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REVIEW

Non-insulin antihyperglycaemic drugs and heart failure: an overview of current evidence from randomized controlled trials

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Abstract

Type 2 diabetes mellitus (T2DM) is highly prevalent in the general population and especially in patients with heart failure (HF). It is not only a risk factor for incident HF, but is also associated with worse outcomes in prevalent HF. Therefore, antihyperglycaemic management in patients at risk of or with established HF is of importance to reduce morbidity/mortality. Following revision of the drug approval process in 2008 by the Food and Drug Administration and European Medicines Agency, several cardiovascular outcome trials on antihyperglycaemic drugs have recently investigated HF endpoints. Signals of harm in terms of increased risk of HF have been identified for thiazolidinediones and the dipeptidyl peptidase 4 inhibitor saxagliptin, and therefore, these drugs are not currently recommended in HF. Sulfonylureas also have an unfavourable safety profile and should be avoided in patients at increased risk of/with HF. Observational studies have assessed the use of metformin in patients with HF, showing potential safety and potential survival/morbidity benefits. Overall use of glucagon-like peptide 1 receptor agonists has not been linked with any clear benefit in terms of HF outcomes. Sodium–glucose cotransporter protein 2 inhibitors (SGLT2i) have consistently shown to reduce risk of HF-related outcomes in T2DM with and without HF and are thus currently recommended to lower risk of HF hospitalization in T2DM. Recent findings from the DAPA-HF trial support the use of dapagliflozin in patients with HF with reduced ejection fraction and, should ongoing trials with empagliflozin, sotagliflozin, and canagliflozin prove efficacy, will pave the way for SGLT2i as HF treatment regardless of T2DM.

Keywords Heart failure; Antihyperglycaemic; Antidiabetic; Type 2 diabetes mellitus; Trials; Guidelines

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Introduction

Heart failure (HF) and type II diabetes mellitus (T2DM) are highly prevalent and inflict a considerable financial burden on health care systems.[1,2] They often coexist, with 40% of patients hospitalized for HF also having diabetes and 12% of patients with diabetes suffering also from HF.[3,4] Patients with concomitant HF and T2DM report worse prognosis as compared with those suffering from only one of these diseases.[5,6]

In 2008, the Food and Drug Administration and the European Medicines Agency revised the approval processes for glucose-lowering therapies, requiring cardiovascular (CV) outcome trials to be completed either before or after approval for any new antidiabetic medication. This decision followed the publication of a meta-analysis showing that rosiglitazone, although significantly lowering glycated haemoglobin, increased the risk of myocardial infarction, which led to questions regarding the use of glycaemic control as efficacy and registration outcome in randomized controlled trials (RCTs) evaluating the efficacy/safety of glucose-lowering drugs.[7] Although regulatory agencies focused on the risk of macrovascular events, rosiglitazone also significantly

increased the risk of HF. Given the important interaction between T2DM and HF, worsening/hospitalization for HF has been used as an important secondary endpoint in all the recent RCTs focusing on T2DM treatments.

The aim of this review is to summarize and structure the current evidence on the interplay between glucose-lowering drugs and HF.

Non-insulin antihyperglycaemic medications inducing harm in heart failure: thiazolidinediones

Thiazolidinediones (TZDs) effectively lower glucose levels by increasing insulin sensitivity in peripheral tissues.[8] In the PROACTIVE RCT, enrolling more than 5000 patients with T2DM and established macrovascular disease, pioglitazone vs. placebo reduced by 10% the risk of the primary outcome, which included any death, non-fatal myocardial infarction, stroke, acute coronary syndrome, coronary or leg arteries revascularization, or amputation above the ankle,[9] but also increased risk of HF hospitalization.[9] Similarly, in the RECORD trial, a 2.6-fold increased risk of HF requiring hospitalization or leading to death was observed in patients randomized to rosiglitazone on top of metformin or sulfonylurea monotherapy vs. a combination of metformin and sulfonylurea, whereas there was no difference in risk of CV death, myocardial infarction, and stroke.[10] Two meta-analyses confirmed these findings, suggesting a class effect for TZD on HF event risk,[11,12] which may be explained by renal sodium retention triggered by the peroxisome proliferator-activated receptor gamma activation by TZD.[13] Therefore, the use of TZD for treatment of T2DM in patients with HF is not recommended in the current European and American HF guidelines.[14,15]

Non-insulin antihyperglycaemic medications inducing potential harm in heart failure: inhibitors of dipeptidyl peptidase 4 and sulfonylureas

Inhibitors of dipeptidyl peptidase 4

Inhibitors of dipeptidyl peptidase 4 (DPP4i) increase pre-prandial and post-prandial levels of GLP1, which promotes insulin secretion and suppresses glucagon secretion, leading to improved glycaemic control.[16]

