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MINI-FOCUS ISSUE: DIABETES AND HEART FAILURE

STATE-OF-THE-ART REVIEW

Distinct Myocardial Targets for Diabetes Therapy in Heart Failure With Preserved or Reduced Ejection Fraction

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ABSTRACT

Noncardiac comorbidities such as diabetes mellitus (DM) have different outcomes in heart failure with preserved ejection fraction (HFpEF) compared with heart failure with reduced ejection fraction (HFrEF). These different outcomes are the result of distinct myocardial effects of DM on HFpEF and HFrEF, which relate to different mechanisms driving myocardial remodeling in each heart failure phenotype. Myocardial remodeling is driven by microvascular endothelial inflammation in HFpEF and by cardiomyocyte cell death in HFrEF. Evidence consists of: different biomarker profiles, in which inflammatory markers are prominent in HFpEF and markers of myocardial injury or wall stress are prominent in HFrEF; reduced coronary flow reserve with microvascular rarefaction in HFpEF; and upregulation of free radical-producing enzymes in endothelial cells in HFpEF and in cardiomyocytes in HFrEF. As biopsies from patients with diabetic cardiomyopathy reveal, DM affects failing myocardium by phenotype-specific mechanisms. In HFpEF, DM mainly increases cardiomyocyte hypertrophy and stiffness, probably because of hyperinsulinemia and microvascular endothelial inflammation. In HFrEF, DM augments replacement fibrosis because of cardiomyocyte cell death induced by lipotoxicity or advanced glycation end products. Because DM exerts distinct effects on myocardial remodeling in HFpEF and HFrEF, the heart failure phenotype is important for DM therapy. (J Am Coll Cardiol HF 2018;6:1–7)

The presence, outcomes, and myocardial effects of noncardiac comorbidities appear to differ in heart failure with preserved ejection fraction (HFpEF) and in HF with reduced ejection fraction (HFrEF) (1,2). The number of comorbidities is higher in HFpEF than in HFrEF (mean 4.0 ± 1.7 vs. 3.5 ± 1.7, respectively; $p < 0.001$) (2), and the clinical outcome of comorbidities also varies between HFpEF and HFrEF. For example, chronic obstructive pulmonary disease confers a higher mortality risk in HFpEF than in HFrEF (2). Diabetes mellitus (DM), likewise, leads to worse clinical outcomes in HFpEF than in HFrEF (3). Overweight and obesity appear to be protective in HFrEF but have an uncertain effect in HFpEF; overweight/obesity had a deleterious effect in a HFpEF trial (4) but a protective effect in a predominantly male HFpEF registry (2).

These unequal outcomes are related to the different myocardial effects of comorbidities on HFpEF and HFrEF. Diabetes mellitus clearly demonstrates these different myocardial effects: in HFpEF, DM worsens left ventricular function through increased cardiomyocyte stiffness, whereas, in HFrEF, the principal myocardial effect is replacement fibrosis (5). Insight into the distinct myocardial effects of DM in HFpEF and HFrEF is a prerequisite for effectively and safely treating DM in HF and is the subject of this review. Updated evidence is presented for cell type-specific myocardial injury in HFpEF (predominantly involving endothelial cells) and HFrEF (predominantly involving cardiomyocytes) (6). Subsequently, cell type-specific myocardial injury inflicted by DM will be addressed in HFpEF and HFrEF. Finally, therapeutic implications for DM therapy in HF are discussed.

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ABBREVIATIONS AND ACRONYMS

DM = diabetes mellitus

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

CELL TYPE-SPECIFIC MYOCARDIAL INJURY IN HFpEF AND HFrEF

A new paradigm for HFpEF is currently gaining widespread acceptance (6,7). According to this paradigm, comorbidities, especially metabolic comorbidities, trigger a systemic inflammatory state that results in coronary microvascular endothelial dysfunction, which alters paracrine signaling between endothelial cells and cardiomyocytes and allows leukocytes to infiltrate the myocardium. Altered paracrine signaling results in low myocardial nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) content, which stiffens cardiomyocytes and removes the brake on cardiomyocyte hypertrophy. Leukocyte infiltration leads to activation of myofibroblasts and interstitial collagen deposition. As shown in the **Central Illustration**, myocardial injury in HFpEF predominantly involves coronary microvascular endothelial cells, whereas myocardial injury in HFrEF mainly involves cardiomyocyte cell death.

