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Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association—European Society of Cardiology

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Introduction

Heart failure (HF) is growing to a modern epidemic and despite advances in therapy, it still carries an ominous prognosis and a significant socioeconomic burden.¹ Many novel agents that emerged as promising HF drugs failed to improve residual morbidity and mortality.^{2,3} Since developing and testing new agents has become increasingly costly,⁴ the concept of repurposing existing drugs for new indications has gained considerable importance.

Conceptually, comorbidities such as type 2 diabetes mellitus (T2DM), obesity or chronic kidney disease, all highly prevalent in HF populations, have shifted from being innocent bystanders to drivers of HF. This applies especially to HF with preserved ejection fraction (HFpEF), a phenotype that accounts for more than 50% of HF patients and for which no effective therapy exists thus far.^{5,6} In particular, the prevalence of T2DM, thereby its combination with HF is rapidly increasing, mainly due to the obesity epidemic.

Cardiovascular (CV) outcomes are addressed by an increasing number of clinical studies in T2DM, mainly as safety endpoints for anti-diabetic agents. Some of those drugs have beneficial CV effects independent of their glucose-lowering action. Consequently, anti-diabetic agents have gained interest for their potential repurposing in HF treatment. In this context, the Translational Research Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) organized a workshop on HF and T2DM, focusing on the pathophysiological and therapeutic aspects of this relationship. Here, we summarize the main points raised during this workshop, providing an overview of current evidence and open issues.

Clinical background

Epidemiology

Patients with HF have a four-fold higher prevalence of T2DM (20%) than patients without HF (4–6%),^{4,7} and this rises to 40% in T2DM patients hospitalized for HF.^{8,9} T2DM worsens prognosis for patients with HF with reduced ejection fraction (HFrEF), but even more with HFpEF, by increasing the risk of death and hospitalization.¹⁰ Patients with T2DM have a 75% higher risk of CV death or HF hospitalization compared with those without T2DM.¹¹ Furthermore, the risk to develop HF is 2.5-fold increased for patients with T2DM¹² and 1.7-fold for patients with impaired glucose tolerance (IGT) or insulin resistance¹³ compared with normal (non-diabetic) individuals, respectively. In T2DM patients who are older than 65 years, the coexistence of HF portends a 10-fold higher mortality risk.⁷ Thus, epidemiological evidence implies a bidirectional association between HF and T2DM (Figure 1), with one increasing the incidence and worsening the prognosis of the respective other.¹⁴

Diabetic cardiomyopathy

Type 2 diabetes mellitus affects the heart through several mechanisms. Diabetic macroangiopathy causes coronary artery disease (CAD) and myocardial ischaemia. In addition, a distinct, ischaemia- and hypertension-independent cardiomyopathy was defined as diabetic cardiomyopathy, describing the direct effects of diabetes-associated metabolic alterations on myocardial function. Its diagnosis requires a history of long-standing and/or poorly controlled T2DM

along with exclusion of significant coronary, hypertensive, valvular and/or congenital heart disease as well as of familial, viral, toxic, or infiltrative cardiomyopathy. As reviewed in more detail elsewhere,¹⁵ diabetic cardiomyopathy was initially described as a dilated, HFrEF-like phenotype occurring in diabetic patients with microvascular complications such as nephropathy and retinopathy. More recently, diabetic cardiomyopathy shifted towards a rather restrictive, HFpEF-like phenotype, occurring more commonly in obese women with poor glycaemic control.¹⁵ However, since it is difficult to study the cardiac phenotype of patients with diabetes without the confounding influence of any other risk factors, the epidemiological evidence for such diabetic cardiomyopathy requires more epidemiological, but also basic research.

Pathophysiology

Mechanisms related to diabetic cardiomyopathy

In HF, the coexistence of T2DM mainly aggravates left ventricular (LV) diastolic dysfunction by increasing LV stiffness and mass, without impairing global pump function.^{16,17} In diabetic patients, LV diastolic dysfunction correlates with fasting blood glucose, HbA1c levels and body mass index (BMI), all markers of insulin resistance.¹⁸ However, it is currently unresolved which factors drive the development of one or the other diabetic cardiomyopathy phenotype. The restrictive phenotype is more prevalent in patients with T2DM and obesity, while the dilated phenotype is more common in type 1 diabetes.¹⁵ Accordingly, hyperglycaemia, hyperinsulinaemia, and lipotoxicity may predispose more to the restrictive phenotype, while autoimmune processes rather favour the dilated phenotype.¹⁵ At the same time, the diverse pathogenetic origins of myocardial dysfunction and remodelling in HFpEF and HFrEF may also determine the development of diabetic cardiomyopathy into either the restrictive or the dilated phenotype, respectively (Figure 1).^{5,15} In HFpEF, endothelial dysfunction of the coronary microvasculature predominates, triggered by comorbidity-related inflammation, while in HFrEF, cardiomyocyte loss caused by ischaemia or toxic agents prevails.¹⁹ In addition, interstitial and perivascular myocardial fibrosis and increased production of advanced glycation end products (AGEs) increase collagen stiffness through cross-linking, enhancing diastolic dysfunction in diabetic cardiomyopathy (Figure 1).²⁰ Fibrosis, although relevant to both phenotypes, appears more important in the dilated form.¹⁶

Changes in intracellular Ca^{2+} homeostasis are another hallmark of cardiac dysfunction in diabetes (Figure 1). Overall, the mechanisms of dysfunctional Ca^{2+} handling observed in diabetic mouse models resemble those in HFrEF, including decreased sarcoplasmic reticulum Ca^{2+} load and decreased amplitudes of cytosolic Ca^{2+} transients, but also elevated intracellular sodium (Na^+).^{21,22} In HFrEF, severe alterations in cytosolic Na^+ and Ca^{2+} handling have a negative impact on mitochondrial Ca^{2+} uptake, thereby the matching of ATP supply and demand and the regeneration of the anti-oxidative capacity, resulting in energetic deficit and oxidative stress.²³ Whether dysregulated cytosolic and mitochondrial Na^+ and Ca^{2+} handling contribute to the development of diabetic cardiomyopathy remains unclear