The SAVOR-TIMI 53 trial was the first large-scale RCT testing DPP4i vs. placebo on top of usual care in more than 16 000 patients with T2DM and either history or high risk of CV disease.[17] Although saxagliptin did not affect the primary major adverse cardiovascular event (MACE) endpoint, it significantly increased the risk of HF hospitalization by 27% as compared with placebo.[17] Notably, saxagliptin-associated increase in risk of HF hospitalization was greater in patients with history or at higher risk of HF (i.e. impaired renal function, or elevated baseline levels of N-terminal pro-B-type natriuretic peptides).[18] Although the underlying mechanisms for these findings are not clear, saxagliptin has been suggested to directly interact with myocytes and affect intracellular Ca^{2+} levels, leading to impaired contractility.[19] In the EXAMINE trial, which tested alogliptin vs. placebo in patients with T2DM hospitalized for acute coronary syndrome, the MACE outcome was not met, and although the risk of HF was not significantly increased by the treatment, a higher number of HF events was observed in patients receiving alogliptin (3.1%) vs. placebo (2.9%).[20,21]

The finding of DPP4i increasing the risk of HF hospitalization could not be confirmed in other RCTs. Indeed, both the TECOS trial,[22] testing sitagliptin vs. placebo in T2DM patients with established CV disease, and the CARMELINA trial,[23] testing linagliptin vs. placebo in T2DM patients at high risk of CV and renal diseases, showed no effect of DPP4i on HF-related endpoints nor on the primary MACE outcome.[24,25] Finally, in the VIVIDD trial, enrolling 254 patients with T2DM and HF with reduced ejection fraction (HFrEF) (<40%), vildagliptin (vs. placebo) did not affect ejection fraction (EF) but increased left ventricular volumes.[26] The study also showed that vildagliptin increased, albeit not significantly, CV mortality. The CAROLINA trial, which randomized 6033 T2DM patients with or at increased risk of CV disease to linagliptin vs. the sulfonylurea glimepiride on top of standard care, showed no increased risk of MACE and of HF-related outcomes with linagliptin vs. glimepiride over a median follow-up of more than 6 years.[27]

An increased risk of HF was thus observed only in the SAVOR-TIMI 53 with concordant signals in EXAMINE and VIVVID. However, a possible increase in occurrence of HF hospitalizations cannot be completely ruled out in the studies with DPP4i reporting a null effect given that HF hospitalizations had not been prospectively assessed and adjudicated. The Food and Drug Administration expanded the warning regarding cautious use in HF patients to the whole DPP4i class and consistently amended product labels.

Sulfonylureas

Sulfonylureas facilitate insulin release and hereby lower blood glucose levels, but clinical use of these drugs is limited by side effects such as weight gain and a high risk of hypoglycaemia.[28] Although CV safety of sulfonylureas has been debated for many years, the evidence on this topic is mostly based on observational data.[28] In a meta-analysis of

observational studies, as well as in a propensity score matched analysis of the National Veterans Health Administration databases, use of sulfonylureas was associated with higher risk of HF as compared with metformin.[29,30] However, in the UKPDS 33 trial, which randomized 3867 patients with T2DM to intensive vs. conventional blood glucose control with sulfonylureas or metformin vs. diet, no study treatment increased risk of CV events, including HF.[31] In the ADOPT trial, randomizing 4360 patients with T2DM to rosiglitazone, glyburide, or metformin, glyburide was associated with a lower risk of CV events (including HF) than was rosiglitazone, and the risk associated with metformin was similar to that with rosiglitazone.[32] Finally, in a recent retrospective cohort study of 132 737 patients with T2DM, starting sulfonylureas on top of metformin or no previous antidiabetic treatment was associated with a higher risk of CV events, and in particular of HF, compared with initiating DPP4i.[33] Conversely, in the CAROLINA trial, the risk of CV events, including also HF, did not differ in patients receiving glimepiride vs. DPP4i linagliptin.[27]

Overall, the available data regarding the risk of HF with sulfonylureas are conflicting, and these agents might be or not be harmful in patients with or at risk of HF. Therefore, other antihyperglycaemic treatments with proven safety/efficacy profile should be preferred to sulfonylureas in T2DM patients with or at high risk of HF.

Non-insulin antihyperglycaemic medications with potential neutral effect in heart failure: glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 (GLP1) increases insulin secretion and downregulates glucagon in response to food intake, improving glycaemic control.[34] GLP1 receptor antagonists (GLP1-RAs) enhance this effect and reduce appetite, inducing also weight loss.[34] Experimental studies in animal models show that lack of GLP-1R results in impaired left ventricular contractility and decreased resting heart rate.[35] Notably, GLP-1 infusion increases left ventricular contractility, stroke volume, and cardiac output in animal models of induced dilated cardiomyopathy.[36] All these data, together with the evidence of a role for GLP-1 on post-ischaemia recovery and myocardial viability, have suggested a potential benefit for GLP-1RA in patients with T2DM and concomitant HF.[37,38]