Since the original publication of the new HFpEF paradigm in 2013 (6), a large amount of supportive evidence has been published and is summarized in **Table 1**. Both HFpEF and HFrEF have been characterized by distinct biomarker profiles. In HFpEF, systemic inflammation is manifested by high plasma levels of inflammatory biomarkers (8,9). Initial studies revealed plasma levels to be similarly elevated in HFpEF and HFrEF (8); however, later studies observed some biomarkers, such as soluble interleukin-1 receptor-like 1 (IL1RL1) and C-reactive protein (CRP), to be higher in HFpEF (9). Conversely, biomarkers of myocardial injury (high-sensitivity troponin T [hsTNT]) or myocardial wall stress (N-terminal pro-B-type natriuretic peptide [NT-proBNP]) are higher in HFrEF (8,9). Higher hsTNT is explained by cardiomyocyte damage resulting from activated cardiomyocyte death pathways, and higher NT-proBNP is explained by eccentric left ventricular remodeling in HFrEF.

Systemic inflammation triggers myocardial microvascular endothelial activation with expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) and E-selectin, both of which have been demonstrated to be present in the coronary microvasculature of HFpEF patients (10). Microvascular endothelial activation leads to structural modifications, such as thickening of the capillary basement membrane, microvessel pruning, and microvascular rarefaction, that depress the coronary hyperemic response (11). Both coronary microvascular rarefaction and reduced coronary flow reserve were recently observed in HFpEF patients by using left ventricular myocardial autopsy material and stress/rest myocardial positron emission tomography, respectively (12,13). Vasomotor responses of extracardiac large and small arteries are similarly blunted (14–16). Coronary microvascular activation also favors myocardial infiltration by activated macrophages. Activated macrophages were shown to be present in endomyocardial biopsies of HFpEF patients and were shown to express transforming growth factor (TGF)-β (17). In vitro administration of TGF-β to the human fibroblasts of HFpEF patients transformed them into myofibroblasts (17), which are associated with intense fibrotic collagen deposition and scar contracture.

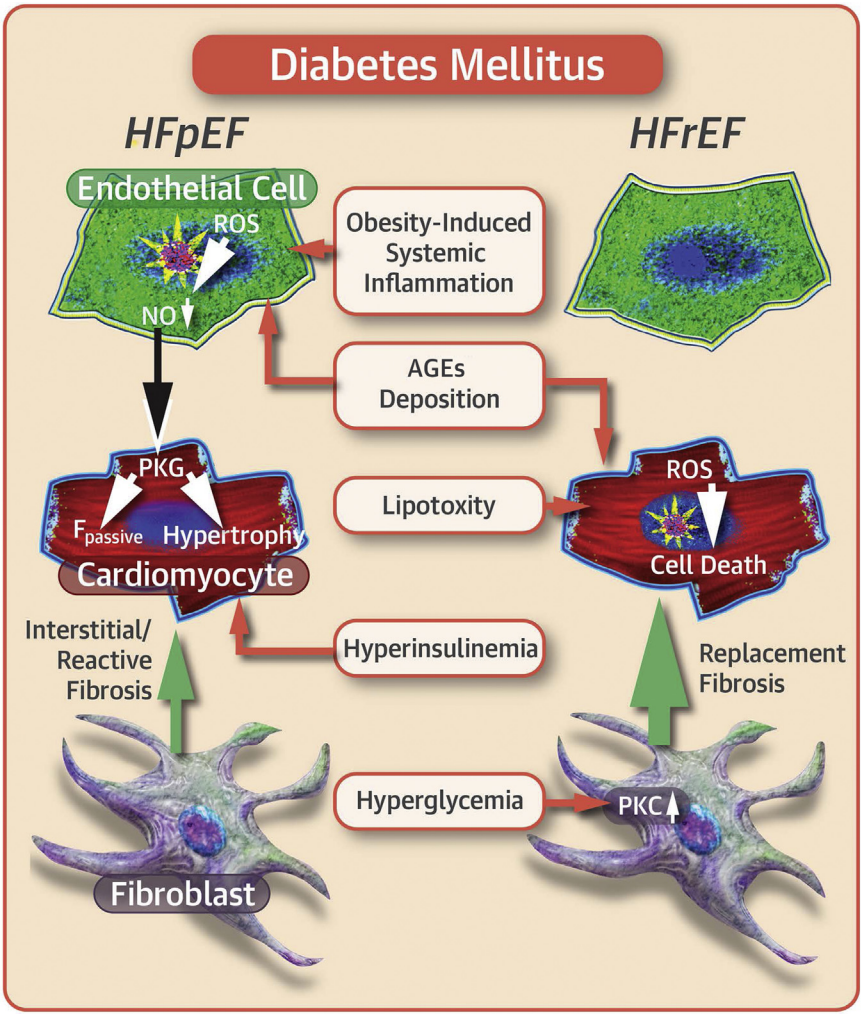
Myocardial cellular localization of oxidative stress differs between HFpEF and HFrEF. In HFpEF, because of exposure to chronic systemic inflammation, the free radical–producing enzyme nicotinamide adenine dinucleotide phosphate oxidase (NOX2) is upregulated in coronary microvascular endothelial cells but not in cardiomyocytes (10). In contrast, NOX2 upregulation also is evident in cardiomyocytes in HFrEF secondary to ischemic or dilated cardiomyopathy (18). Free radicals uncouple endothelial nitric oxide synthase and lower NO production. This process was clearly evident in HFpEF patients, where low concentrations of nitrite/nitrate have been reported both in myocardium (10) and in plasma (19,20). Low myocardial NO reduces protein kinase G activity and stiffens cardiomyocytes, which is evident from the decrease in resting tension observed in single cardiomyocytes of HFpEF patients after in vitro administration of protein kinase G (21).

