

# Treatment of patients with heart failure and type 2 diabetes: a review of the literature

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## ABSTRACT

Heart failure (HF) and type 2 diabetes (T2D) often coexist and having both diseases compared with having only one is associated with greater challenges in their management/treatment and worse outcomes. The present review of the literature is aimed at providing a comprehensive synopsis of the main pieces of evidence of the treatment of the two coexisting conditions. In particular, the recent introduction of new glucose-lowering drugs has been deeply changing the therapeutic approach to T2D. Big randomized controlled trials (RCTs) developed to test the cardiovascular safety of these new drugs consistently highlighted a reduction in the risk of hospitalization for HF in patients with T2D treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, suggesting a potential and revolutionary class effect probably related to their natriuretic effect. Moreover, a renal protective effect of this drug class is also emerging and the beneficial effect of SGLT2 inhibitors on the risk of HF hospitalization seems to be even greater in patients with worse renal function. In conclusion, although the underlying mechanisms are not fully understood, SGLT2 inhibitors appear to be a promising tool to treat HF and T2D. Ongoing RCTs specifically enrolling patients with HF treated with SGLT2 inhibitors will provide more insights and further information.

## Introduction

### Definitions and classifications

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (*e.g.*, breathlessness, ankle swelling and fatigue) that may be accompanied by signs (*e.g.*, elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or under stress.<sup>1</sup>

Based on the measurement of left ventricular ejec-

tion fraction (LVEF), HF is currently classified as *heart failure with reduced ejection fraction* (HFrEF) when LVEF <40%, and *heart failure with preserved ejection fraction* (HFpEF) when LVEF ≥50%. This distinction has practical implications since HFrEF and HFpEF present differences in epidemiology/etiology and they require different therapeutic approaches. In particular, the diagnosis of HFpEF is more challenging than the one of HFrEF. In fact, patients with HFpEF compared to those with HFrEF are usually older, more likely women, with a greater body mass index, a greater number of comorbidities, and a greater likelihood of having arterial hypertension or atrial fibrillation rather than a coronary disease. Moreover, while angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers and mineralocorticoid receptor antagonists (MRAs) improve survival and are recommended in patients with HFrEF, they have all failed to reduce mortality in patients with HFpEF. Consequently, guidelines recommend in patients with HFpEF diuretic therapy to improve congestive symptoms and optimization of comorbidities management. However, HFpEF is still associated with elevated mortality. Of note, 2016 European Society of Cardiology (ESC) guidelines identify a third group including patients with an LVEF in the range of 40-49%, referred as *heart failure with mid-range ejection fraction* (HFmrEF). This group actually represents a *grey area*, whose meaning is not yet fully understood; further studies are required. So far, patients with HFmrEF have generally been included in trials of HFpEF and guidelines recommend approaching them similarly to HFpEF.<sup>1</sup>

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Key words: Heart failure; type 2 diabetes; therapy; SGLT2 inhibitors.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 19 May 2019.

Revision received: 29 July 2019.

Accepted for publication: 19 August 2019.

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Italian Journal of Medicine 2019; 13:205-224

doi:10.4081/ijm.2019.1184

According to the World Health Organization, diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced, resulting in increased concentrations of glucose in the blood. There are two main types of diabetes: *type 1 diabetes*, due to autoimmune  $\beta$ -cell destruction leading to absolute insulin deficiency, whose onset is usually <30 years of age, and *type 2 diabetes* (T2D), due to a progressive loss of  $\beta$ -cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome, whose onset is usually >40 of age.<sup>2,3</sup>

For the purpose of this review, we will refer only to T2D.

### Epidemiology and prognosis

HF and T2D often coexist<sup>4</sup> and the presence of both diseases is associated with worse outcomes than having only one disease.<sup>5</sup>

Increasing age is a major risk factor for both HF and T2D. Thus, due to the population ageing, the prevalence of patients with both diseases is considerably rising, triggering complex challenges in their management. In particular, the prevalence of HF is about 12% in patients with T2D,<sup>6</sup> while the prevalence of T2D is 35-40% in patients with HF.<sup>7</sup>

Noteworthy, the presence of T2D is associated with increased all-cause and cardiovascular mortality both in HFpEF and in HFrEF. Furthermore, patients with HF and T2D have a worse clinical status and New York Heart Association (NYHA) functional class, poorer quality of life, and higher risk of hospitalization for HF, longer hospital length and greater risk of re-hospitalization after discharge.<sup>4,8</sup>