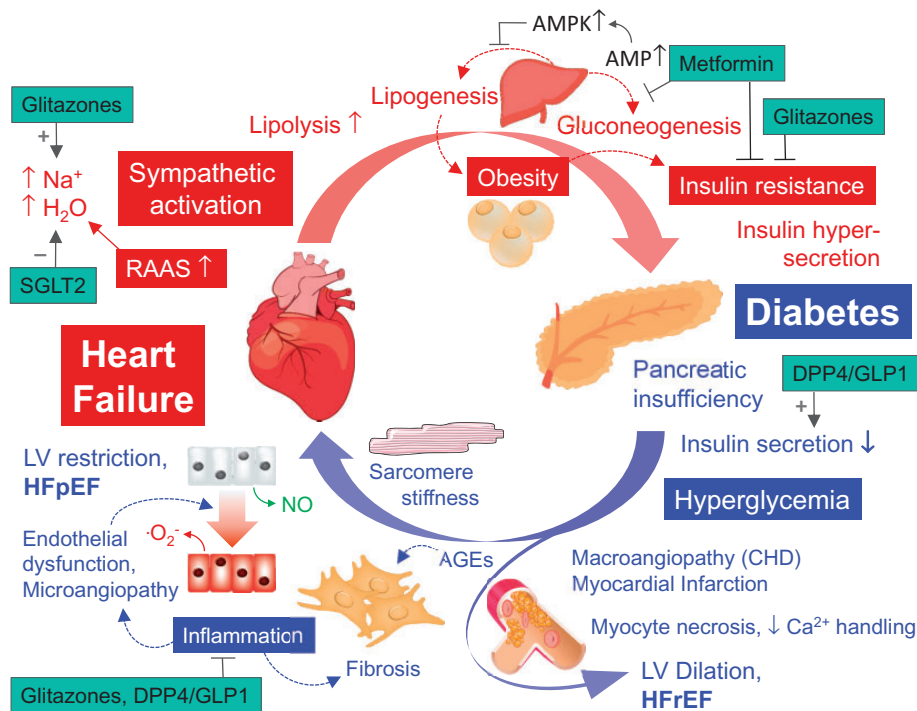


Figure 1 Systemic interdependence of heart failure and type 2 diabetes mellitus. In heart failure, neuroendocrine activation alters haemodynamics and metabolism, predisposing to the development of diabetes through insulin resistance. In diabetes, hyperglycaemia induces macro- and microvascular dysfunction, and myocardial ischaemia and/or infarction bias towards systolic dysfunction (heart failure with reduced ejection fraction), while in the absence of ischaemia, diastolic dysfunction (heart failure with preserved ejection fraction) prevails through a combination of sarcomere stiffness and fibrosis. Inflammation is a key systemic factor that contributes to several of these processes. The specific points of intervention by glucose-lowering drugs are indicated (all have in common that they lowered hyperglycaemia). AGEs, advanced glycation end products; AMP, adenosine monophosphate; AMPK, AMP-kinase; DPP4/GLP1, DPP4-inhibitors/GLP-1 analogs; SGLT2, SGLT2-inhibitors.

in vivo, despite recent *in vitro* data pointing towards such mechanisms.^{21,22,24}

A number of relevant mechanisms including derangement of myocardial energy substrates, insulin resistance and endothelial dysfunction, resulting from a series of underlying conditions and risk factors such as obesity, link T2DM, and myocardial dysfunction through inflammation, nutrient imbalance, and neurohormonal activation.²⁵

Myocardial energy substrate

The normal heart mainly consumes free fatty acids (FFA; ~70%) and glucose (~30%) (Figure 2).²⁶ It is, however, an 'omnivore' and can adapt its choice of fuels according to their availability. This metabolic flexibility is predominantly regulated by the 'Randle cycle', by which high circulating levels of glucose decrease rates of FFA oxidation and vice versa.²⁷

- In HF, uptake of glucose and FFA into cardiac myocytes is increased, while their further uptake and oxidation in mitochondria is decreased (Figure 2). This leads to accumulation of metabolic intermediates in the cytosol, inducing maladaptive signalling.²⁶
- In T2DM, increased FFA levels activate peroxisome proliferator-activated receptor (PPAR)- α , a nuclear receptor increasing transcripts of FFA metabolism, shifting substrate utilization towards

FFA (Figure 3). Together with increasing insulin resistance, this minimizes glucose utilization and makes the heart metabolically less flexible.^{26,28}

The dominance of FFA utilization in diabetic hearts contributes to energetic inefficiency. First, FFA oxidation requires 11% more O₂ per carbon unit than glucose oxidation. Second, FFA induce expression of mitochondrial uncoupling protein (UCP) 3 through PPAR- α ,²⁹ dissipating the mitochondrial proton gradient. This deteriorates ATP production efficiency, as more O₂ is required for ATP synthesis, a process termed 'mitochondrial uncoupling' (Figure 3).³⁰ A similar concept emerged for UCP2 and UCP3 in HF.³¹

In T2DM, nutritional supply accounts for elevated FFA and glucose plasma levels. Conversely, in HF, sympathetic activation promotes lipolysis and release of FFA from adipose tissue into the plasma (Figure 1). Elevated FFA plasma levels are associated with LV diastolic dysfunction, while their lowering improves diastolic function.^{32–34} Drugs that interfere with FFA utilization, thereby shift substrate utilization towards glucose, such as trimetazidine and perhexiline, (Figure 4), improve cardiac function in patients with ischaemic heart disease and/or HF, respectively.^{35,36}

Ketone bodies (mainly, D-beta-hydroxybutyrate) increase as a response to energy depletion or starvation, providing an alternative substrate for oxidative phosphorylation.³⁷ Ketone bodies are not