Several CV outcome trials have evaluated efficacy and safety of GLP1-RA. The ELIXA trial randomized 6068 patients with T2DM and a recent acute coronary syndrome to lixisenatide vs. placebo. Lixisenatide did not reduce the primary outcome of the trial (composite of CV death, myocardial infarction, stroke, or hospitalization for unstable angina) or any of the secondary endpoints, including also HF hospitalization.[39] Similarly, the EXSCEL trial, randomizing 14 752 patients with T2DM with or without pre-existing CV disease, showed that exenatide was not superior to placebo in terms of MACE risk reduction.[40] Although exenatide reduced the composite endpoint of all-cause mortality and hospitalization for HF in the overall cohort, this benefit was attenuated in patients with prevalent HF at baseline.[41] In the LEADER, SUSTAIN-6, and HARMONY OUTCOMES trials, the GLP1-RA liraglutide, semaglutide, and albiglutide, respectively, reduced the MACE endpoint as compared with placebo, but, once again, not the risk of HF hospitalization.[42–44] Finally, PIONEER-6, randomizing 3183 subjects at high CV risk, showed semaglutide being non-inferior to placebo for risk of MACE and HF hospitalization, but decreasing the risk of CV death by 51% and the risk of all-cause death by 49%.[45] Interestingly, in a recent meta-analysis of all major CV outcome trial on GLP1-RA, these drugs were reported to slightly reduce the risk of HF hospitalization.[46]

Two phase II RCTs have focused on investigating liraglutide vs. placebo in HF patients with or without concomitant T2DM. The FIGHT trial randomized 300 patients hospitalized for acute HFrEF ($<$40%).[47] The primary outcome was a global rank score in which all patients, regardless of treatment assignment, were ranked across three hierarchical tiers: time to death, time to HF rehospitalization, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days.[47] The LIVE trial randomized 241 patients with clinically stable HFrEF ($<$45%) and on optimal HF treatment with or without T2DM.[48] The primary endpoint was change in EF from randomization to end of follow-up.[48] Neither FIGHT nor LIVE met their primary outcome.[47,48] Notably, in LIVE, a significant increase in heart rate as well as in the occurrence of serious cardiac and HF-related events was observed in the liraglutide vs. the placebo arm.[48] Albeit the exploratory nature and the small number of patients and events, these results have questioned the use of GLP1-RA in patients with HF. Finally, the REWIND trial, which has randomized 9901 T2DM patients with or at high risk of CV disease to dulaglutide vs. placebo, also showed a reduction in risk of the primary MACE outcome but no differences for HF hospitalization.[49]

Non-insulin antihyperglycaemic medications with potential benefit in heart failure: metformin

Besides classical glucose-lowering mechanisms, that is, reduction of hepatic gluconeogenesis and increasing peripheral

insulin sensitivity, metformin has been recently suggested to act on the intestine by increasing GLP-1 secretion and possibly altering the microbiome.[50] Metformin has been the cornerstone of T2DM therapy for decades, which has led to a deep clinical experience with its use. The cardioprotective role of metformin has emerged in the UKPDS trials, with the UKPDS 34 showing a reduction in risk of diabetes-related endpoints and mortality in overweight patients with newly diagnosed T2DM receiving metformin vs. diet.[51] In the UKPDS 80 trial, metformin was shown to reduce the risk of any diabetes-related endpoint, including also HF, and of myocardial infarction and mortality compared with diet over a follow-up of 10 years.[52] However, a recent meta-analysis of RCTs could not report any reduction in risk of HF linked with use of metformin vs. placebo or other treatments.[53]

Metformin may be beneficial in patients with HF by enhancing glucose uptake in insulin-resistant cardiomyocytes and attenuating remodelling as suggested by experimental studies[54,55] and by improving myocardial efficiency by reducing myocardial oxygen consumption.[56] Importantly, metformin use was initially limited to non-HF T2DM patients due to concerns regarding a potentially increased risk of lactic acidosis,[57] which has been proven to be very low in clinical practice ($<$10 cases per 100 000 patient-years).[58] Similarly, the glomerular filtration rate label criterion for metformin has been lowered from $\geq$60 to $\geq$30 mL/min in the past years, as concerns regarding its safety in patients with moderately reduced kidney function could not be confirmed.[59] The European Society of Cardiology (ESC) guidelines on HF and the recent ESC guidelines on diabetes recommend metformin as a treatment option for T2DM patients with HF (class IIa; level C),[14,28] whereas the American Heart Association/American College of Cardiology guidelines are more cautious.[60] Notably, current evidence on metformin is mainly based on extensive clinical experience, observational studies and smaller RCTs assessing primarily glycaemic control, because metformin has not been tested in CV outcome trials.[61] In a nested case–control study enrolling around 3500 patients with both HF and T2DM, metformin use was significantly associated with improved survival, as compared with patients not exposed to any antidiabetic drug.[62] Similarly, in a propensity score matched analysis of around 6000 patients with T2DM and concomitant HF, treatment with metformin vs. other antidiabetic treatments was associated with a 24% improved survival.[63] In a propensity score matched analysis of around 130 000 patients with T2DM, those receiving metformin had 32% lower risk of being hospitalized or dying for HF as compared with patients treated with a sulfonylurea.[30] However, metformin did not improve exercise capacity in a randomized trial of 62 HFrEF patients comparing metformin vs. placebo and had no effect on risk of HF in a meta-analysis of RCTs.[61,64]