Specifically, the relationship between the two diseases is likely to be bidirectional, with each one independently increasing the risk of the other.<sup>8</sup>

### Physiopathology

The two main pathological conditions causally linking HF and T2D are coronary artery disease (CAD) and hypertension.<sup>4</sup> However, a sizeable proportion of HF in patients with T2D develops in the absence of CAD and these patients are at high risk of mortality compared to those with a history of CAD.<sup>5</sup>

The term *diabetic cardiomyopathy* refers to a specific heart muscle disease, which occurs in diabetic patients in the absence of other cardiac risk factors such as CAD and hypertension. Specifically, insulin resistance and consequent hyperinsulinemia and hyperglycemia lead to specific changes in myocardial structure, metabolism and function which result in cardiac remodeling, fibrotic diastolic dysfunction and, ultimately, decreased ejection fraction.<sup>8,9</sup> The main biological mechanisms un-

derlying the development of diabetic cardiomyopathy include glucotoxicity, increased in advanced glycation end products, lipotoxicity, mitochondrial dysfunction and oxidative stress, impaired cardiomyopathy autophagy, inappropriate renin-angiotensin-aldosterone activation, maladaptive immune response and endothelial dysfunction, as extensively explained in previous specific reports on this topic.<sup>8-10</sup>

Left ventricular diastolic dysfunction and HFpEF occurred in about 75% and 50% of patients respectively with T2D, especially in older, hypertensive and female ones. On the other hand, the major cause of HFrEF in patients with T2D is CAD, which is usually diffuse, multi-vessel and may lead to silent myocardial infarction.<sup>4</sup>

### Treatment of heart failure in patients with type 2 diabetes

Treatment of HF in patients with T2D is similar to treatment of HF in general, as recommended by 2016 ESC guidelines.<sup>1</sup> Specifically, none of the drugs routinely used in the therapy of HF is contraindicated in the diabetic population.

As previously anticipated, the therapeutic approach should be based on the distinction between HFrEF and HFpEF/HFmrEF.

For the treatment of HFrEF, ACEis (or alternatively ARBs) plus  $\beta$ -blockers are recommended as first line therapy, with titration to the maximum tolerated dose. If patients are still symptomatic and have LVEF $\leq$ 35%, MRAs should be added. If still symptomatic, several options are possible. In patients who tolerate ACEis (or ARBs) in doses equivalent to enalapril 10 mg b.i.d., angiotensin receptor neprilysin inhibitor, specifically LCZ696, which is a molecule that combines valsartan and sacubitril (a neprilysin inhibitor), should be used in place of ACEis (or ARBs). Alternatively, in patients with sinus rhythm and QRS  $\geq$ 130 milliseconds, cardiac resynchronization therapy should be evaluated. Finally, in patients with sinus rhythm and heart rate  $\geq$ 70 bpm ivabradine should be considered.

In patients with HFpEF/HFmrEF trials of ACEis, ARBs,  $\beta$ -blockers and MRAs have all failed to reduce mortality. Therefore, 2016 ESC guidelines recommend to screen for and treat both cardiovascular (CV) and non-CV comorbidities, including T2D, to improve symptoms, well-being and/or prognosis).

Of note, in both HFrEF and HFpEF/HFmrEF diuretics are recommended as symptomatic therapy to alleviate congestive symptoms and signs, without any effect on survival.

### Angiotensin-converting enzyme inhibitors

Data from the studies of left ventricular dysfunction (SOLVD Investigators) showed that enalapril signifi-

cantly reduced the occurrence of HF development and hospitalization, and the combined endpoint of HF development and CV death in asymptomatic patients with reduced LVEF ( $\leq 35\%$ ) regardless of their diabetic status.<sup>11-13</sup> Moreover, data from the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial demonstrated the efficacy and the safety of high-dose lisinopril in patients with chronic HF at high CV risk, including those with diabetes mellitus.<sup>14</sup> A meta-analysis of six randomized clinical trials confirms that ACEis reduce mortality in patients with HFrEF and T2D.<sup>15</sup>

Of note, enalapril was also found to reduce the incidence of T2D in patients with left ventricular dysfunction.<sup>16</sup>