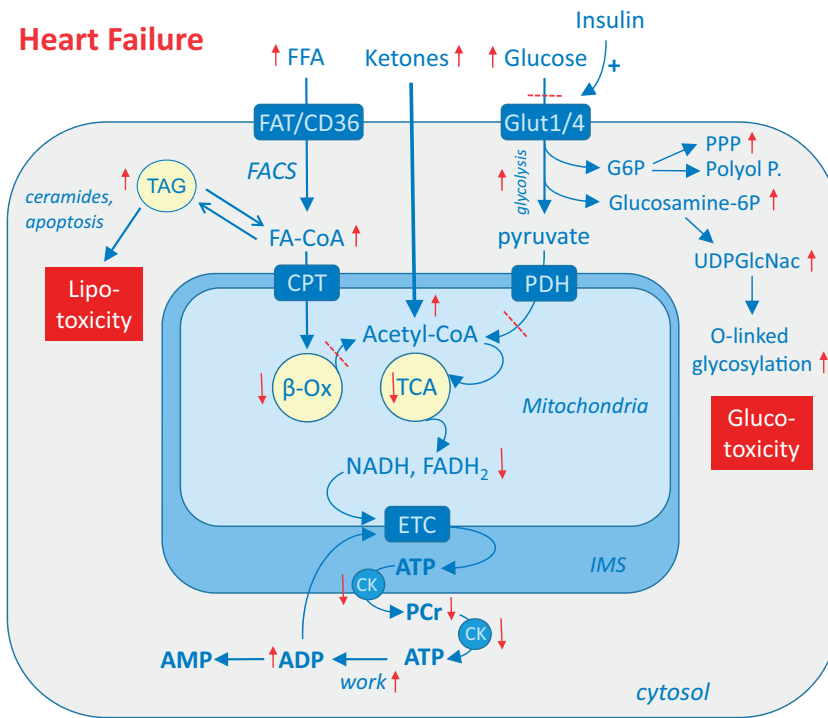


Figure 2 Cardiac metabolic alterations in heart failure. In heart failure, increased uptake of free fatty acids and glucose into the cytosol is uncoupled from mitochondrial uptake and oxidation of free fatty acid and pyruvate, respectively. This provokes accumulation of metabolic intermediates in the cytosol which can trigger lipo- and glucotoxicity. Instead, utilization of ketone bodies is increased in heart failure. Impaired overall substrate oxidation reduces Krebs cycle (TCA) activity, oxidizing electron donors NADH and FADH₂ for the electron transport chain (ETC). This reduces metabolic flux through creatine kinase (CK), thereby the phosphocreatine (PCr) to ATP ratio. β -Ox., β -oxidation; CPT-1/2, carnitine palmitoyltransferase type 1/2; FA-CoA, fatty acyl-coenzyme A; FACS, fatty acyl-coenzyme A synthetase; FAT/CD36, fatty acid translocase; GLUT 1/4, glucose transporters 1/4; G6P, glucose-6-phosphate; PDH, pyruvate dehydrogenase complex; PPP, pentose phosphate pathway; Polyol P., Polyol pathway; TAG, triacylglycerol; UDPGlcNac, UDP-glycnacylation. Red arrows (\uparrow) indicate the changes in heart failure.

readily available from food, but produced in the liver by incomplete oxidation of FFA released from adipose tissue in response to fasting.³⁸ The enzymes regulating ketone body metabolism are up-regulated in mice and humans with end-stage HF, while those regulating glucose and FFA metabolism are down-regulated (Figure 2).^{39–41} Accordingly, the failing heart oxidizes ketone bodies when metabolism of other energy substrates is impaired.⁴² However, whether enhanced ketone body metabolism is a cause, a consequence, a bystander or a compensating mechanism in HF is presently unknown.⁴² Furthermore, ketone bodies induce FFA uptake into adipocytes, therefore decreasing FFA in the circulation and in turn, increasing glucose uptake into myocytes, thus improving substrate provision and possibly energy production in the heart. A dietary increase in ketone bodies is difficult to accomplish and requires strict adherence to a high-fat and low-carbohydrate diet, the so called 'ketogenic diet'. A synthetic ketone ester drink (ΔG°) that achieved 10-fold higher circulating D- β -hydroxybutyrate levels than any dietary approach⁴³ improved physical performance and cognitive function in rats and humans.^{37,43,44} Furthermore, ΔG° reduced fasting lipid, HbA1c, fasting and postprandial glucose levels in T2DM patients as well as liver fat in obese subjects (Kieran Clarke, unpublished data); however, controlled trials are yet missing.

Insulin resistance in heart failure

Insulin resistance, the impaired ability of cells to take up glucose from the bloodstream in response to insulin, is associated with increased lipolysis, hepatic lipogenesis, and hepatic gluconeogenesis (Figure 1), thus increasing substrate supply to the heart.⁴⁵ However, myocardial substrate overload decreases substrate oxidation, leading to metabolic maladaptation and myocardial dysfunction through lipo- and glucotoxicity (Figure 3).⁴⁶ In this context, myocardial insulin resistance may even be an adaptive mechanism to ameliorate substrate overload,^{46,47} possibly explaining (at least to some extent) the adverse CV effects of tight glycaemic control with insulin and of some insulin-sensitizing agents such as the group of thiazolidinediones (TZD).^{46,48–51}

Endothelial function

Diabetes is associated with endothelial dysfunction (Figure 1), disturbing endothelial-cardiomyocyte communication and vascular function.^{5,52} Intensified glucose control reduced diabetic microvascular complications but has less impact on macrovascular complications and HF in T2DM patients, indicating direct HF protective effects of anti-diabetic drugs on endothelial function independent of their

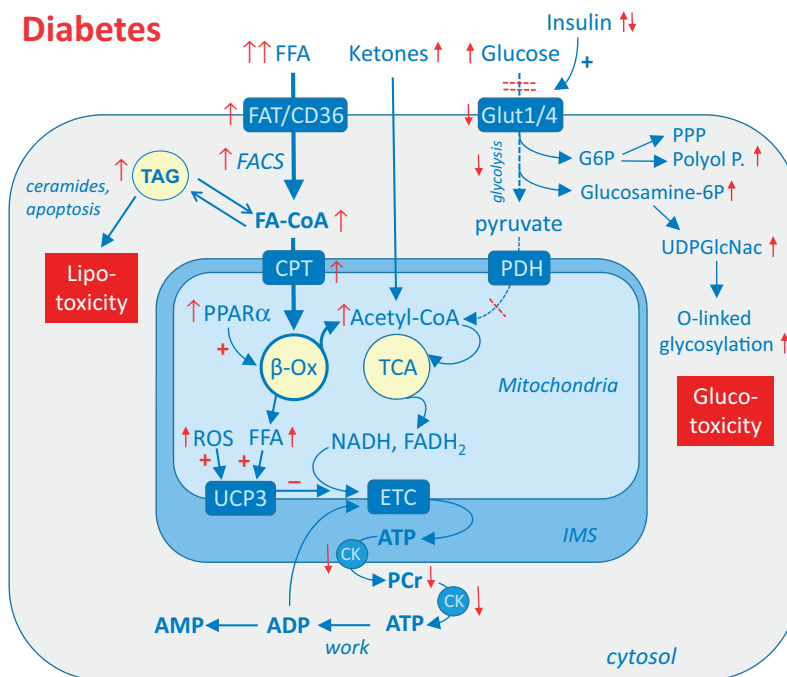


Figure 3 Cardiac metabolic alterations in diabetes. In diabetes, strongly increased free fatty acid activate peroxisome proliferator-activated receptor α (PPAR α), which up-regulates expression of genes involved in fatty acid (FA) oxidation. Increased FA oxidation shuts down glucose uptake and oxidation (insulin resistance), thereby blunts metabolic flexibility. Excessive FA are stored as triacylglycerol (TAG), which can mediate lipotoxicity. FA and reactive oxygen species (ROS) activate uncoupling protein 3 (UCP3), which makes ATP production less efficient. Abbreviations see legend of Figure 2.

glycaemic effects.⁵³ A common mechanism of several anti-diabetic drugs is activation of phosphatidylinositol 3-kinase (PI3K), which controls the activity of endothelial nitric oxide synthase (eNOS) (Figure 4).