DIABETES MELLITUS IN HFpEF AND HFrEF

Diabetes mellitus affects remodeling and dysfunction of failing myocardium through various mechanisms, including hyperglycemia, hyperlipidemia, hyperinsulinemia, systemic inflammation, and microvascular or interstitial deposition of advanced glycation end products (AGEs) (**Central Illustration**).

Although hyperglycemia affects all cell types, it especially increases protein kinase C activity in fibroblasts, which augments collagen production and deposition (22). Because of the presence of replacement fibrosis, augmented collagen deposition is especially evident in DM patients with HFrEF (5). Hyperlipidemia leads to myocardial triglyceride accumulation and can induce cell death. This process is referred to as lipotoxicity and involves mitochondrial dysfunction (23). High circulating levels of fatty acids also have been implicated in insulin resistance (24), and because of activation of peroxisome proliferator-activated receptors, in the altered expression of

CENTRAL ILLUSTRATION DM and Heart Failure Phenotype



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Phenotype-specific mechanisms are shown by which DM affects left ventricular remodeling in HFpEF and HFrEF. In HFpEF, obesity-induced systemic inflammation and deposition of endothelial AGEs uncouple NO synthesis with increased production of ROS. This results in low protein kinase G (PKG) activity in cardiomyocytes, which raises their $F_{passive}$ and favors hypertrophy development, especially in the presence of hyperinsulinemia. In HFrEF, lipotoxicity and deposition of AGEs lead to cardiomyocyte cell death and extensive replacement fibrosis because hyperglycemia boosts PKC activity in fibroblasts. AGEs = advanced glycation end products; DM = diabetes mellitus; $F_{passive}$ = passive tension; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NO = nitric oxide; PKG = protein kinase G; ROS = reactive oxygen species.

genes involved in fatty acid uptake and β-oxidation (25,26). Because of insulin resistance, hyperinsulinemia is another important metabolic disturbance present in patients with type 2 DM who are obese (27). With production of heat rather than adenosine triphosphate (ATP), insulin resistance impairs high-energy phosphate production through increased expression of myocardial uncoupling proteins (28). As a result, a low phosphocreatine-to-adenosine triphosphate (PCr/ATP) ratio has been observed in type 2 DM patients (29). A similarly low PCr/ATP ratio is reported in obesity and HFpEF, and under all these conditions, this low ratio is related to diastolic left ventricular dysfunction at rest or during exercise. Insulin induces cardiomyocyte hypertrophy; therefore, hyperinsulinemia explains the pronounced cardiomyocyte hypertrophy observed in HFpEF patients with DM (5).