### Angiotensin receptor blockers

In the Valsartan Heart Failure Trial (Val-HeFT), valsartan 160 mg compared to placebo was associated with a significant reduction in the combined primary endpoint of death and HF hospitalization in more than 5000 patients with HF of NYHA class II, III or IV, and with and without T2D.<sup>17,18</sup> Moreover, in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) trial, enrolling about 7600 patients with HFrEF, Candesartan significantly reduced all-cause mortality, CV death and HF hospitalization, independent of their diabetic status.<sup>19-21</sup>

Furthermore, in the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study, losartan was found to reduce HF hospitalization in patients with T2D and nephropathy.<sup>22</sup> Specifically, higher dose of losartan (150 mg daily) significantly reduced death and HF hospitalization compared to lower dose (50 mg daily) in patients with HFrEF and intolerance to ACEi, irrespective of their diabetes status.<sup>23</sup> In addition, data from Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Losartan Intervention For Endpoint reduction in hypertension (LIFE) studies showed that losartan reduces the risk of HF hospitalization in patients with T2D at high renal or CV risk.<sup>24</sup> Finally, candesartan was found to prevent diabetes in patients with HF.<sup>25</sup>

### Aliskiren

Aliskiren is a direct renin inhibitor that blocks the renin-angiotensin-aldosterone system at the most proximal step. The Aliskiren trial in Type 2 Diabetes Using cardio renal Endpoint (ALTITUDE) was designed to investigate the effect of aliskiren in T2D patients with proteinuria or CV disease but it was stopped early because of an increased risk of adverse effects including renal dysfunction and hyperkalemia.<sup>26</sup> The Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) enrolled patients

with T2D hospitalized for HF but it showed an increased risk of 12-month mortality probably mediated by the increased adverse effects.<sup>27</sup> In the Aliskiren Trial of Minimizing OutcomeS for Patients with HEart failuRE (ATMOSPHERE), 7016 patients HFrEF were randomized to enalapril plus aliskiren, aliskiren alone, or enalapril. As it results, the addition of aliskiren to enalapril led to more adverse events without an increase in benefit. In addition, non-inferiority was not shown for aliskiren as compared with enalapril.<sup>28</sup> A subsequent subgroup analysis in patients with and without T2D confirmed that there was no signal of harm and a trend towards benefit when direct renin inhibition monotherapy was compared with an angiotensin-converting enzyme inhibitor, whereas combined aliskiren and enalapril treatment led to more adverse events with no improvement in outcomes.<sup>29</sup>

### $\beta$ -blockers

In the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF), metoprolol reduced the risk of hospitalization for HF by 37% in the diabetic group [95% confidence interval (CI) 53%-15%], and by 35% in the non-diabetic group (95%CI 48%-19%).<sup>30</sup> Moreover, in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), bisoprolol demonstrated significant mortality benefits in patients with chronic HF irrespectively of their diabetic status.<sup>31,32</sup> Furthermore, in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, patients with severe chronic HFrHF receiving carvedilol in addition to their usual medications for HF presented a significant reduction in death and hospitalization compared to those receiving placebo.<sup>33,34</sup> Besides, concomitant diabetes was found not to influence the efficacy and tolerability of carvedilol administration in 193 patients with chronic HF.<sup>35</sup> Additionally, in the Carvedilol Or Metoprolol European Trial (COMET), carvedilol extends survival as compared with metoprolol<sup>36</sup> and new onset diabetes is more likely to occur during treatment with metoprolol than during treatment with carvedilol.<sup>37</sup>

A meta-analysis of six large randomized clinical trials found that  $\beta$ -blocker therapy as compared with placebo in chronic HF was beneficial in patients with or without T2D, but the absolute risk reduction in mortality was greater in those without T2D than in those with T2D.<sup>38</sup> A further meta-analysis of three studies (CIBIS, COPERNICUS, MERIT-HF) found that the relative risk (95%CI) of mortality was 0.65 (0.57-0.74) in the non-diabetic group and 0.77 (0.61-0.96) in the diabetic group.<sup>15</sup> An additional meta-analysis of seven large placebo-controlled randomized trials with carvedilol showed similar survival benefits in HF patients with and without T2D.<sup>39</sup> Noteworthy,  $\beta$ -blockers use did not worsen glycemic control in patients with

HFrEF and T2D.<sup>40</sup> Finally, in a recent study increasing  $\beta$ -blocker dose was associated with a greater prognostic advantage in chronic HF patients with diabetes than in those without diabetes.<sup>41</sup>