The drugs: anti-diabetic agents and the heart—mechanisms and evidence

Metformin

Metformin is the first-line drug for the treatment of T2DM, although its mechanisms of action have not yet been fully elucidated.⁵⁴ Metformin inhibits respiratory chain enzymes (complex I) in mitochondria, hence decreasing ATP production with a parallel increase in AMP (Figure 4).⁵⁵ This inhibits glucose synthesis from pyruvate, thereby reducing hepatocytes gluconeogenesis (Figure 1). Furthermore, increased AMP stimulates AMP-activated protein kinase (AMPK), which inhibits acetyl-CoA carboxylase, malonyl-CoA, lipid and cholesterol synthesis (Figure 1).⁵⁴

In addition to its metabolic actions, metformin protects against myocardial ischaemia/reperfusion injury in animal models, limiting infarct size and attenuating post-ischaemic myocardial remodelling, irrespective of the presence of diabetes.⁵⁶ These effects are mediated by AMPK and eNOS (Figure 4), adenosine release and prevention of

mitochondrial permeability transition pore opening during reperfusion.⁵⁷ Metformin also prevented HF progression in dogs through AMPK activation (Figure 4).⁵⁸ Furthermore, metformin improves endothelial function *in vivo* by reducing superoxide production and increasing NO bioavailability (Figure 4). It also exerts anti-inflammatory effects in mammals independent of AMPK,⁵⁹ while attenuating myocardial fibrosis.⁶⁰ Interestingly, the anti-inflammatory action of metformin in humans was independent of the presence of T2DM.

In one randomized controlled trial (RCT), metformin reduced mortality and CV morbidity in T2DM patients,⁶¹ and positive outcomes confirmed by cohort studies and meta-analyses.^{62,63} While no prospective RCT with metformin in patients with T2DM and prevalent HF is available, a series of case-control- or cohort studies, systematic reviews and one meta-analysis showed that metformin (mono- or add-on-therapy) resulted in lower all-cause mortality, HF readmission and lower rates of lactic acidosis in diabetic patients with HF.^{64–69} Accordingly, metformin is recommended as first line therapy for the management of diabetes mellitus (DM) in patients with HF by the current ESC Guidelines (class IIa, level of evidence C).⁷⁰

Reducing infarct size and preventing post-ischaemic myocardial dysfunction and remodelling could be a potential beneficial mechanism of metformin in diabetic patients that provides some ground for drug repurposing in non-diabetic individuals. However, with the exception of one retrospective analysis,⁷¹ coexistent metformin therapy was not associated with reduced infarct size or improved LV systolic or diastolic function in T2DM patients with ST-elevation

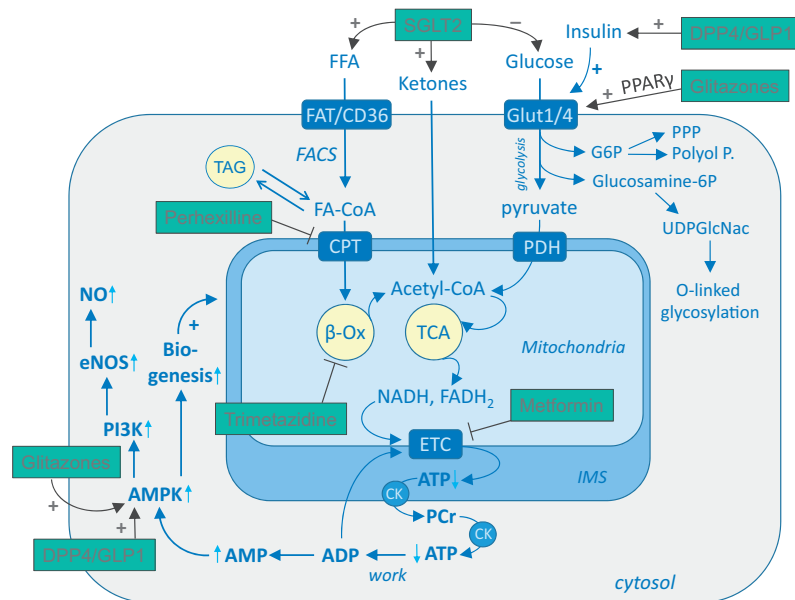


Figure 4 Metabolic interventions in diabetes and heart failure. For details see text. DPP4/GLP1, DPP4-inhibitors/GLP-1 analogs; SGLT2, SGLT2-inhibitors.

myocardial infarction (STEMI).^{72–74} Although a prospective trial in diabetic and non-diabetic patients with STEMI is missing, short-term metformin pre-treatment did not limit myocardial injury in non-diabetic patients undergoing coronary artery bypass grafting.⁷⁵ Lastly, the anti-inflammatory properties of metformin in non-diabetic HF could provide additional grounds for investigating the drug's repurposing in non-diabetic individuals, given the recent CANTOS trial establishing proof-of-concept of inflammation as a target in CV disease.⁷⁶

Main findings for metformin in T2DM and HF

- Metformin is a first-line therapy for glycaemic control in T2DM patients, particularly those with HF.
- Retrospective and cohort studies suggest reduced mortality and CV morbidity in DM patients with or without HF.
- Clinical data do not support protection against ischaemia–reperfusion injury despite positive preclinical studies.

Open questions for metformin in T2DM and HF

- What are the mechanisms supporting a beneficial effect in T2DM with HF?
- How does metformin compare with newer anti-diabetic agents in T2DM with HF?
- Does metformin during coronary reperfusion prevent HF in STEMI patients?

Glitazones (Thiazolidinediones)

Glitazones, or TZD, are insulin-sensitizing agents that activate the nuclear receptor PPAR- γ , a transcription factor that regulates multiple genes implicated in several metabolic pathways related to insulin sensitivity. These drugs improve glucose metabolism by increasing insulin sensitivity (Figures 1 and 4), thereby reducing hyperglycaemia and hyperinsulinaemia. The main effect of TZD is to shift FFA towards adipose tissue and away from other tissues, hence inducing a 'lipid-steal' effect that, in turn, improves glucose utilization. In addition, PPAR- γ agonists restore other metabolic derangements in insulin resistance and obesity by attenuating macrophage pro-inflammatory cytokine expression, adipocyte differentiation, and adipokine expression in adipocytes.^{77,78} Furthermore, PPAR- γ activation abrogates vasoconstriction and atherogenic effects of angiotensin II and improves eNOS-dependent vasodilation (Figures 1 and 4).⁷⁹ Its activation may also exert anti-remodelling effects by inhibiting glucose-induced induction of TGF β 1 and TGF β 1-mediated fibronectin expression.^{80,81} PPAR γ activation with pioglitazone may improve diastolic function,⁸² and a recent meta-analysis suggests that TZD may protect against atrial fibrillation.⁸³ Furthermore, TZD exert beneficial effects on endothelial function, as rosiglitazone AMPK-dependently stimulates NO synthesis (Figure 4), and glitazones improve endothelial function in non-diabetic individuals with CAD.⁸⁴ However, PPAR- γ agonism also confers some adverse effects, as it causes Na⁺ and fluid retention and oedema, body weight increase and bone fractures (Figure 1).

