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POSITION PAPER

Diabetic myocardial disorder. A clinical consensus statement of the Heart Failure Association of the ESC and the ESC Working Group on Myocardial & Pericardial Diseases

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The association between type 2 diabetes mellitus (T2DM) and heart failure (HF) has been firmly established; however, the entity of diabetic myocardial disorder (previously called diabetic cardiomyopathy) remains a matter of debate. Diabetic myocardial disorder was originally described as the occurrence of myocardial structural/functional abnormalities associated with T2DM in the absence of coronary heart disease, hypertension and/or obesity. However, supporting evidence has been derived from experimental and small clinical studies. Only a minority of T2DM patients are recognized as having this condition in the absence of contributing factors, thereby limiting its clinical utility. Therefore, this concept is increasingly being viewed along the evolving HF trajectory, where patients with T2DM and asymptomatic structural/functional cardiac abnormalities could be considered as having pre-HF. The importance of recognizing this stage has gained interest due to the potential for current treatments to halt or delay the progression to overt HF in some patients. This document is an expert consensus statement of the Heart Failure Association of the ESC and the ESC Working Group on Myocardial & Pericardial Diseases. It summarizes contemporary understanding of the association between T2DM and HF and discusses current knowledge and uncertainties about diabetic myocardial disorder that deserve future research. It also proposes a new definition, whereby diabetic myocardial disorder is defined as systolic and/or diastolic myocardial dysfunction in the presence of diabetes. Diabetes is rarely exclusively responsible for myocardial dysfunction, but usually acts in association with obesity, arterial hypertension, chronic kidney disease and/or coronary artery disease, causing additive myocardial impairment.

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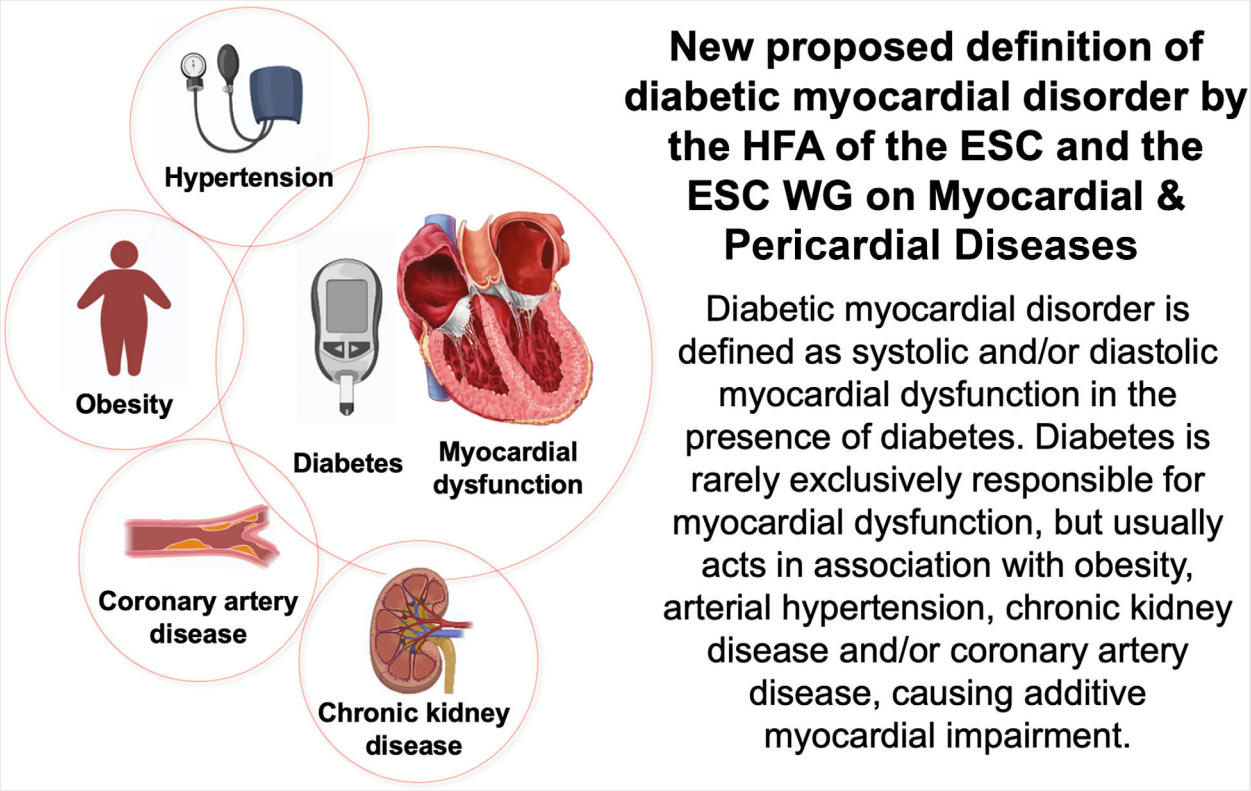
Graphical Abstract



Proposed Heart Failure Association (HFA) of the ESC definition of diabetic myocardial disorder.