TABLE 1 Evidence for the Microvascular Paradigm in HFpEF

Evidence	Systemic Factors (Ref. #)	Myocardial Factors (Ref. #)
Inflammation	High IL1RL1, CRP in plasma (9)	Endothelial NOX2 in EMB (10)
Endothelial activation		ICAM, E-selectin in EMB (10) Macrophages in EMB (17) TGF-β expression in macrophages (17) Induction of myofibroblasts (17)
Endothelial dysfunction	PAT reactive hyperemia (14,15) Pressure myography of small arteries in fat biopsy (16)	PET MFR (13)
Low NO	Nitrite/nitrate in plasma (19,20)	Nitrite/nitrate in EMB (10)
Low cGMP		cGMP content in EMB (21) Lower resting tension of cardiomyocytes after PKG (21)

cGMP = cyclic guanosine monophosphate; CRP = C-reactive protein; EMB = endomyocardial biopsy; ICAM = intercellular adhesion molecule; IL1RL1 = interleukin 1 receptor-like 1; MFR = myocardial flow reserve; NO = nitric oxide; NOX2 = nicotinamide adenine dinucleotide phosphate oxidase; PAT = peripheral arterial tonometry; PET = positron emission tomography; PKG = protein kinase G; TGF = transforming growth factor.

Deposition of AGEs has been observed in both HF phenotypes (5). Light microscopy immunohistochemical visualization of the AGE *N*-epsilon-carboxymethyl-lysine (CML) showed deposition of AGEs in the myocardial microvasculature (5). Microvascular deposition of AGEs triggers vascular inflammation and quenches endothelium-produced NO (30). As observed in HFpEF, this process lowers NO bioavailability for adjacent cardiomyocytes and predisposes them to hypertrophy and high stiffness. Electron microscopy immunohistochemical visualization of the AGE CML revealed that it also was deposited in the interstitial space between cardiomyocytes (31). Binding of interstitial AGEs to receptors for advanced glycation end products on cardiomyocytes triggers oxidative stress (32), activates nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and its downstream target genes (33), and ultimately can induce cardiomyocyte cell death and replacement fibrosis as observed in HFrEF (34).

In HF, DM can act as sole perpetrator or as an accomplice to other causes such as ischemic heart disease or myocarditis. When DM acts as the sole perpetrator, diabetic cardiomyopathy is held responsible for the development of HF. Diabetic cardiomyopathy is a cumbersome clinical diagnosis because it requires exclusion of coronary artery disease (CAD) or arterial hypertension and procurement of endomyocardial biopsies to rule out inflammatory infiltration or myocardial deposits (35). Diabetic cardiomyopathy can manifest itself either as a restrictive cardiomyopathy with HFpEF or as a dilated cardiomyopathy with HFrEF (35). Restrictive cardiomyopathy is very common and usually occurs in patients with type 2 DM, whereas dilated cardiomyopathy is rare, is mainly observed in patients with type 1 DM, and is still a subject for debate. The most compelling argument for its existence is the higher prevalence of diabetes in a cohort of patients with dilated cardiomyopathy than in control subjects (36). This higher prevalence, however, also can be related to neurohumoral activation increasing the incidence of diabetes in HF patients (37).

In an invasive biopsy study, HFpEF and HFrEF patients with diabetic cardiomyopathy were compared to HFpEF and HFrEF patients with no CAD or DM, respectively (5). In HFpEF patients, DM worsened left ventricular diastolic dysfunction, and in the left ventricular biopsies, these hemodynamic abnormalities were attributed to larger and stiffer cardiomyocytes. In HFrEF patients, presence of DM also worsened left ventricular diastolic dysfunction, but in the left ventricular biopsies, widespread replacement fibrosis appeared to be responsible. These findings could have resulted from variable involvement of DM-related mechanisms in both phenotypes (**Central Illustration**). In diabetic cardiomyopathy with a restrictive cardiomyopathy/HFpEF phenotype, cardiomyocyte hypertrophy and stiffness could result from hyperinsulinemia and lack of cGMP because of endothelial dysfunction. The lack of cGMP is probably related to obesity-induced systemic inflammation and deposition of AGEs. In diabetic cardiomyopathy with a dilated cardiomyopathy/HFrEF phenotype, cardiomyocyte cell death and replacement fibrosis assume the main focus. Cardiomyocyte cell death probably is related to lipotoxicity or activation of NFκB by AGEs, and this cell death triggers intense replacement fibrosis because hyperglycemia stimulates protein kinase C activity in fibroblasts. Involvement of lipotoxicity in diabetic cardiomyopathy with a restrictive cardiomyopathy/HFpEF phenotype, however, cannot be excluded because excess fatty acids also are toxic for endothelial cells (38). Although lipotoxic cardiomyocyte death has not been observed in this phenotype, myocardial lipid content has been shown to correlate with diastolic left ventricular stiffness (39).