Meta-analyses of TZD studies suggested that rosiglitazone conferred an increased risk of myocardial infarction and HF, with or without an increased risk of CV death.^{50,51,85–87} The latter was not replicated by the RECORD trial in T2DM patients without a history of HF,⁸⁸ but HF occurrence did increase with rosiglitazone, leading

the European Medicines Agency to recommend suspension of the drug's license in 2010. In the PROactive trial in patients with T2DM and CAD, ischaemic stroke or peripheral arterial disease but not HF, pioglitazone actually reduced the composite endpoint of all-cause death, non-fatal myocardial infarction and non-fatal stroke.⁸⁴ Here, the drug increased the risk of episodes of HF worsening, but the decrease in the composite endpoint was maintained in severe HF patients.^{84,89} The differential clinical outcome of rosiglitazone and pioglitazone may reflect their aforementioned differential effects on lipid metabolism. In a meta-analysis, pioglitazone even increased the risk of HF, without, however, an increase in the composite endpoint of death, myocardial infarction or stroke.^{49,87} These findings lead to the concept that HF worsening was a class effect of TZD.⁹⁰ In this context, the ESC Guidelines for HF state that TZD are contraindicated for the treatment of T2DM in patients with HF (class III, level of evidence A).⁷⁰

Fluid retention by TZD is central in the pathophysiology of drug-induced hospitalizations for HF worsening, as the prevalence of oedema with TZD increases. Combined action of PPAR- γ activation in kidneys and the vasculature, including increased Na⁺ and water retention in distal tubules, arterial vasodilatation, and increased vascular volume capacity and capillary permeability may underlie these clinical observations.⁷⁹ In this context, the observed effect of the drug might have been simple fluid retention and not true HF in the PROactive trial.^{84,91} On the other hand, since insulin resistance may actually be an adaptive mechanism of the failing heart to resist substrate overload, insulin sensitization by TZD may be detrimental by increasing fuel supply.⁴⁶

The clinical side effects of full PPAR γ agonism sparked interest in partial PPAR γ agonists. INT131 is the most advanced member of this novel class of selective PPAR γ modulators (SPPARM), which may provide similar glucose-lowering potential but less fluid retention. INT131 is currently evaluated in phase I and II clinical studies in diabetes.

Main findings for glitazones in T2DM and HF

- PPAR γ activation confers benefits in metabolic signalling, vascular function, inflammation, fibrosis, and diastolic function in the diabetic heart.
- PPAR γ activation by glitazones may cause fluid retention and worsening in HF.
- Glitazones are not recommended in patients with pre-existing HF.
- Pioglitazone reduces all-cause death, non-fatal myocardial infarction and non-fatal stroke, a benefit maintained in patients who experienced HF worsening.

Open questions for glitazones in T2DM and HF

- What is the exact pathophysiology of glitazone-induced HF worsening (fluid retention, insulin sensitization with cardiac substrate overload)?
- What is the value of partial PPAR γ activation, including the novel SPPARMs causing less fluid retention in diabetic HF?

Incretin-based therapies: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors

Glucagon-like peptide-1 receptor agonists

Incretins, i.e. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are intestinal hormones released in response to food intake and inflammatory stimuli.^{92,93} Activation of the GLP-1 receptor impacts the pancreas, stomach, and brain to accommodate food ingestion, including decreased gastric motility and appetite. Dipeptidyl peptidase-4 (DPP-4) breaks GLP-1 down to the inactive GLP-1 metabolite (9-36 amide).

Glucagon-like peptide-1 receptor agonists lower blood glucose by increasing insulin and decreasing glucagon release (Figure 1), while further decreasing body weight in T2DM patients.^{94–96} In animal models, GLP-1 receptor agonists reduced infarct size and improved cardiac function after ischaemia/reperfusion through pro-survival pathways such as PI3K, Akt, and ERK1/2 (Figure 4)^{97,98} and attenuated post-ischaemic LV remodelling by activating AMPK/eNOS/cGMP/PKG pathways.^{98,99} They also improved LV function in non-ischaemic HF models, such as anthracycline-induced cardiotoxicity, potentially by increasing myocardial glucose uptake.^{99,100} In another preclinical model, GLP-1 lowered blood pressure by atrial natriuretic peptide release, which was, however, not recapitulated in humans.¹⁰¹ GLP-1 and GLP-1 receptor agonists may also improve endothelial function by PI3K-induced eNOS activation (Figures 1 and 4).¹⁰²

Some trials on GLP-1 receptor agonists yielded beneficial CV outcomes. The long-lasting and structurally related GLP-1-agonists liraglutide or semaglutide reduced CV death, non-fatal myocardial infarction or non-fatal stroke in high-risk T2DM patients, as shown by the LEADER and SUSTAIN-6 trials, respectively.^{95,96} In contrast, the short-acting lixisenatide (ELIXA) and the long-acting exenatide (EXSCCEL) GLP-1 receptor agonists had neutral CV effects.^{103,104}

The mechanisms for this differential response remain elusive.^{95,96,104,105} The beneficial CV outcomes provided by liraglutide and semaglutide occurred in high-risk T2DM patients with a history of CAD, ischaemic stroke, peripheral arterial disease, HF or kidney disease and therefore concern mostly secondary prevention.^{95,96} None of the GLP-1 receptor agonists improved HF outcomes in these populations, but rather increased heart rate by approximately 3 b.p.m.^{95,96,103,104} In addition, in the FIGHT and LIVE studies in patients with HFrEF with or without T2DM, liraglutide increased adverse CV events compared with placebo.^{106,107} Safety concerns were also raised for vildagliptin, but no increase in adverse CV events was confirmed by subsequent retrospective studies or meta-analyses.^{108,109} Ongoing RCTs with long-acting GLP-1 receptor agonists dulaglutide (REWIND, NCT01394952) and albiglutide (HARMONY outcomes, NCT0246551; both expected to report 2019) will provide further insights into their potential effect on CV outcome in high-risk patients with DM.