Keywords Diabetic myocardial disorder • Type 2 diabetes mellitus • Heart failure • Cardiac abnormalities • Risk assessment • Prevention • Treatment

Introduction

There are currently ~540 million people living with diabetes mellitus globally and 61 million in Europe, with 90% of them having type 2 diabetes mellitus (T2DM).[1] Cardiovascular diseases represent a leading cause of morbidity and mortality in patients with T2DM, with heart failure (HF) being one of the most common presentations.[2,3] A recent population-based study including 1.9 million individuals with and without T2DM, free of cardiovascular disease at baseline, demonstrated that HF occurred in patients with T2DM more frequently than myocardial infarction or stroke over the 5.5 years of follow-up.[3] The adjusted relative risk of incident HF was significantly higher (hazard ratio [HR] 1.56, 95% confidence interval [CI] 1.45–1.69) in individuals with T2DM compared to those without T2DM.[3] Several longitudinal studies confirmed that T2DM is a strong and independent predictor of new-onset HF in the general population.[3–5] In patients with concurrent T2DM and HF, the presence of each disorder adversely affects the prognosis of the other, significantly increasing the risk of complications, HF hospitalization and death.[6,7]

One part of the close association between T2DM and HF is the recognition that a subset of patients affected by both conditions may have diabetic myocardial disorder, previously referred to as 'diabetic cardiomyopathy', which has been variably defined by several expert documents.[8–12] A prevailing idea was to underscore the association between T2DM and development of myocardial structural and functional abnormalities responsible for HF, in the absence, or independently of coronary artery disease (CAD), hypertension, valvular disease, obesity, or other cardiometabolic risk factors. More recently, in line with the concept of evolving HF stages, patients with T2DM without cardiac abnormalities have been regarded as those at risk of developing HF (stage A), whilst those with asymptomatic structural/functional cardiac abnormalities and/or elevated natriuretic peptides have been considered to have pre-HF (stage B).[13] The importance of recognizing these early stages is of major interest, since advances in the management of

T2DM may offer the possibility of preventing or delaying the occurrence of HF, at least in some of these patients.[14–16]

The presence of cardiac structural and functional abnormalities, along with a higher risk of developing HF have also been recognized in patients with type 1 diabetes mellitus.[17,18] Although there may be an overlap with T2DM, the underlying mechanisms and the phenotype of diabetic myocardial disorder in patients with type 1 diabetes mellitus are less clear and remain to be further elucidated.[19]

The present document summarizes current understanding on the association between T2DM and HF, briefly discussing the pathophysiological mechanisms and underscoring well-documented cardiac abnormalities preceding overt HF, which may be seen along the line of diabetic myocardial disorder. It emphasizes the significance of risk assessment for the development of HF in patients with T2DM based on validated risk models. Furthermore, it highlights current evidence-based options for the prevention of HF in T2DM. Finally, it summarizes current knowledge and uncertainties and proposes a new definition of diabetic myocardial disorder. This document is developed by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on Myocardial & Pericardial Diseases, and is based on an expert consensus reached at the Heart Failure Association of the ESC Workshop and subsequent expert discussions.

Pathophysiological correlates between type 2 diabetes mellitus and heart failure

The development of structural/functional abnormalities leading to HF in patients with T2DM involves multiple mechanisms, which remain incompletely elucidated.[9] They broadly encompass systemic factors, including hyperglycaemia, insulin resistance, hyperlipidaemia, excessive production of advanced glycation end products (AGEs), activation of the renin–angiotensin–aldosterone system and autonomic dysregulation.[12,20,21] These are important drivers of hypertension, accelerated coronary atherosclerosis and microvascular dysfunction, which play a key role in HF development in a significant proportion of patients with T2DM. Systemic factors also promote interrelated pathological cellular and molecular processes in the myocardium that contribute to the development of HF independently of, or in conjunction with the above mechanisms.[22] These processes include the following:

- Myocardial metabolic changes, impaired energy efficiency and contractile impairment: hyperinsulinaemia and insulin resistance decrease myocardial glucose uptake and utilization for energy production.[23] There is a concurrent increase in cardiac delivery and uptake of free fatty acids leading to increased dependence on fatty acid β-oxidation for energy production.[24,25] This metabolic shift, however, comes at a price of increased myocardial oxygen consumption, lower cardiac efficiency, and contractile impairment.[26] Increased reliance on fatty acid metabolism also leads to uncoupling of mitochondrial proteins and mitochondrial dysfunction, with a consequent increase in oxidative stress.[27]
- Glucotoxicity, lipotoxicity and oxidative stress: chronic hyperglycaemia results in increased activity of the aldose reductase in the polyol pathway, increased protein O-GlcNAcylation and excessive production of AGEs.[22] These processes impair cellular antioxidative mechanisms and promote mitochondrial dysfunction, which further exacerbates oxidative stress.[22,28] The excessive oxidative stress is responsible for endoplasmic reticulum dysfunction,[29] impaired Ca^{2+} handling and depressed cardiac myofilament function.[30] Increased O-GlcNAcylation also leads to impaired autophagy, increased cardiomyocyte apoptosis and microvascular endothelial dysfunction.[31–33] Furthermore, excessive cardiac uptake of non-esterified fatty acids, not metabolized by β-oxidation, results in cardiomyocyte lipid accumulation and lipotoxicity,[34–37] which further aggravates oxidative stress and promotes cardiomyocyte apoptosis.[38]
- Fibrosis, hypertrophy, and diastolic dysfunction: overproduction of AGEs decreases extracellular matrix turnover due to downregulation of matrix metalloproteinases and increased cross-linkage of collagen.[39,40] Lipotoxicity also promotes the activation of profibrotic pathways (e.g. hexosamine, polyol, protein kinase B, protein kinase C/mitogen-activated protein kinase, etc.) and excessive collagen deposition.[41–43] Progressive interstitial fibrosis contributes to diastolic dysfunction, which is further aggravated by an alteration in the expression (a switch to a 'stiffer' isoform) and posttranslational modification (hypo-phosphorylation) of titin, which plays a crucial role in passive myocardial tension.[44,45] In addition, myocardial hypertrophy is a common finding in patients with T2DM. Epigenetic changes due to DNA methylation, dysregulated expression of non-coding RNAs (e.g. microRNAs) and histone protein acetylation have been implicated in the activation of cellular pathways responsible for cardiomyocyte hypertrophy.[22,46] Renin–angiotensin–aldosterone system activation, overproduction of AGEs and autonomic dysregulation lead to microvascular dysfunction and decreased nitric oxide bioavailability, also implicated in stimulating myocardial hypertrophy.[47]

Collectively, these processes promote cardiac remodelling, systolic and diastolic dysfunction and microvascular disease and predispose to the development of HF, whilst the prevailing pathophysiological mechanisms may be responsible for distinct phenotypes of diabetic myocardial disorder.[9,48,49] *Figure 1* provides a summary of the most pertinent processes responsible for cardiac dysfunction in T2DM. A more detailed discussion of these processes can be found elsewhere.[22,41,45,50–55]

Asymptomatic structural and functional abnormalities preceding heart failure in patients with type 2 diabetes mellitus

Numerous studies have reported a high burden of asymptomatic abnormalities in cardiac structure and function in patients with T2DM, as assessed with different imaging modalities. In a cohort of elderly patients with T2DM (≥60 years) without known HF,

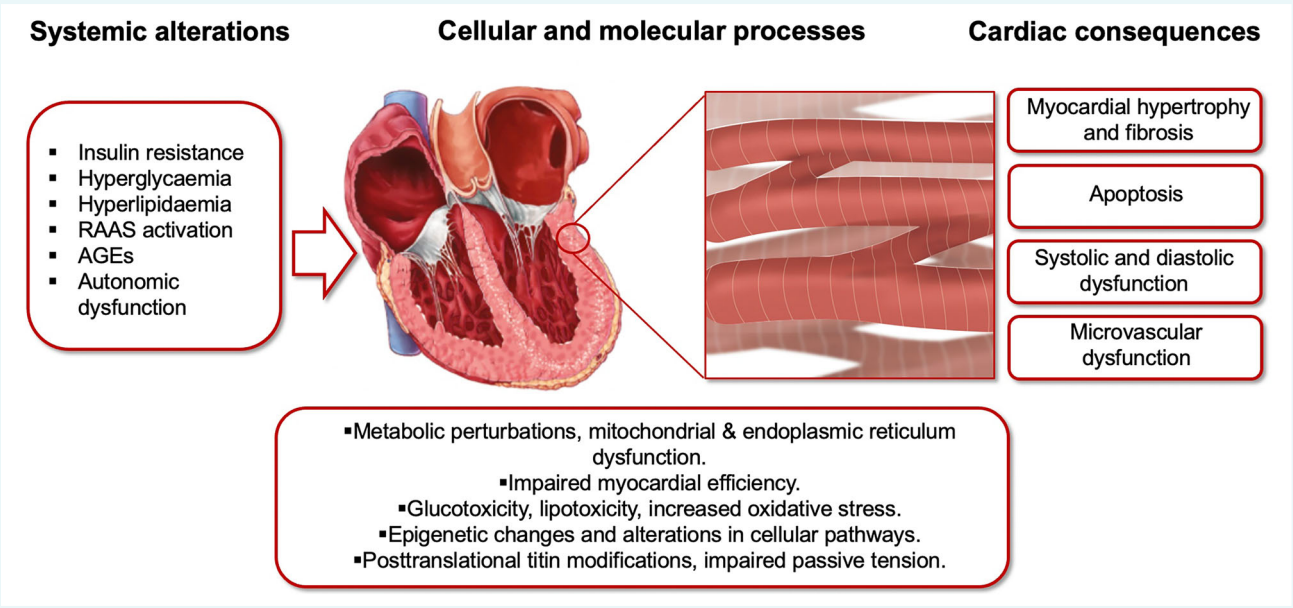


Figure 1 Mechanisms underlying cardiac dysfunction in type 2 diabetes. AGE, advanced glycation end-product; RAAS, renin–angiotensin–aldosterone system. Based on references[41,45,50–54]