Non-insulin antihyperglycaemic medications with benefit in heart failure: sodium–glucose cotransporter protein 2 inhibitors

Sodium–glucose cotransporter protein 2 inhibitors (SGLT2i) block the sodium–glucose cotransporter protein 2 in the proximal convoluted tube of the kidney. They increase urinary glucose excretion (i.e. glycosuria) but do not increase the risk of hypoglycaemia (unless paired with insulin or sulfonylurea), as the extent of glucose lowering depends on starting glucose (and is therefore smaller in patients with low glucose levels). The glycosuria and concomitant natriuresis lead to a decrease in extracellular volume,[65] which may promote a reduction in vascular wall stress, less congestion, and improved cardiac function.[66] By preventing coupled glucose and sodium reabsorption in the proximal tubule, sodium delivery to the macula densa increases, which leads through tubulo-glomerular feedback to afferent arteriole adenosine-induced vasoconstriction and therefore attenuation of chronic hyperfiltration responsible for nephron loss.[65] Interestingly, it has been suggested that while conventional diuretics reduce intravascular volume and thus cause maladaptive neurohormonal activation, SGLT2i may be associated with greater vascular refill and greater reduction of interstitial fluid.[67] SGLT2i have also metabolic effects on the heart. By increasing glucagon levels, they may exert a positive inotropic and chronotropic effect.[68] Additionally, by increasing hydroxybutyrate levels, they may foster a shift in myocardial fuel supply from fatty acids and glucose to the more energy-efficient ketones in the diabetic heart.[69] Finally, SGLT2i foster the inhibition of the sodium–hydrogen exchanger in the heart, which has been shown to minimize cardiomyocyte injury and attenuate the development of cardiac hypertrophy, remodelling, systolic dysfunction, and fibrosis.[70] Both haemodynamic, metabolic, and renal effects induced by SGLT2i may be particularly beneficial in patients with HF.[70]

The first landmark trial to evaluate the efficacy and safety of SGLT2i in T2DM patients was the EMPA-REG OUTCOME.[71] This RCT allocated 7020 individuals with T2DM and established CV disease to receive empagliflozin vs. placebo. Over a median follow-up of 3.1 years, empagliflozin reduced the risk of the primary outcome (i.e. composite of CV death, myocardial infarction, or stroke) by 14%, CV death by 38%, all-cause mortality by 32%, and notably, risk of HF hospitalization by 35%.[71] These benefits were consistent in patients with and without HF at baseline, as well as in patients at different risk of HF outcomes.[72] A post hoc analysis of the EMPA-REG OUTCOME trial showed that empagliflozin may reduce the risk of HF hospitalization, CV, and any death following a first hospitalization for HF, providing a rationale for studying SGLT2i specifically in the post-acute HF window.[73]

More recently, the CANVAS trial,[74] which investigated canagliflozin vs. placebo in T2DM patients with established or high risk of CV disease, canagliflozin significantly reduced the primary MACE endpoint by 24% but not its individual components.[74] Like empagliflozin,[72] canagliflozin significantly reduced the risk of HF hospitalization by 33%.[74] Notably, the observed absolute, but not relative, risk reductions of CV death or HF hospitalization and of HF hospitalization alone were greater in patients with vs. without a history of HF.[75] Additionally, the CREDENCE trial, which was planned to randomize 6000 patients with T2DM and chronic kidney disease to either canagliflozin or placebo, was stopped earlier as a planned interim analysis showed a 30% lower risk of the primary endpoint (end-stage renal disease/doubling of serum creatinine/death from renal or CV cause) in the intervention arm.[76] Interestingly, canagliflozin was also shown to reduce the risk of HF hospitalization by 39%.[76] The EMPA-KIDNEY and the DAPA-CKD trials, which evaluate the effect of empagliflozin/dapagliflozin in patients with chronic kidney disease, are currently ongoing and will provide further evidence.[77,78] Of note, DAPA-CKD has recently been stopped for efficacy, per a press release issued by the manufacturer.[79]

Recently, the results of the third landmark trial evaluating efficacy/safety of SGLT2i were published. The DECLARE TIMI 58 trial randomized 17 160 T2DM patients with history or at high risk of CV disease to dapagliflozin or placebo. Dapagliflozin did not significantly reduce the risk of MACE, but led to a 17% significant reduction of risk of CV death or HF hospitalization, which was mainly driven by a reduction of HF hospitalization.[80] Notably, in a post hoc analysis, dapagliflozin reduced the risk of HF hospitalization in patients with HF, regardless of EF, as well in those without HF, but reduced the risk of CV and all-cause death only in patients with HFrEF.[81] One more trial on the SGLT2i ertugliflozin vs. placebo, the VERTIS-CV, is currently ongoing and enrolling patients with T2DM and established CV disease. It is expected to enrol 8000 patients, and results are expected in 2020. HF hospitalization is one of the secondary endpoints considered in this trial.[82]