Interestingly, the first-in-class angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan also lowered HbA1c in patients with HFrEF and T2DM.¹¹⁰ This effect may be mediated by GLP-1 enhancement through decreased metabolism by neutral endopeptidase, the target of sacubitril.^{110–112} However, the change in HbA1c and the composite primary outcome did not correlate in the seminal PARADIGM-HF trial.¹¹⁰

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors lower blood glucose by increasing insulin and decreasing glucagon release (Figure 1) without decreasing body weight in T2DM patients.^{94–96} In diabetic mice, DPP-4 inhibition improved cardiac contractility after myocardial infarction and improved LV diastolic function,^{113,114} although another study failed to confirm those beneficial effects.¹¹⁵

In contrast to GLP-1 receptor agonists and despite the beneficial vascular effects of DPP-4 inhibitors in pre-clinical¹¹⁶ and clinical studies,¹¹⁷ RCTs with DPP-4 inhibitors were neutral regarding major adverse CV events at glucose equipoise.^{105,118,119} In the SAVOR-TIMI 53 trial, saxagliptin even increased the risk for HF hospitalization by 27% in patients with a history of CAD, ischaemic stroke, peripheral artery disease or CV risk factors.¹¹⁹ This was, however, neither the case for alogliptin in T2DM patients with a recent acute coronary syndrome (EXAMINE) nor with sitagliptin in T2DM patients with a history of CAD, ischaemic stroke or peripheral artery disease (TECOS).^{105,120} A meta-analysis of RCTs revealed a non-significant 14% increased HF risk with DPP-4 inhibition, but with large heterogeneity between different substances.¹²¹ Nevertheless, the FDA added a HF warning for this class of drugs. Ongoing RCTs with linagliptin (CARMELINA and CAROLINA expected to report 2018 and 2019) will provide more evidences on safety of DPP-4 inhibitors in HF.

Main findings for Incretin-based therapies in T2DM and HF

- Incretin-based therapies do not increase the risk of major adverse CV events (MACE).
- In LEADER and SUSTAIN-6, GLP-1 receptor agonists reduced MACE.

Open questions for incretin-based therapies in T2DM and HF

- Do incretin-based therapies prevent macrovascular events?
- Are incretin-based therapies efficient in T2DM with HF?
- What are the mechanisms of CV mortality reduction by long-acting GLP-1 receptor agonist liraglutide, and how can this affect patient selection?

Sodium glucose co-transporter 2 inhibitors

The sodium glucose co-transporter 2 (SGLT2) is located in the proximal renal tubule and accounts for 90% of glucose reabsorption.¹²² The remaining urinary glucose is reabsorbed by SGLT1, which is also expressed in the intestine and the heart. Inhibition of SGLT2 by empagliflozin, dapagliflozin, ertugliflozin, or canagliflozin (with the latter also featuring some SGLT1-inhibitory capacity) increases urinary glucose excretion, thereby urine volume.¹²³ The concept of SGLT2-inhibition is different from other glucose-lowering strategies since glucose is removed from the 'system', thereby reducing total body and cellular glucose toxicity independent of insulin. The mode of

action of SGLT2-inhibitors has metabolic and haemodynamic consequences.

Metabolic consequences

Besides reducing fasting and postprandial blood glucose levels, SGLT2-inhibitors decrease uric acid but increase glucagon, FFA, and ketone body (beta-hydroxybutyrate) levels (Figure 1). In addition, SGLT2 inhibition increases endogenous glucose production, which partly compensates glucose excretion, preventing hypoglycaemia.^{124,125} Through early diuretic and longer-term metabolic effects, SGLT2-inhibitors reduce body weight.^{123,126} In addition, SGLT2 inhibitors affect cardiac metabolism by changing myocardial substrate supply and by altering myocardial energy demand.¹²⁵

Substrate supply: SGLT2 inhibitors decrease glucose and increase FFA and ketone bodies (Figure 4), thereby shifting myocardial substrate supply.^{125,127} In DM patients, SGLT2 inhibitors up-regulate ketone body levels and oxidation; ketone bodies may represent a more efficient metabolic substrate than lipids (but not glucose) as they liberate more energy per carbon unit (the 'thrifty substrate hypothesis'; Figure 4).¹²⁸ Furthermore, empagliflozin increases BCAA catabolism in T2DM,¹²⁹ which is diminished in HF. Whether these actions are translated into clinically meaningful effects on the myocardium is presently unclear.¹³⁰

Mitochondrial function: While the natriuretic effect of empagliflozin occurs only transiently at the onset of therapy,¹³¹ empagliflozin reduced $[Na^+]_i$ in cardiac myocytes, presumably by inhibiting the Na^+/H^+ exchanger (NHE).¹³² This may increase mitochondrial Ca^{2+} by slowing mitochondrial Na^+/Ca^{2+} exchange.¹³² In mitochondria, Ca^{2+} is required to match ATP supply to demand and regenerate the antioxidative capacity through Krebs cycle activation.²³ In DM and HF, $[Na^+]_i$ is elevated and causes energetic mismatch and oxidative stress.^{21,23} Therefore, empagliflozin may exert beneficial effects by preventing energetic mismatch and oxidative stress in cardiac myocytes by lowering $[Na^+]_i$ (the 'Na⁺ hypothesis'),²⁴ which may also have consequences for preventing arrhythmias.¹³³

Haemodynamic consequences

In the kidney, empagliflozin lowers intra-glomerular pressure through the 'tubulo-glomerular feedback' mechanism: due to increased Na^+ concentrations at the macula densa, afferent arteriole vasoconstriction lowers glomerular pressure, thereby reducing albuminuria and conferring renal protection.^{134,135} The diuretic effect lowers blood pressure and the heart rate-blood pressure product as determinants of myocardial O_2 consumption,^{136,137} thereby unloading the heart. Furthermore, this ameliorates arterial stiffness, decreases the aortic and carotid augmentation index as well as LV mass.¹³⁸ Finally, anti-inflammatory and anti-oxidative properties were observed.¹³⁹

In the EMPA-REG OUTCOME trial, empagliflozin reduced the composite primary endpoint of CV death, nonfatal myocardial infarction, and nonfatal stroke in type 2 DM patients with CV disease.¹²⁶ This effect was driven by a 38% reduction in CV death, while empagliflozin also reduced all-cause death and HF hospitalizations. In particular, the risk of HF hospitalization was lowered by 35%, and this reduction reached 40% in patients with estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/1.73 m² at baseline. The early separation of the curves in favour of

Table 1 Effects of anti-diabetic agents on combined cardiovascular and heart failure endpoints according to key randomized trials (hazards ratio and 95% confidence intervals or percent of events in active treatment vs. placebo and P values)