a cross-sectional, community-based survey in the Netherlands revealed echocardiographic evidence of asymptomatic left ventricular (LV) dysfunction in 25.8% of them, the majority of whom had diastolic dysfunction (25.1% of the total cohort).[56] Even in patients without hypertension or CAD, echocardiographic abnormalities were reported in LV diastolic and systolic function (e.g. LV hypertrophy, lower LV ejection fraction [LVEF] and mitral annular plane systolic excursion, abnormal ratio of mitral inflow peak early diastolic velocity to tissue Doppler mitral annular early diastolic velocity), as well as impaired myocardial strain (reduced global longitudinal strain) and left atrial enlargement.[57–60] Cardiac magnetic resonance (CMR) imaging has confirmed early alterations in volume and function of both left- and right-sided cardiac chambers in a community-based sample of 3984 patients with T2DM, without known cardiovascular disease and with preserved LVEF ≥50%.[61] Furthermore, a CMR study of asymptomatic hypertensive patients with and without T2DM (free of CAD) suggested the presence of more severe LV concentric hypertrophy, worse myocardial strain and a greater burden of replacement and interstitial fibrosis in patients with T2DM compared to patients with hypertension only.[62] These early adverse cardiac abnormalities occurred in patients with T2DM despite having similar LV mass and blood pressure as patients with hypertension alone, and were associated with a distinct proinflammatory and profibrotic biomarker profile (i.e. increased activity of inflammatory response and immune cell trafficking in serum protein pathway analysis and an association between growth differentiation factor 15 and replacement fibrosis/expansion of extracellular matrix).[48,62]

Several studies have observed an association between asymptomatic cardiac dysfunction and a higher risk of incident HF in patients with T2DM, even in the absence of CAD or hypertension.[63,64] A recent pooled analysis of three cohort studies in the United States, comprising 10 208 individuals without known cardiovascular disease or HF (with and without T2DM), revealed a high prevalence of echocardiographic structural and functional abnormalities among patients with T2DM (i.e. left atrial enlargement, LV hypertrophy, diastolic dysfunction), and suggested their prognostic relevance for incident HF over a 5-year follow-up.[64] Patients with T2DM and one or more echocardiographic abnormalities were considered to have 'T2DM with cardiomyopathy' and its prevalence varied from 67.0% (based on a single echocardiographic abnormality), to ∼11.7% (based on multiple echocardiographic abnormalities and elevated natriuretic peptide levels).[64] The presence of cardiac abnormalities was predictive of incident HF over a 5-year follow-up, with a gradual increase in the relative risk (HR ranging from 1.65, 95% CI 1.16–2.36 to HR 1.75, 95% CI 1.18–2.61) when the least and most restrictive criteria, respectively, were applied. An increased risk of future HF was also observed in patients with T2DM without hypertension or obesity.[64] Similarly, a recent analysis of two prospective cohorts including 842 individuals with T2DM also demonstrated a growing risk of adverse cardiovascular events (including incident HF) associated with an increasing complexity of asymptomatic echocardiographic abnormalities, with the worst prognosis being observed with a clustering of LV hypertrophy, slight systolic dysfunction and impaired myocardial strain.[65]

Risk assessment of incident heart failure in patients with type 2 diabetes mellitus

There is a considerable heterogeneity in the risk of developing HF in patients with T2DM, particularly among those without a

Table 1 Risk assessment scores for heart failure events in patients with type 2 diabetes mellitus

Risk score	Variables included	Predictive value (derivation C-statistic)
Yang *et al.*, 2008[66]	Age, BMI, spot UACR, HbA_{1c}, blood haemoglobin at baseline and CAD during follow-up	0.920
WATCH-DM, 2019[67]	BMI, age, hypertension, creatinine, high-density lipoprotein cholesterol, fasting plasma glucose, QRS duration, myocardial infarction, and coronary artery bypass graft	0.70
Williams *et al.*, 2020[68]	Age, CAD, blood urea nitrogen, atrial fibrillation, HbA_{1c}, blood albumin, systolic blood pressure, chronic kidney disease, and smoking history	0.782
TRS-HF_{DM}, 2021[69,70]	Prior HF, atrial fibrillation, CAD, eGFR <60 ml/min/1.73 m^2, and UACR	0.78
Pandey *et al.*, 2021[71]	hsTnT ≥6 ng/L, NT-proBNP ≥125 pg/ml, hsCRP ≥3 mg/L, LV hypertrophy by electrocardiogram	0.74
DM-CURE, 2022[72]	Sociodemographic (education, age at T2DM diagnosis), metabolic (HbA_{1c}, systolic blood pressure, BMI, high-density lipoproteins), diabetes-related complications (myocardial infarction, revascularization, cardiovascular medications, neuropathy, hypertension duration, albuminuria, UACR, end-stage kidney disease), and healthcare utilization (all-cause hospitalization, emergency room visits)	0.838
Sun *et al.*, 2022[73]	Sex-specific: age, rural residence, hypertension duration, haemoglobin, HbA_{1c}, and cardiovascular diseases were common predictors in both sexes. Mood disorder and alcoholism (women-specific) and income and liver disease (men-specific) predictors	0.75 (men) 0.79 (women)

BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin T; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

history of HF. This emphasizes the significance of risk assessment to identify higher-risk individuals that may derive greater benefit from preventive strategies. Recently, several risk scores have been developed to predict the risk of future HF among patients with T2DM (*Table 1*).[66–73] The predictive value of several of these scores has been confirmed in other populations,[73,74] whilst the others await external validation.

Most scores were based on readily available clinical, electrocardiographic and laboratory variables, but have not accounted for possible asymptomatic cardiac structural and/or functional abnormalities (due to their limited availability in population-based studies). These scores have been shown to reliably discriminate medium-term (i.e. 5 years) risk of HF in cohorts with different baseline risk.[74,75] Furthermore, a biomarker-based score including biomarkers of chronic myocardial injury, neurohumoral stress, systemic inflammation, and LV hypertrophy by electrocardiogram has demonstrated good predictive validity to stratify a 5- and 10-year risk of HF in patients with T2DM, but without established cardiovascular disease from three community-based cohorts.[71] Although a high biomarker score (≥3) was present in <10% of all patients at baseline, it accounted for 35% of all HF events over a 5-year follow-up.[71]

Duration of T2DM is another aspect to consider for assessing the risk of future HF, though incident HF is already high in people with pre-diabetes, that is impaired glucose intolerance.[76] In a community-based study in the United States, including 9734 participants without baseline HF (with and without T2DM), the risk of incident HF increased by 17% for each 5 years of T2DM duration with the highest relative risk observed among patients with T2DM lasting ≥15 years (HR 2.82, 95% CI 2.25–3.63, with respect to patients without T2DM), after controlling for intercurrent CAD and other risk factors.[77] This association was particularly strong among younger (≤65 years) and obese patients, women, self-identified African Americans, and those without adequate glycaemic control (glycated haemoglobin levels ≥7%).[77] A caveat needs to be recognized when considering T2DM duration for risk assessment, because there might be a delay in diagnosing T2DM in some patients, and an extended T2DM duration typically correlates with an older age.[78]

The 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes recommend systematic survey for HF symptoms and/or signs in all patients with diabetes as well as measurement of natriuretic peptides in cases of suspected HF.[79] The use of established risk scores (e.g. WATCH-DM) to screen patients with T2DM for the risk of developing HF has also been mentioned in the guidelines,[79] and is advised by this expert panel. The WATCH-DM score demonstrated good predictive properties, particularly in intermediate risk patients, and performed slightly better compared with the TRS-HF_{DM} score, both in intermediate and high-risk patients.[74] It can be calculated from data readily available in everyday clinical practice, which can facilitate its broader use. SCORE2-Diabetes is also guideline-recommended to assess the 10-year risk of fatal and non-fatal cardiovascular events (myocardial infarction and stroke) but not HF, in patients with T2DM.[79]

Prevention of heart failure in patients with type 2 diabetes mellitus

Prevention of HF events is a major challenge in patients with T2DM, particularly in those with asymptomatic cardiac structural/functional abnormalities (i.e. possibly early diabetic

myocardial disorder) for whom the evidence is sparse. Current preventive strategies encompass lifestyle interventions, glycaemic control, blood pressure control and use of medical therapies with favourable cardiovascular effects.

The importance of addressing modifiable risk factors (e.g. hypertension, smoking, obesity, etc.) and implementing regular exercise and healthy diet cannot be overemphasized in patients with T2DM.[79,80] However, controlling risk factors alone may not be sufficient to prevent HF in real-world settings. As demonstrated by a recent cohort study in Sweden, patients with T2DM (a total of 271 174 individuals) who had multiple risk factors under control (glycated haemoglobin, low-density lipoprotein cholesterol, albuminuria, smoking, and blood pressure) experienced a significant reduction in the relative risk of cardiovascular events (myocardial infarction, stroke and death), but remained at a higher risk of developing HF (HR 1.45, 95% CI 1.34–1.57) during 5.7 years of follow-up compared to matched controls.[81] Furthermore, the randomized Look AHEAD (Action for Health in Diabetes) trial of intensive lifestyle interventions, with a focus on weight loss, failed to demonstrate a significant reduction in cardiovascular events, including HF hospitalization, in overweight and obese individuals with T2DM.[82] However, patients without cardiovascular disease in the lifestyle intervention arm demonstrated a non-significant reduction in cardiovascular outcomes with a 20% reduction in HF hospitalizations.[82]