The consistent finding of SGLT2i reducing HF-related hospitalizations in patients with/without established HF supports a potential class effect for these drugs on HF events. These trial findings, together with an emerging understanding of mechanisms of action of this pharmacological class, have led to the hypothesis whether SGLT2i may be beneficial in terms of mortality/morbidity reduction also in HF patients without T2DM, who were not enrolled in the above-mentioned trials. Several RCTs are testing this hypothesis, that is, SGLT2i as an HF treatment, irrespective of coprevalent T2DM. The DAPA-HF, randomizing 4744 patients with symptomatic HFrEF (≤40%), with and without T2DM, to dapagliflozin vs. placebo, was the first and so far only RCT to report.[83] Over a median follow-up of 18.2 months, dapagliflozin reduced the primary composite outcome of CV death or worsening HF by 26%.[83] This effect was consistent for all the individual components of the composite endpoint as well as across several pre-specified subgroups, including patients with and without T2DM at baseline.[83] Notably, the benefit in terms of hard outcomes was paralleled by an improvement in symptoms, physical function, and quality of life.[84] Furthermore, the trial did not raise any relevant drug-related safety concern regardless of age, as there was no higher incidence of volume depletion or serious adverse renal events in the treatment group.[84,85] Later in the DEFINE-HF trial, randomizing 263 patients with HF and EF $\leq$ 40%, NYHA classes II–III, elevated natriuretic peptides, with and without T2DM, to dapagliflozin 10 mg daily vs. placebo for 12 weeks, patients receiving dapagliflozin were more likely to experience clinically meaningful improvements in a dual primary endpoint of HF-related health status or $\geq$20% decrease in natriuretic peptide levels, although there was no significant difference in the mean natriuretic peptide levels between study groups.[86] More recently, the EMPERIAL-Reduced (EF $\leq$ 40%) and EMPERIAL-Preserved (EF $>$ 40%) trials, both randomizing 300 patients with chronic HF to empagliflozin vs. placebo, could not show an effect on exercise capacity (change in 6-min walk distance from baseline to a 12-week follow-up).[87] In an RCT enrolling 80 acute HF patients with and without T2DM, empagliflozin 10 mg/day vs. placebo for 30 days did not significantly improve dyspnoea, diuretic response, natriuretic peptide levels, and length of hospital stay.[88]

Upcoming evidence on sodium–glucose cotransporter protein 2 inhibitors

Several phase III RCTs on SGLT2i are currently ongoing in HF with both reduced and preserved EF. The DELIVER trial aims to test the efficacy of dapagliflozin in terms of reduction of CV death or HF hospitalization/urgent visit in 4700 patients with symptomatic HF with EF $>$ 40% regardless of T2DM status.[89] The EMPEROR-Preserved trial enrolling patients with HF with EF $>$ 40% and the EMPEROR-Reduced in HF with EF $\leq$ 40% will randomize 5750 and 3600 symptomatic HF patients regardless of T2DM status, respectively, to empagliflozin vs. placebo.[90,91] Both trials use a different primary endpoint as compared with DAPA-HF, that is, composite of CV death and HF hospitalization, excluding urgent visits not leading to hospitalization. Furthermore, the EMPEROR-Reduced trial aims to enrol patients with more severe HF as compared with DAPA-HF, as explained by the higher N-terminal pro-B-type natriuretic peptide cut-off for patient inclusion.[90] Finally, the SOLOIST-WHF trial was estimated to randomize 4000 patients with haemodynamically stable HF, regardless of EF, and T2DM, following a hospital admission for worsening HF, to sotagliflozin vs. placebo,[92] but was closed out early due to funding and COVID-19