Drug class	Agent (trial)	Composite CV endpoints	Heart failure endpoints
Biguanides	Metformin (Meta-analysis; 35 trials) ⁹⁰	CV death, MI, HF, stroke 0.94 (0.82–1.07)	Not reported
Glitazones (thiazolidinediones)	Pioglitazone (PROactive; n = 5238) ¹¹⁹	Death, MI, stroke 0.84 (0.72–0.98)	Any HF event 11% vs. 8% (P < 0.0001)
	Rosiglitazone (RECORD; n = 4447) ¹¹⁸	CV death or hospital 0.99 (0.85–1.16)	HF death or hospital 2.10 (1.35–3.27)
GLP-1 receptor agonists	Lixisenatide (ELIXA; n = 6068) ¹³⁶	CV death, MI, UA, stroke 1.02 (0.89–1.17)	HF hospital 0.96 (0.75–1.23)
	Liraglutide (LEADER; n = 9340) ¹²⁷	CV death, MI, stroke 0.87 (0.78–0.97)	HF hospital 0.87 (0.73–1.05)
	Semaglutide (SUSTAIN-6; n = 3297) ¹²⁶	CV death, MI, stroke 0.74 (0.58–0.95)	HF hospital 1.11 (0.77–1.61)
	Exenatide (EXSCEL; n = 14752) ¹³⁷	CV death, MI, stroke 0.91 (0.83–1.00)	HF hospital 0.94 (0.78–1.13)
DDP-4 inhibitors	Alogliptin (EXAMINE; n = 5380) ¹²⁰	CV death, MI, stroke 0.96 (≤1.16)	Not reported
	Saxagliptin (SAVOR-TIMI 53; n = 16492) ¹¹⁹	CV death, MI, stroke 1.00 (0.89–1.12)	HF hospital 1.27 (1.07–1.51)
	Sitagliptin (TECOS; n = 14671) ¹⁰⁵	CV death, MI, UA, stroke 0.98 (0.88–1.09)	HF hospital 1.00 (0.83–1.20)
SGLT2 inhibitors	Empagliflozin (EMPA-REG; n = 7020) ¹²⁶	CV death, MI, stroke 0.86 (0.74–0.99)	HF hospital 0.65 (0.50–0.85)
	Canagliflozin (CANVAS; n = 10142) ¹⁴⁴	CV death, MI, stroke 0.86 (0.75–0.97)	HF hospital 0.67 (0.52–0.87)

CV, cardiovascular; DDP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; MI, myocardial infarction; SGLT2, sodium glucose co-transporter 2; UA, unstable angina.

empagliflozin and the unexpected action on HF hospitalizations suggest that the favourable effects of empagliflozin are mainly due to a reduction in HF-associated events. Although only 10% of patients in EMPA-REG had a history of HF at baseline, the beneficial effects on HF hospitalizations and CV death were consistent in patients with or without HF.¹⁴⁰ Since mortality and hospitalization rates in the placebo group of the EMPA-REG OUTCOME trial were comparable to the rates in trials on patients with HFpEF,¹⁴¹ it may be speculated that a higher fraction of patients than the 10% had undiagnosed HF, and in particular, HFpEF. However, it seems plausible that by its mode of action, empagliflozin may also provide benefit in HFrEF patients, although this view was recently challenged.¹⁴² Empagliflozin slowed the progression of kidney disease and related events, including incident albuminuria, and incident or worsening nephropathy.¹⁴³

Canagliflozin also reduced the primary endpoint of CV death, non-fatal myocardial infarction and nonfatal stroke in patients with T2DM at high CV risk vs. placebo in the CANVAS trial program, and—comparable to empagliflozin—also HF hospitalization.¹⁴⁴ However, it did not reduce all-cause mortality, but increased the risk for amputation and bone fracture. The EMPA-REG OUTCOME trial, however, did not confirm such findings.¹⁴⁵

Ongoing large studies evaluate the CV efficacy of dapagliflozin (DECLARE; expected to report 2018) and ertugliflozin (VERTIS CV; expected to report 2020) in patients with diabetes in a primary and secondary prevention setting. The effects on HF outcomes may be considered a class effect of SGLT2-inhibitors. Several new studies are underway, including two new trials with empagliflozin in HFrEF and HFpEF (EMPEROR-Reduced/Preserved) and one trial with dapagliflozin in HFrEF (DAPA-HF).¹⁴⁶ Those trials will provide evidence on whether SGLT2-inhibitors may improve outcome in HF patients with or without DM.

Main findings for SGLT2-inhibitors in T2DM and HF

- In EMPA-REG OUTCOME, empagliflozin reduced CV death and HF hospitalizations.
- The favourable effect of empagliflozin occurred in patients with and without HF history.
- Patients with renal impairment benefited from empagliflozin.
- In CANVAS, canagliflozin also reduced HF hospitalization, suggesting a class-effect.

Table 2 Open issues and gaps of evidence regarding the co-treatment of diabetes mellitus and heart failure

Open issue	Gaps in evidence
Insulin resistance and the failing heart	Role of insulin resistance as an adaptive mechanism in heart failure
Beneficial metabolic effects of ketone bodies	Myocardial glucose uptake and energy production in the presence of increased circulating ketone levels
	Role of ketone metabolism in heart failure
Pleiotropic effects of metformin	Clinical trials of the synthetic ketone ester Delta-G [®] in diabetic and non-diabetic patients with heart failure
	Prospective evidence on ischaemia/reperfusion injury in non-diabetic patients
Detrimental effects of glitazones	Clinical effects of anti-inflammatory action
	Pathophysiology of glitazone-induced heart failure
	Differentiation between glitazone-induced heart failure and fluid retention
	Potential detrimental effects of insulin sensitization in the failing heart
Cardiovascular effects of incretin-based therapies	Evaluation of selective PPAR-gamma modulators to improve clinical efficacy and decrease side effects
	Effect of insulin increase in the failing heart
	Relevance of the GLP-1 receptor agonism in cardioprotection; signalling pathways of GLP-1 metabolite (9–36 amide)
	Cardiovascular outcomes of liraglutide and semaglutide in primary prevention setting (diabetic patients without cardiovascular disease)
	Cardiovascular outcomes of liraglutide and semaglutide in non-diabetic patients
	Effects of GLP-1 receptor agonists left ventricular diastolic function
	Effects of GLP-1 receptor agonists on vascular endpoints (central pressures, arterial stiffness, endothelial function) and ventriculo-arterial coupling
Cardioprotective effect of SGLT2 inhibitors	Effects of SGLT2 on myocardial substrate utilization, energy production and energy demand
	Cardiovascular outcomes of gliflozins in primary prevention setting (T2DM patients without cardiovascular disease)
	Cardiovascular outcomes of gliflozins in non-diabetic patients
Heart failure phenotype	Effects of antidiabetic agents specifically on HFrEF and HFpEF

GLP-1, glucagon-like peptide-1; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PPAR, peroxisome proliferator-activated receptors; SGLT2, sodium glucose co-transporter 2.