The role of optimal glycaemic control in preventing HF in T2DM remains unclear. Observational data in patients receiving glucose-lowering medications suggest a U-shaped relationship between glycated haemoglobin and incident HF, with an independently increased risk being observed in individuals with glycated haemoglobin levels <6% and >10%, respectively.[83] Strategies of intensified glycaemic control in patients with T2DM and established cardiovascular disease have been observed to result in increased risk of mortality, without decreasing the risk of cardiovascular outcomes.[84] Prospective data in patients at lower cardiovascular risk are scarce but observations from the Swedish study suggest that obtaining glycaemic targets may fall short of preventing HF.[81]

Significant progress in HF prevention in T2DM has occurred following the results of cardiovascular outcome trials with sodium–glucose cotransporter 2 (SGLT2) inhibitors, which have shown a consistent reduction in the risk of HF hospitalization (by approximately 30%) with several of these therapies (*Table 2*).[85–88] However, the trials were confined to patients with established atherosclerotic cardiovascular disease or with multiple risk factors, and the efficacy of SGLT2 inhibitors in patients at lower cardiovascular risk is less clear.[89] Real-world data offer some promising insights. In a multinational cohort study of 309 056 patients with T2DM, newly initiated treatment with SGLT2 inhibitors versus other glucose-lowering drugs was associated with a significantly lower risk of HF hospitalization (HR 0.61, 95% CI 0.51–0.73) and death (HR 0.49, 95% CI 0.41–0.57).[90] Considering that most patients in the study did not have a cardiovascular disease, it is possible that therapeutic benefits of SGLT2 inhibitors might extend to patients with T2DM at lower risk than those recruited into earlier cardiovascular outcome trials.[90] In contrast, unlike SGLT2 inhibitors, other classes of antidiabetic medications either have demonstrated a neutral effect or have been associated with a higher risk of HF (e.g. rosiglitazone, pioglitazone, saxagliptin).[91–93]

In addition to the promising data with SGLT2 inhibitors, another encouraging strategy for HF prevention in asymptomatic patients with T2DM without overt cardiovascular disease has been the use of renin–angiotensin system (RAS) inhibitors and beta-blockers. The evidence is derived from PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease) study, a small, randomized trial of 300 patients with T2DM without a history of CAD, HF, low LVEF or other features of cardiac disease, except diastolic dysfunction, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels ≥125 pg/ml.[14] The participants were randomized to intensified medical treatment versus standard care, which has resulted in a considerably higher uptake of RAS inhibitors and beta-blockers, and a significantly lower 1-year incidence of a composite cardiovascular outcome, including HF hospitalizations.[14] These results are in concert with observations from the STOP-HF (The St Vincent's Screening to Prevent Heart Failure) study, involving 1374 participants with cardiovascular risk factors (~20% with T2DM), in which screening with B-type natriuretic peptide test (≥50 pg/ml), followed by collaborative care and treatment with RAS inhibitors, resulted in a greater likelihood of detecting asymptomatic LV diastolic or systolic dysfunction or HF.[15] This has translated into a lower risk of emergency cardiovascular hospitalizations, including admissions for HF (HR 0.60, 95% CI 0.45–0.81).[15] Moreover, a recent study confirmed that NT-proBNP measurement is practical and can be pragmatically targeted for screening people with T2DM and hypertension for HF risk stratification in routine clinical practice.[94] Whether the strategy of an early, intensive management with RAS inhibitors and beta-blockers could halt the progression to overt HF is currently being assessed in a larger population of patients with T2DM and elevated NT-proBNP, without pre-existing cardiac disease (PONTIAC II trial, NCT02817360).

Given that comorbidities (e.g. obesity, chronic kidney disease [CKD], CAD, etc.) frequently coexist with diabetic myocardial disorder, emerging new options for HF prevention in comorbid patients merit consideration. In patients with T2DM and CKD, several clinical trials demonstrated beneficial effects on renal outcomes, as well as a significant attenuation in the risk of HF hospitalization with SGLT2 inhibitors compared with placebo (*Table 2*).[95–98] More recently, a pre-specified analysis of the FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trial in individuals with T2DM and albuminuric CKD, demonstrated a significant reduction in the risk of new-onset HF (HR 0.68, 95% CI 0.50–0.93, $p = 0.0162$), and other HF outcomes with finerenone (a selective, non-steroidal mineralocorticoid receptor antagonist) versus placebo.[99] Treatment effects of finerenone were consistent regardless of a history of HF, and seemingly stronger in patients simultaneously receiving an SGLT2 inhibitor.[99] Patients with symptomatic HF with reduced ejection fraction (HFrEF) were excluded, and a history of cardiovascular disease or HF was reported in ~45% and 7.8% of patients, respectively,[99,100] suggesting that a significant proportion of patients in the trial comprised those 'at risk of HF' or with subclinical cardiac abnormalities (stages A and B). This observation points to the

Table 2 Cardiovascular and renal outcome trials in patients with type 2 diabetes mellitus

