Circulation* 2002;106:394-8.
121. Domanski M, Krause-Steinrauf H, Deedwania P, et al. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol* 2003;42:914-22.
122. Deedwania PC, Giles TD, Klibaner M, et al. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005;149:159-67.
123. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;106:2194-9.
124. Bobbio M, Ferrua S, Opasich C, et al. Survival and hospitalization in heart failure patients with or without diabetes treated with beta-blockers. *J Card Fail* 2003;9:192-202.
125. Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Eur J Heart Fail* 2001;3:469-79.
126. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol* 2003;41:1529-38.

127. Nodari S, Metra M, Dei Cas A, Dei Cas L. Efficacy and tolerability of the long-term administration of carvedilol in patients with chronic heart failure with and without concomitant diabetes mellitus. *Eur J Heart Fail* 2003;5:803-9.
128. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.
129. Torp-Pedersen C, Metra M, Charlesworth A, et al. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007;93:968-73.
130. von Bibra H, Hansen A, Dounis V, Bystedt T, Malmberg K, Rydén L. Augmented metabolic control improves myocardial diastolic function and perfusion in patients with non-insulin dependent diabetes. *Heart* 2004;90:1483-4.
131. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.
132. Sorajja P, Chareonthaitawee P, Rajagopalan N, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. *Circulation* 2005;112:1311-6.
133. Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. *Am J Physiol Endocrinol Metab* 2001;281:E1115-21.
134. Ukena C, Dobre D, Mahfoud F, et al. Hypo- and hyperglycemia predict outcome in patients with left ventricular dysfunction after acute myocardial infarction: data from EPHEBUS. *J Card Fail* 2012;18:439-45.
135. Eurich DT, Majumdar SR, McAlister FA, et al. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care* 2005;28:2345-51.
136. Eurich DT, McAlister FA, Blackburn DF, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *Br Med J* 2007;335:497.
137. MacDonald MR, Eurich DT, Majumdar SR, et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. *Diabetes Care* 2010;33:1213-8.
138. Ouyang J, Parakhia RA, Ochs RS. Metformin activates AMP kinase through inhibition of AMP deaminase. *J Biol Chem* 2011;286:1-11.
139. Dyck JR, Lopaschuk GD. AMPK alterations in cardiac physiology and pathology: enemy or ally? *J Physiol* 2006;574:95-112.
140. Shah DD, Fonarow GC, Horwich TB. Metformin therapy and outcomes in patients with advanced systolic heart failure and diabetes. *J Card Fail* 2010;16:200-6.
141. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 2005;111:583-90.
142. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet* 2005;366:1279-89.
143. Horio T, Suzuki M, Suzuki K, et al. Pioglitazone improves left ventricular diastolic function in patients with essential hypertension. *Am J Hypertens* 2005;18:949-57.

144. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298:1180-8.
145. Giles TD, Miller AB, Elkayam U, Bhattacharya M, Perez A. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail* 2008;14:445-52.
146. Lefer DJ, Nichols CG, Coetzee WA. Sulfonylurea receptor 1 subunits of ATP-sensitive potassium channels and myocardial ischemia/reperfusion injury. *Trends Cardiovasc Med* 2009;19:61-7.
147. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
148. Andersson C, Gislason GH, Jørgensen CH, et al. Comparable long-term mortality risk associated with individual sulfonylureas in diabetes patients with heart failure. *Diabetes Res Clin Pract* 2011;94:119-25.
149. Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *Br Med J* 2009;339:b4731.
150. McAlister FA, Eurich DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. *Eur J Heart Fail* 2008;10:703-8.
151. Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. *Am Heart J* 2005;149:168-74.
152. Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 2006;151:91.
153. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319-28.
154. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation* 2008;117:2340-50.
155. Zhao T, Parikh P, Bhashyam S, et al. Direct effects of glucagon-like peptide-1 on myocardial contractility and glucose uptake in normal and postischemic isolated rat hearts. *J Pharmacol Exp Ther* 2006;317:1106-13.
156. Noyan-Ashraf MH, Momen MA, Ban K, et al. GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes* 2009;58:975-83.
157. Liu Q, Anderson C, Broyde A, et al. Glucagon-like peptide-1 and the exenatide analogue AC3174 improve cardiac function, cardiac remodeling, and survival in rats with chronic heart failure. *Cardiovasc Diabetol* 2010;9:76.