Table 1 Recent trials of antidiabetic therapies focusing heart failure outcomes

Drug	Clinical trial	Design	Primary outcome	HF-related outcome
Thiazolidinediones				
Pioglitazone	PROACTIVE[9]	▪34.5 months, 1:1 randomized, placebo-controlled trial ▪5238 patients with T2DM and macrovascular disease	Non-inferiority for the primary outcome (death, non-fatal MI, stroke, ACS, coronary or leg artery revascularization, amputation)	Increased risk of HF hospitalization
Rosiglitazone	RECORD[10]	▪5.5 years, 1:1 randomized, placebo-controlled trial ▪4447 patients with T2DM and elevated HbA1c	Non-inferiority for the primary outcome (CV hospitalization or CV death)	Increased risk of HF hospitalization or HF death
Inhibitors of dipeptidyl peptidase 4				
Saxagliptin	SAVOR-TIMI 53[17]	▪2.1 years, 1:1 randomized, placebo-controlled trial ▪16 492 patients with T2DM and history/at high risk of CV disease	Non-inferiority for the primary outcome (composite of CV death, MI, or ischaemic stroke)	Increased risk of HF hospitalization, especially in patients with prevalent HF or at high risk of HF
Alogliptin	EXAMINE[20]	▪18 months, 1:1 randomized, placebo-controlled trial ▪5380 patients with T2DM and a recent ACS	Non-inferiority for the primary outcome (composite of CV death, MI or ischaemic stroke)	Numerically higher HF event rate
Sitagliptin	TECOS[22]	▪3 years, 1:1 randomized, placebo-controlled trial ▪14 671 patients with T2DM and established CV disease	Non-inferiority for the primary outcome (composite of CV death, MI, stroke, or hospitalization for unstable angina)	No effect on HF-related endpoints
Linagliptin	CARMELINA[23]	▪2.2 years, 1:1 randomized, placebo-controlled trial ▪6979 patients with T2DM and high risk of CV/renal disease	Non-inferiority for the primary outcome (composite of CV death, MI, or ischaemic stroke)	No effect on HF-related endpoints
	CAROLINA[27]	▪6.3 years, 1:1 randomization vs. glimepiride ▪6033 patients with T2DM and risk of/established CV disease	Non-inferiority for the primary outcome (composite of CV death, MI, or ischaemic stroke)	No effect on HF-related endpoints
Vildagliptin	VIVIDD[26]	▪52 weeks, 1:1 randomized, placebo-controlled trial ▪254 patients with T2DM and HFrEF	No difference in change in ejection fraction	Increased left ventricular volume
Glucagon-like peptide 1 receptor agonists				
Lixisenatide	ELIXA[39]	▪25 months, 1:1 randomized, placebo-controlled trial ▪6068 patients with T2DM and a recent ACS	Non-inferiority for the primary outcome of CV death, MI, stroke, or hospitalization for unstable angina	No effect on HF hospitalization
Exenatide	EXSCEL[40]	▪3.2 years, 1:1 randomized, placebo-controlled trial ▪14 752 patients with T2DM	Non-inferiority for the primary outcome (composite of CV death, MI, or stroke)	Reduced risk of all-cause mortality and HF hospitalization, although this was attenuated in patients with prevalent HF
Liraglutide	LEADER[44]	▪3.8 years, 1:1 randomized, placebo-controlled trial ▪9340 patients with T2DM and high CV risk	Superiority for the primary outcome (composite of CV death, MI, or stroke)	No effect on HF-related endpoints
	FIGHT[47]	▪180 days, 1:1 randomized, placebo-controlled trial ▪300 patients with HFrEF and a recent hospitalization	No difference in time to death, time to HF hospitalization, and time-averaged proportional change in NTproBNP	
	LIVE[48]	▪24 weeks, 1:1 randomized, placebo-controlled trial ▪241 patients with stable HFrEF	No difference in change in ejection fraction	Significant increase in heart rate and occurrence of serious cardiac events
Semaglutide	SUSTAIN-6[43]			

(*Continues*)

Table 1 (continued)

Drug	Clinical trial	Design	Primary outcome	HF-related outcome
		▪104 weeks, 1:1 randomized, placebo-controlled trial ▪3297 patients with T2DM	Superiority for the primary outcome (composite of CV death, MI, or stroke)	No effect on HF-related endpoints
	PIONEER-6[45]	▪1.3 years, 1:1 randomized, placebo-controlled trial ▪3183 patients at high CV risk	Non-inferiority for the primary outcome (composite of CV death, MI, or ischaemic stroke)	No effect on HF-related endpoints
Albiglutide	HARMONY OUTCOMES[42]	▪1.5 years, 1:1 randomized, placebo-controlled trial ▪9463 patients with T2DM and CV disease	Superiority for the primary outcome (composite of CV, MI, or stroke)	No effect on HF-related endpoints
Biguanide				
Metformin	UKPDS 80[52]	▪10 years, 1:1 randomized controlled trial ▪4209 T2DM patients	Reduction of any diabtes-related endpoint including also HF	
Sodium–glucose transport protein 2 inhibitors				
Empagliflozin	EMPA-REG Outcome[71]	▪37 months, 1:1 randomized, placebo-controlled trial ▪7020 patients with T2DM and CV disease	Reduction in the primary outcome (composite of CV death, MI, or stroke)	Reduced risk of HF hospitalization irrespective of baseline HF status
	EMPERIAL reduced[87]	▪12 weeks, 1:1 randomized, placebo-controlled trial ▪300 patients with HFrEF	No effect on exercise ability	
	EMPERIAL preserved[87]	▪12 weeks, 1:1 randomized, placebo-controlled trial ▪300 patients with HFpEF	No effect on exercise ability	
	EMPA-RESPONSE-AHF[88]	▪30 days, 1:1 randomized, placebo-controlled trial ▪80 patients with acute HF	No improvement in dyspnoea, diuretic response, natriuretic peptide levels, or length of hospital stay, but no safety concerns and reduction of a combined endpoint of worsening HF, HF rehospitalization, or death at 60 days	
Canagliflozin	CANVAS[74]	▪188 weeks, 1:1 randomized, placebo-controlled trial ▪10 142 patients with T2DM and high CV risk	Superiority for the primary outcome (composite of CV death, MI, or stroke)	Reduced risk of HF hospitalization, possibly more pronounced in patients with prevalent HF
Dapagliflozin	DECLARE TIMI 58[80]	▪4.2 years, 1:1 randomized, placebo-controlled trial ▪17 160 patients with T2DM and established/at high risk of CV disease	Non-inferiority for the primary outcome (composite of CV death, MI, or stroke)	Reduced risk of HF hospitalization, reduced risk of death in patients with HFrEF
	DAPA-HF[83]	▪18 months, 1:1 randomized, placebo-controlled trial ▪4744 patients with HFrEF	Reduction in the primary composite outcome of CV death and worsening of HF	
	DEFINE-HF[86]	▪12 weeks, 1:1 randomized, placebo-controlled trial 263 patients with symptomatic HFrEF and elevated natriuretic peptides	Improvement in HF related health status or natriuretic peptides, but no reduction of mean natriuretic peptide levels	