In large HFpEF or HFrEF trials, the myocardial structural and functional effects of DM appear to be comparable to diabetic cardiomyopathy, even though DM is no longer acting as the sole perpetrator but rather as an accomplice to other HF causes such as CAD (**Table 2**). In HFpEF trials, DM raised left ventricular mass and reduced left ventricular diastolic distensibility, which was evident from identical or smaller left ventricular end-diastolic size at a higher left ventricular early diastolic mitral flow velocity-to-early diastolic mitral annular re-lengthening velocity

TABLE 2 Effects of Diabetes Mellitus on Left Ventricular End Diastolic Size, Left Ventricular Filling Pressures Estimated From E/e′ Ratio, and Left Ventricular Mass

Trial/Registry (Ref. #)	LVED Size DM$^-$	LVED Size DM$^+$	LVE/e′ DM$^-$	LVE/e′ DM$^+$	LV Mass DM$^-$	LV Mass DM$^+$
HFpEF trials and registries						
I-PRESERVE (41)	LVEDID 4.8 ± 0.6 cm	LVEDID 4.9 ± 0.6 cm*	10.4 ± 3.9	11.7 ± 6.4†	161 ± 48 g	173 ± 48 g*
RELAX (40)	LVEDIDI 2.3 cm/m^2 (2.1–2.5)	LVEDIDI 2.1 cm/m2 (1.9–2.3)†	14.6 (11–22)	18.0 (13–25)*	50 g/m (43–58)	65 g/m (53–76)†
Olmsted (42)	LVEDV **128** ml	LVEDV **132** ml	**16.0**	**18.4***	**109** g	**201** g†
HFrEF trials and registries						
STICH (43)	LVEDVI 117 ml/m^2 (93–146)	LVEDVI 105 ml/m^2 (85–128)†	17.3 (10–20)	20 (13–25)†		
ASPIRE (44)	LVEDV 133.3 ± 31.9 ml	LVEDV 129.6 ± 35.1 ml	9.1 ± 4.3	11.1 ± 5.3†	246 g‡	248 g‡
Frederiksberg (45)	LVEDV 132 ± 48 ml	LVEDV 134 ± 40 ml	11.4 ± 5.0	13.9 ± 4.8*		
Leiden CRT (46)	LVEDVI ml/m^2 117 ± 41	LVEDVI ml/m^2 103 ± 40†	21 ± 14	21 ± 11		

Values are mean ± SD, median (interquartile range [IQR]), or adjusted geometric mean (in **bold**). *p ≤0.05. †p ≤0.001. ‡p < 0.10; calculated from LVEDV and wall thickness data.

ASPIRE = Aliskiren Study in Post MI Patients to Reduce Remodelling; CRT = cardiac resynchronization therapy; DM$^-$ = absence of diabetes mellitus; DM$^+$ = presence of DM; E/e′ = ratio of left ventricular early diastolic mitral flow velocity to early diastolic mitral annular re-lengthening velocity; ED = end diastolic; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction trial; LV = left ventricular; LVEDID = left ventricular end diastolic internal dimension; LVEDIDI = LVEDID index; LVEDV = left ventricular end diastolic volume; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; STICH = Surgical Treatment for Ischemic Heart Failure.

(E/e′) ratio (which was used as an estimate of left ventricular filling pressures) (40–42). In HFrEF trials, DM also reduced left ventricular diastolic distensibility, which was again evident from smaller left ventricular end-diastolic size at a higher E/e′ ratio (43–46). Three HFrEF trials did not report differences in left ventricular mass (43,45,46). One HFrEF trial observed a small increase in relative wall thickness, which in the presence of a smaller left ventricular end-diastolic volume, yielded a comparable left ventricular mass (44). In both HFpEF and HFrEF trials, DM did not induce a shift of HF phenotype from HFpEF to HFrEF or vice versa because DM patients in HFpEF trials had no decrease in left ventricular systolic performance, and HFrEF trials produced no convincing evidence for a larger left ventricular mass. Because of the identical hemodynamic effects of DM in diabetic cardiomyopathy and in trials, the mechanisms by which DM affects the left ventricular myocardium as a sole perpetrator or as an accomplice are probably similar.