158. Poornima I, Brown SB, Bhashyam S, Parikh P, Bolukoglu H, Shannon RP. Chronic glucagon-like peptide-1 infusion sustains left ventricular systolic function and prolongs survival in the spontaneously hypertensive, heart failure-prone rat. *Circ Heart Fail* 2008;1:153-60.
159. Vyas AK, Yang KC, Woo D, et al. Exenatide improves glucose homeostasis and prolongs survival in a murine model of dilated cardiomyopathy. *PLoS One* 2011;6: e17178.
160. Khan MA, Deaton C, Rutter MK, Neyses L, Mamas MA. Incretins as a novel therapeutic strategy in patients with diabetes and heart failure. *Heart Fail Rev* 2013;18:141-8.
161. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail* 2006;12:694-9.
162. Best JH, Hoogwerf BJ, Herman WH, et al. Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. *Diabetes Care* 2011;34:90-5.
163. Ratner R, Han J, Nicewarner D, Yushmanova I, Hoogwerf BJ, Shen L. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. *Cardiovasc Diabetol* 2011;10:22.
164. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327-35.
165. Hocher B, Reichetzedler C, Alter ML. Renal and cardiac effects of DPP4 inhibitors— from preclinical development to clinical research. *Kidney Blood Press Res* 2012;36: 65-84.
166. Idris I, Donnelly R. Sodium-glucose co-transporter-2 inhibitors: an emerging new class of oral antidiabetic drug. *Diabetes Obes Metab* 2009;11:79-88.
167. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care* 2010;33: 2217-24.
168. Bayeva M, Gheorghiane M, Ardehali H. Mitochondria as a therapeutic target in heart failure. *J Am Coll Cardiol* 2013;61:559-610.
169. Holubarsch CJ, Rohrbach M, Karrasch M, et al. A double-blind randomized multicentre clinical trial to evaluate the efficacy and safety of two doses of etomoxir in comparison with placebo in patients with moderate congestive heart failure: the ERGO (etomoxir for the recovery of glucose oxidation) study. *Clin Sci (Lond)* 2007;113:205-12.
170. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. *Circulation* 2005;112:3280-8.
171. Fragasso G, Pallosi A, Puccetti P, et al. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. *J Am Coll Cardiol* 2006;48:992-8.

172. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res* 2000;86:580-8.
173. Zhang L, Lu Y, Jiang H, et al. Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. *J Am Coll Cardiol* 2012;59:913-22.
174. Sossalla S, Maier LS. Role of ranolazine in angina, heart failure, arrhythmias, and diabetes. *Pharmacol Ther* 2012;133:311-23.
175. Chisholm JW, Goldfine AB, Dhalla AK, et al. Effect of ranolazine on A1C and glucose levels in hyperglycemic patients with non-ST elevation acute coronary syndrome. *Diabetes Care* 2010;33:1163-8.
176. Kosiborod M, Arnold SV, Spertus JA, et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina). *J Am Coll Cardiol* 2013;61:2038-45.
177. Dhalla AK, Yang M, Ning Y, et al. Blockade of Na⁺ channels in pancreatic α -cells has anti-diabetic effects. *Diabetes* 2014<http://dx.doi.org/10.2337/db13-1562>.
178. Towler MC, Hardie DG. AMP-activated protein kinase in metabolic control and insulin signaling. *Circ Res* 2007;100:328-41.
179. Arad M, Seidman CE, Seidman JG. AMP-activated protein kinase in the heart: role during health and disease. *Circ Res* 2007;100:474-88.