ACS, acute coronary syndrome; CV, cardiovascular; HF, heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.

concerns affecting enrolment and the ability to complete the trial.[93]

Implications for clinical practice

According to the 2019 ESC guidelines on diabetes, SGLT2i are recommended (class I; level A) as a first-line therapy for T2DM in patients with established CV disease, such as those with HF, either alone or in combination with metformin.[28,94] In agreement, the consensus report update from the American Diabetes Association and European Association for the Study of Diabetes specifically recommends the use of SGLT2i in patients with T2DM and HF.[95] While TZD and the DPP4i saxagliptin are clearly not recommended in HF because of the associated increased risk of HF hospitalization (class III; level A), GLP1-RA (class IIb; level A) and the DPP4i sitagliptin

Table 2 Upcoming trials of antidiabetic therapies focusing heart failure patients

Drug	Clinical trial	Design	Primary endpoint
Empagliflozin	EMBRACE HF (NCT03030222)	▪12 week 1:1 randomized, placebo-controlled trial ▪60 symptomatic HF patients with implanted PAP monitor	Change in PAP
	EMPEROR reduced (NCT03057977)	▪38 month 1:1 randomized, placebo-controlled trial ▪ 2850 symptomatic HFrEF patients	Composite of time to first adjudicated CV death of HHF
	EMPEROR preserved (NCT03057951)	▪38 month 1:1 randomized, placebo-controlled trial ▪6000 symptomatic HFpEF patients with recent structural heart disease or HHF	Composite of time to first adjudicated CV death of HHF
	EMPA-VISION (NCT03332212)	▪12 week 1:1 randomized, placebo-controlled trial ▪86 symptomatic HFrEF and HFpEF patients	Change in phosphocreatine-ATP-ratio by MR spectroscopy
	RECEDE-CHF (NCT03226457)	▪6 week 1:1 randomized, cross-over, placebo-controlled trial ▪34 symptomatic HF patients with established diagnosis of T2DM	Change in urine output
	ERA-HF (NCT03271879)	▪6 month 1:1 randomized, cross-over, placebo-controlled trial ▪128 HFrEF patients with ICD/CRT, established diagnosis of T2DM and at high risk of arrhythmic events	Burden of premature ventricular complexes (defined as the percentage of all betas in a pre-specified period captured on ICD/CRT)
	Borisov et al. (NCT03753087)	▪38 month 1:1 randomized, placebo-controlled trial ▪100 symptomatic HFpEF patients with established diagnosis of T2DM	Change in exercise capacity measured by 6MWT
	SUGAR (NCT03485092)	▪40 weeks 1:1 randomized, placebo-controlled trial ▪130 symptomatic HFrEF patients with stablished diagnosis of T2DM	Left ventricular end systolic volume index and global longitudinal strain by MR imaging
	EMMY (NCT03087773)	▪26 weeks 1:1 randomized, placebo-controlled trial ▪476 patients with a recent myocardial infarction and significant myocardial necrosis	Change in NTproBNP
	EMPA-TROPISM (NCT03485222)	▪26 weeks 1:1 randomized, placebo-controlled trial ▪80 patients with symptomatic HFmrEF or HFrEF	Left ventricular end systolic volume and end diastolic volume
Dapagliflozin	PRESERVED-HF (NCT03030235)	▪12 weeks 1:1 randomized, placebo-controlled trial ▪320 patients with symptomatic HFpEF with recent evidence of worsening HF	Change in NTproBNP
	DEFINE-HF (NCT02653482)	▪12 weeks 1:1 randomized, placebo-controlled trial ▪263 patients with symptomatic HFrEF	Change in NTproBNP and change in HF specific quality of life questionnaire
	DELIVER (NCT03619213)	▪33 months 1:1 randomized, placebo-controlled trial ▪4700 patients with symptomatic HFpEF	Composite of CV death, HHF or urgent HF visit
	DETERMINE preserved (NCT03877224)	▪16 week 1:1 randomized, placebo-controlled trial ▪400 patients with symptomatic HFpEF	Change in exercise capacity measured by 6MWT
	DETERMINE reduced (NCT03877237)	▪16 week 1:1 randomized, placebo-controlled trial ▪300 patients with symptomatic HFrEF	Change in exercise capacity measured by 6MWT
	Asaad et al. (NCT03794518)	▪3 year 1:1 randomized, placebo-controlled trial	Time to first HHF