THERAPEUTIC IMPLICATIONS FOR DM THERAPY IN HEART FAILURE

Tight glycemic control with insulin did not have a beneficial effect on left ventricular diastolic dysfunction (47). A similar inefficacy of tight glycemic control on HF risk also was reported in a large meta-analysis that included not only insulin but also oral antihyperglycemic agents (48). The failure of insulin probably resulted from body weight gain (49). This is especially relevant to obese patients with HFpEF and suggests that increased obesity overrides improved glycemic control. The potent effect of obesity on HFpEF was recently illustrated by a study of older, obese HFpEF patients that imposed a 20-week caloric restriction diet (50). Diet significantly improved peak oxygen consumption (Vo_2) and quality-of-life scores. Furthermore, the combination of diet and exercise training was additive and produced a larger increase in peak Vo_2 than the increases most drug treatments produced in HFrEF. In this study, the increase in peak Vo_2 was strongly correlated with lower biomarkers of inflammation, which is consistent with obesity driving HFpEF through systemic inflammation (6).

Because of its adenosine monophosphate kinase-activating effects, metformin is of potential interest for treatment of cardiovascular diseases, including HF. In patients with DM, metformin improved both tissue Doppler long-axis lengthening velocity (e′) and isovolumic relaxation time (51). However, in patients without DM who presented with a recent myocardial infarction, metformin did not improve LVEF (52).

Thiazolidinediones have been largely discredited because of a class effect consisting of aggravated edema without excess cardiovascular death (53). Notwithstanding this class effect, pioglitazone has been shown to improve diastolic left ventricular stiffness in men with uncomplicated type 2 DM (54). This improvement was not associated with altered myocardial substrate or metabolism of high-energy phosphates and, therefore, was the result of other pathways directly affecting diastolic left ventricular dysfunction. The same trial also revealed that baseline diastolic left ventricular dysfunction was related to plasma osteoprotegerin, a soluble member of the tumor necrosis factor receptor superfamily (55). This last finding again supports the importance of systemic inflammation for diastolic left ventricular dysfunction.

Dipeptidyl peptidase (DPP)-4 inhibitors have been linked to an increased incidence of HF hospitalizations, especially in the presence of previous HF and elevated natriuretic peptides (56–58). A recent large

systematic review of randomized and observational studies using DPP-4 inhibitors concluded that the risk for HF remains uncertain but more likely to be present in patients with existing cardiovascular disease and risk factors (59). Similar safety concerns also apply to the use of glucagon-like polypeptide (GLP)-1 analogues such as liraglutide (60). No specific evidence is available for HFpEF patients; however, in HFrEF patients with and without DM, liraglutide did not improve LVEF and increased the number of adverse cardiac events (61). Insulin, DPP-4 inhibitors, and GLP-1 analogues all force glucose to enter the myocytes. In the presence of metabolic inflexibility (i.e., inability of diabetic myocytes to switch metabolic substrate), forced glucose entry leads to acidosis, myofilamentary desensitization, and further reduction of contractile performance. This is especially deleterious for HFrEF, where left ventricular systolic function is compromised.

In contrast to insulin, DPP-4 inhibitors, and GLP-1 analogues, sodium glucose cotransporter-2 inhibitors, or gliflozins lower glycemia through blocked renal glucose reabsorption and enhanced glucosuria. In the EMPA-REG OUTCOME (Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients) trial, use of empagliflozin resulted in a 35% reduction in HF risk (62). In the CANVAS trial, administration of canagliflozin resulted in a 33% reduction of HF hospitalizations (63). How these beneficial effects were achieved and whether it applies equally to HFpEF or HFrEF phenotypes requires further investigations (64).

CONCLUSIONS

The mechanisms by which DM affects left ventricular myocardium, either as the sole perpetrator in diabetic cardiomyopathy or as an accomplice in HF of some other cause, differ between HFpEF and HFrEF. Therefore, HF outcomes from DM therapy need to be specifically evaluated in HFpEF and HFrEF patient populations.

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