Trial, medication	Patients, *n*	Patient characteristics	History of HF	Follow-up (mean or median) years	Primary outcome (treatment vs. placebo)	HF hospitalization (treatment vs. placebo)
CV outcome trials						
EMPA-REG OUTCOME[85] Empagliflozin 25 or 10 mg vs. placebo	7020	Known ASCVD	~10%	3.1	Death from CV causes, non-fatal MI or non-fatal stroke: HR 0.86; 95% CI 0.74–0.99; $p < 0.001$ for non-inferiority and $p = 0.04$ for superiority	HR 0.65; 95% CI 0.50–0.85; $p = 0.002$
CANVAS Program[86] Canagliflozin 100 or 300 mg vs. placebo	10 142	Known ASCVD (66%) Multiple CV risk factors (34%)	~14.4%	3.2	Death from CV causes, non-fatal MI or non-fatal stroke: HR 0.86; 95% CI 0.75–0.97; $p < 0.001$ for non-inferiority; $p = 0.02$ for superiority	HR, 0.67; 95% CI 0.52–0.87
DECLARE-TIMI 58[87] Dapagliflozin 10 mg vs. placebo	17 160	Known ASCVD (41%) Multiple CV risk factors (59%)	~10%	4.2	Two co-primary outcomes: Death from CV causes, non-fatal MI or non-fatal stroke: HR 0.93; 95% CI 0.84–1.03; $p = 0.17$ CV death or HF hospitalization: HR 0.83; 95% CI 0.73–0.95; $p = 0.005$	HR 0.73; 95% CI 0.61–0.88
VERTIS-CV[88] Ertugliflozin 5 or 15 mg vs. placebo	8246	Known ASCVD	~24%	3.5	Death from CV causes, non-fatal MI or non-fatal stroke: HR 0.97; 95% CI 0.85–1.11; $p < 0.001$ for non-inferiority)	HR 0.70; 95% CI 0.54–0.90; $p = 0.006$
Renal outcome trials						
CREDENCE[95] Canagliflozin 100 mg vs. placebo	4401	T2DM + CKD (eGFR 30–<90 ml/min/1.73 m^2 and UACR >300 to 5000 mg/g)	~14.8%	2.6	ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml/min/1.73 m^2), a doubling of the serum creatinine level, or death from renal or CV causes: HR 0.70; 95% CI 0.59–0.82; $p < 0.001$	HR 0.61; 95% CI 0.47–0.80; $p < 0.001$
SCORED[96] Sotagliflozin 200 or 400 mg vs. placebo	10 584	T2DM + CKD (eGFR 25–60 ml/min/1.73 m^2), and additional CV risk factors	~31%	1.3	Total number of CV deaths, HF hospitalizations, and urgent visits for HF	Total number of HF hospitalizations, and urgent visits for HF: HR 0.67; 95% CI 0.55–0.82; $p < 0.001$
DAPA-CKD[97] Dapagliflozin 10 mg vs. placebo	Total population: 4304 T2DM: 2906	CKD (eGFR ≥25 to ≤75 ml/min/1.73 m^2 and UACR ≥200 mg/g to ≤5000 mg/g)	~11%	2.4	Worsening kidney function (i.e. >50% sustained decline in eGFR or ESKD), or death from renal or CV causes: HR 0.6; 95% CI 0.51–0.72; $p < 0.001$	HR 0.71; 95% CI 0.55–0.92; $p < 0.001$
EMPA-KIDNEY[98] Empagliflozin 10 mg vs. placebo	Total population: 6609 T2DM: 2936	CKD (eGFR ≥20 to <45 ml/min/1.73 m^2, regardless of albumlmin/1.73 m^2 and UACR 200 mg/g)	~10%	2.0	Progression of kidney disease or CV death: HR 0.72; 95% CI 0.64–0.82; $p < 0.001$[a]	HF hospitalization or CV death: HR 0.84; 95% CI 0.67–1.07; $p = 0.15$

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.
[a]ESKD (initiation of maintenance dialysis or receipt of a kidney transplant), a sustained decrease in eGFR to <10 ml/min/1.73 m^2, a sustained decrease from baseline eGFR ≥40%, or death from renal causes.

potentially beneficial role of finerenone in preventing HF progression early along the cardio-renal-metabolic continuum in patients with T2DM and comorbid CKD.

Semaglutide, a glucagon-like peptide-1 receptor agonist, has emerged as an effective treatment for managing both obesity and T2DM. In addition to providing sustained weight loss, recent evidence suggests a beneficial role of semaglutide in cardiovascular risk reduction in overweight/obese patients with pre-existing cardiovascular disease without T2DM,[101] as well as in improving symptoms and functional status in obesity-related HF with preserved ejection fraction (HFpEF) and T2DM.[102] It remains to be seen whether these effects translate into

Table 3 Unresolved issues in diabetic myocardial disorder

Heterogeneous prior definitions
Uncertain clinical phenotype(s) and development stages
Difficulties in differential diagnosis with other cardiomyopathies
Non-specificity of asymptomatic cardiac structural and functional abnormalities
Lack of validated risk prediction models accounting for asymptomatic cardiac abnormalities
Open issues in heart failure prevention
Open issues in heart failure treatment in patients with type 2 diabetes mellitus, without hypertension, coronary artery disease or other comorbidities

improved clinical outcomes in the lower risk obese patients with T2DM.