(*Continues*)

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Table 2 (continued)

Drug	Clinical trial	Design	Primary endpoint
		▪648 patients with HFrEF, a recent HHF and established diagnosis of T2DM	
Ertugliflozin	ERTU-GLS (NCT03717194)	▪24 week 1:1 randomized, placebo-controlled trial ▪120 patients with stage B HF and established diagnosis of T2DM	Change in global longitudinal strain
Sotagliflozin	SOLOIST-WHF (NCT03521934)	▪32 months 1:1 randomized, placebo-controlled trial ▪4000 HFrEF patients with established diagnosis of T2DM who are hospitalized for HF	Composite of CV death of HHF
Metformin	DANHEART (NCT03514108)	▪60 months, 1:1 randomized trial of metformin vs. placebo ▪1500 symptomatic HFrEF patients with or at risk of T2DM	Composite of all-cause death, HHF, acute myocardial infarction or stroke

6MWT, 6-min walk test; CRT, cardiac resynchronization therapy; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; ICD, implantable cardioverter defibrillator; MR, magnetic resonance; PAP, pulmonary artery pressure; T2DM, type 2 diabetes mellitus.

and linagliptin (class IIb; level B) may be considered for T2DM treatment in HF patients even though these treatments have not been shown to reduce the risk of HF outcomes.[28] Metformin, based on the above-discussed potential beneficial effect in HF, should be considered for T2DM treatment in HF patients with estimated glomerular filtration rate $>$ 30 mL/min/1.73m^2.[28]

In HF patients with an established, non-TZD/saxagliptin based antihyperglycaemic therapy and with good glycaemic control, current ESC guidelines recommend to add a SGLT2i-based regimen to counteract worsening HF.[28] Dapagliflozin is the only SGLT2i, which, up to date, has been shown to be effective in HF without T2DM. Use of SGLT2i as HF treatment, that is, regardless of T2DM status, is not considered yet in either American or European guidelines and does not yet have a regulatory label. Ongoing trials will add to the evidence in HFrEF and will show whether the effect shown by dapagliflozin in HFrEF will also hold true in HFpEF.

At present, it is possible to advocate a class effect for SGLT2i for the prevention of HF in patients with T2DM while only dapagliflozin should be considered for the treatment of HF regardless of the presence of T2DM.

SGLT2i are well tolerated, and in general, side effects of this drug class are genital and urinary tract infections. However, increased urinary tract infections were not demonstrated with dapagliflozin in DAPA-HF. SGLT2i can also cause polyuria with volume depletion.[94] Whether the combination of SGLT2i and sacubitril/valsartan might lead to excessive diuresis/hypotension represents a current gap in the evidence according to the guidelines and deserves further investigation.[28] The combination of dapagliflozin and sacubitril/valsartan was well tolerated in DAPA-HF and no increased risk of hypotension leading to discontinuation of either drug was observed, although the subsample of subjects receiving both medications was relatively small. Additionally, in a recent post hoc analysis of the DAPA-HF trial, the benefit of dapagliflozin was consistent regardless of background HF therapy, including sacubitril/valsartan.[96] Concomitant diuretic therapy, however, should be carefully monitored and, if needed, reduced upon initiation of SGLT2i or initiation or uptitration of sacubitril/valsartan. These issues might be of particular importance in patients with pre-existing chronic kidney disease and in older patients, who might be more sensitive to shifts in volume status. Finally, more severe complications such as diabetic keto acidosis or Fournier's gangrene (the latter only seen with canagliflozin) are rare but should be kept in mind.[94] Additionally, diabetic keto acidosis was not increased by dapagliflozin in diabetic and non-diabetic HF patients in DAPA-HF (*Table*s *1* and *2*).

Conclusions

The interplay and mutual risk increase in T2DM and HF highlight the need to identify antihyperglycaemic agents able to prevent HF in T2DM patients and to improve mortality/morbidity in those with T2DM and established HF. Current evidence supports the use of SGLT2i as primary treatment for T2DM in patients with and at high risk of HF. At present, dapagliflozin has shown benefit for the treatment of diabetic and non-diabetic patients with HFrEF. Should the trials with the other SGLT2i replicate the results of DAPA-HF, these agents may receive an HF indication as a class.

Conflict of interest

G.S. reports grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, personal

fees from Societa´ Prodotti Antibiotici, grants from MSD, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, grants from Boston Scientific, grants from Boehringer Ingelheim, and personal fees from GENESIS, Medtronic, and Cytokinetics, outside the submitted work.

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G.R. has nothing to disclose.

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J.B. reports other from Amgen, other from Astra Zeneca, other from Bayer, other from Boehringer Ingelheim, other from Bristol Mayers Squib, other from CVRx, other from G3 Pharmaceutical, other from Janssen, other from Luitpold, other from Medtronic, other from Merck, other from Novartis, other from Vifor, and other from Novo Nordisk, outside the submitted work.

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