Open questions for SGLT2-inhibitors in T2DM and HF

- What are the underlying mechanisms explaining the beneficial effect of SGLT2 inhibitors on HF hospitalization and CV mortality?
- Is the protective effect of SGLT2 inhibitors on HF restricted to patients with T2DM or does it also apply to non-diabetic HF patients?
- Which subgroup of T2DM patients has the greatest benefit from SGLT2-inhibitors?
- Is the benefit maintained in T2DM patients without CV comorbidities or high CV risk?

Open issues and perspectives for future research

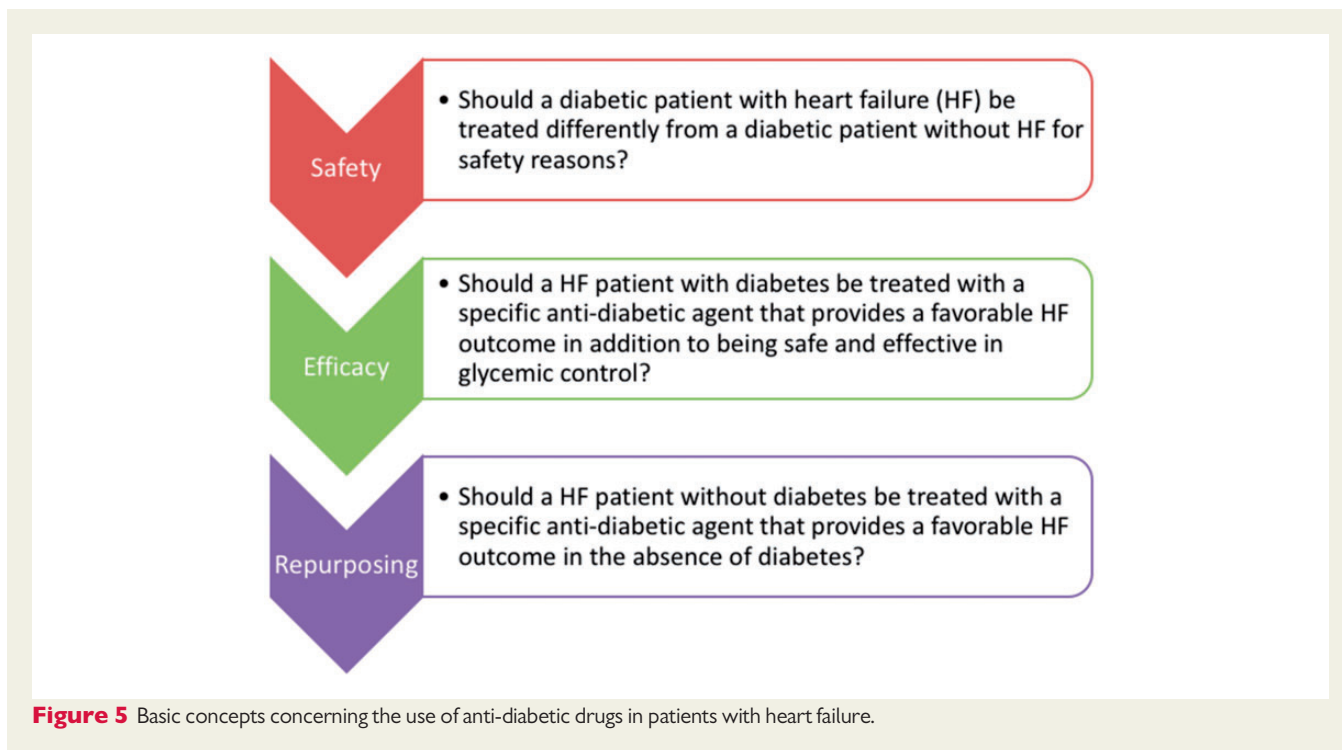
Knowledge on the CV safety of anti-diabetic drugs and in particular, their potential benefits for patients with HF is increasing (Table 1). The treatment of patients with HF and T2DM still remains challenging as many issues regarding the properties of anti-diabetic drugs in HF remain unresolved (Table 2). However, the recent benefits with GLP-1 receptor agonists and SGLT2-inhibitors re-spurred enthusiasm.

Defining whether the favourable effects of specific anti-diabetic agents are preserved in patients with HF in the absence of T2DM is the next logical step towards the concept of drug repurposing (Figure 5). In this context, SGLT2-inhibitor trials designed to prove their efficiency rather than safety in patients with HF with or without T2DM are currently underway.

Understanding the pathophysiology of CV alterations in HF and T2DM is important. Key open questions include the relevance of insulin resistance in the failing heart (adaptive vs. maladaptive),⁴⁷ the impact of substrate switch in response to SGLT2-inhibition, the role of SGLT2-inhibitors on cardiac Na⁺ metabolism and many others. Selection of proper preclinical models that reflect a specific HF phenotype is crucial as experimental results obtained by different models may not be comparable.

The CV effects of several anti-diabetic agents are not fully resolved. As patient populations recruited in large clinical trials are quite heterogeneous, this may prevent the detection of potential benefits. Identifying subpopulations of responding patients may be useful in guiding the design of future clinical trials.¹⁴⁷

An important and yet under-investigated issue is the differential efficacy of anti-diabetic drugs in men and women. In two meta-analyses, diabetes was associated with a less favourable CV risk profile and a higher risk of death from CAD in females compared with males,^{148,149} while women also display a reduced response to low-dose aspirin.^{150,151} Emerging evidence suggests that treatment with



glitazones may lower bone density, increasing the risk of fractures in diabetic women.

Therapy of T2DM often involves combination of anti-diabetic agents, but the additive or synergistic effects of combined drugs in HF remains to be investigated. For instance, metformin alone or in combination with sulfonylurea reduced CV morbidity and mortality compared with sulfonylurea monotherapy in T2DM with HF in a retrospective study,¹⁵² but this was not confirmed in a systemic review of observational studies.⁶⁷

Finally, the selection of endpoints remains a crucial issue that was lately debated. ‘Hard’ endpoints, required for regulatory reasons, are suitable for large safety trials of anti-diabetic agents in broad CV populations, but impose large sample sizes and huge expenditures. Clinically relevant ‘soft’ or surrogate (patient-oriented) endpoints require smaller samples and considerably less costs and may be used in focused efficacy trials in selected subpopulations.

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