Unresolved issues in diabetic myocardial disorder

There are several unresolved issues underpinning the longstanding uncertainty in the clinical approach to diabetic myocardial disorder. They are summarized in *Table 3*.

1. Until now the consensus about the definition of diabetic myocardial disorder has not been reached. After several discussions, this Expert Panel suggested that diabetic myocardial disorder can be defined as systolic and/or diastolic myocardial dysfunction in the presence of diabetes. Diabetes is rarely exclusively responsible for myocardial dysfunction, but usually acts in association with arterial hypertension, obesity, CAD, and/or CKD, causing additive myocardial impairment.
2. Uncertainties still exist about the clinical phenotype and evolution stages of diabetic myocardial disorder. An expert document proposed the existence of two separate phenotypes: one being the restrictive phenotype responsible for HFpEF, and another being the dilated phenotype responsible for HFrEF.[9] The foundation of these phenotypes is mostly based on experimental findings and limited clinical data.[9] Despite extensive research, these (or other) phenotypes have not been conclusively established in clinical practice and there remains a need to further address this issue.
3. The differential diagnosis and overlapping features with other cardiomyopathies remain uncertain. The coexistence of T2DM with other cardiomyopathies may blur the distinguishing line between the entities.
4. Cardiac structural/functional abnormalities observed in patients with T2DM are frequent, but non-specific. Similar abnormalities may occur in relation to aging[103] or other concurrent conditions in patients with T2DM (e.g. hypertension, obesity, microvascular dysfunction, etc.),[104,105] challenging differentiation between their distinct and combined contributions. Furthermore, there may be a considerable phenotypic variability in patients with T2DM and there may be an overlap with cardiac changes seen in euglycaemic individuals.[65] It was proposed that the minimal diagnostic criteria for diabetic myocardial disorder should include LV diastolic dysfunction and/or reduced LVEF, pathological LV hypertrophy and interstitial fibrosis,[106] but considering the non-specificity of the above criteria, there remains doubt about their clinical applicability.
5. Current risk prediction models for incident HF in T2DM have been based on clinical, biomarker and electrocardiographic variables, but asymptomatic cardiac structural/function abnormalities have not been considered and their potential added predictive value remains uncertain. Although clustering of multiple echocardiographic abnormalities has been associated with an incremental increase in the risk of future HF, even minor cardiac abnormalities were found to independently predict the risk of new-onset HF.[64,65] Considering a strong association between T2DM and incident HF, the use of less restrictive criteria to define a pre-clinical HF phenotype (i.e. possibly early diabetic myocardial disorder) may be a more pragmatic approach to risk assessment and implementation of preventive strategies.[64] This deserves further validation in prospective studies.
6. There is an open issue of HF prevention in patients with T2DM and asymptomatic cardiac abnormalities without established cardiovascular disease or multiple risk factors. Despite promising results with the real-world use of SGLT2 inhibitors, intensive neurohumoral inhibition and finerenone in individuals with T2DM and CKD, there remains a necessity to further peruse evidence-based approaches.
7. A lack of an established definition of diabetic myocardial disorder has limited exploration of targeted treatment option. Strategies targeting cardiac remodelling, inflammation, oxidative stress, and adverse cellular pathways are currently in the early phases of assessment. The ongoing ARISE-HF trial (NCT04083339) will prospectively address whether an intervention with a potent aldolase inhibitor (AT-001) in patients with T2DM and asymptomatic cardiac abnormalities (free of overt cardiovascular disease) will be successful in halting a decline in exercise capacity, as well the progression to overt HF, along with other indices of cardiovascular status.[107]
8. There are no insights from randomized clinical trials of patients with HF (either with HFpEF or HFrEF) as to the potential aetiological contribution of diabetic myocardial disorder. This entity was not considered for study inclusion, and the vast majority of patients had concomitant comorbidities, limiting generalizability of trial results to the treatment of (a small number) of patients with HF solely due to diabetic myocardial disorder.

Conclusions and future perspectives

Major uncertainties still exist about diabetic myocardial disorder. Despite these uncertainties, an indisputable association between T2DM and development of HF identifies patients with T2DM and asymptomatic cardiac abnormalities as those at a high risk along the HF trajectory. These patients may benefit from further risk assessment and prevention but frequently remain unrecognized. Therefore, further efforts at improving the understanding of diabetic myocardial disorder and recognition of its place along the cardiometabolic continuum are clinically relevant. In addition, future research should focus on providing effective strategies to prevent the progression of subclinical cardiac disease in a broader spectrum of patients with T2DM, in order to reduce the overall burden of HF.

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