### Mineralocorticoid receptor antagonists

In the Randomized Aldactone Evaluation Study (RALES), spironolactone as compared with placebo significantly reduced death and HF hospitalization in patients with HFrEF.<sup>42</sup> Subsequently, in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) eplerenone compared to placebo was found to significantly reduce mortality and HF hospitalization in patients with HFrEF irrespective of their diabetic status.<sup>43</sup> Moreover, eplerenone was found to have no effect on new-onset diabetes in patients with chronic HF.<sup>44</sup> Furthermore, in the Miner Alorcorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF), the effects of finerenone were compared to eplerenone in patients with worsening HFrEF and chronic kidney disease (CKD) or T2D presenting at the emergency department.<sup>45</sup> As a result, finerenone safety profile was comparable to that of eplerenone. In addition, change in NT-proBNP from baseline to Day 90 was similar between finerenone and eplerenone. However, the incidence of the exploratory composite endpoint of death from any cause, cardiovascular hospitalization, or emergency presentation for worsening HF at Day 90 was lower in patients treated with finerenone compared with eplerenone.<sup>46</sup>

### Sacubitril/Valsartan (LCZ696)

In the PARADIGM-HF trial, 8442 patients with HFrEF were randomized to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. As a result, LCZ696 was superior to enalapril in reducing the risk of death from any cause [17% vs 19.8%, hazard ratio (HR) 0.84, 95%CI, 0.76 to 0.93;  $P < 0.001$ ] and CV death (13.3% vs 16.5%, HR 0.80, 95% CI, 0.71 to 0.89;  $P < 0.001$ ). Moreover, LCZ696 reduced the risk of hospitalization for HF by 21% ( $P < 0.001$ ).<sup>47</sup> Furthermore, a subsequent subgroup analysis demonstrated that the beneficial effect of LCZ696 was irrespective of the diabetic status.<sup>48</sup> Finally, a *post hoc* analysis showed that patients with T2D and HFrEF enrolled in PARADIGM-HF who received sacubitril/valsartan had a greater long-term reduction in HbA<sub>1c</sub> and a lower rate of initiation of insulin than those receiving enalapril.<sup>49</sup>

Noteworthy, several mechanisms might underlie the hypoglycemic effect of sacubitril/valsartan.

First, in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGA-

TOR) study valsartan significantly reduced the incidence of T2D among patients with impaired glucose tolerance and established CV disease or CV risk factors.<sup>50</sup> Consistently with these findings, a subsequent study showed that valsartan improves insulin sensitivity and  $\beta$ -cell function in subjects with impaired glucose metabolism.<sup>51</sup>

Moreover, sacubitril inhibits neprilysin, an enzyme that is responsible for the breakdown of a series of peptides, including glucagon-like peptide-1 (GLP-1), natriuretic peptides and bradykinins, resulting in increased levels of such peptides with consequent positive effects on glucose metabolism.<sup>49</sup> In particular, GLP-1 is an incretin that stimulates the pancreatic secretion of insulin and inhibits the one of glucagon. Noteworthy, GLP-1 is degraded not only by dipeptidyl peptidase-4 (DPP4) but also by neprilysin.<sup>52</sup> Therefore, neprilysin inhibition potentiates the effect of GLP-1 and decreases blood glucose.<sup>53</sup> Consistently, experimental studies found that levels of GLP-1 are increased in neprilysin-deficient mice, leading to improved glycaemic control.<sup>54</sup> Natriuretic peptides, including atrial and brain natriuretic peptides (ANP and BNP respectively), are heart hormones produced by the right atrium in response to overload and mechanical stretch in order to regulate blood volume and pressure. Besides their well-known cardiovascular effects, several studies documented that natriuretic peptides have also an important role in the regulation of the energy metabolism. In particular, ANP was found to increase lipid mobilization from adipose tissue<sup>55</sup> and postprandial lipid oxidation.<sup>56</sup> Moreover, natriuretic peptides enhance the oxidative capacity of human skeletal muscle<sup>57</sup> and play an important role in maintaining long-term insulin sensitivity.<sup>58</sup> Consistently, blood glucose concentrations have been found to decrease after infusion of BNP.<sup>59</sup> Besides, in a prospective analysis including 7822 participants from the Atherosclerosis Risk in Communities (ARIC) study, baseline higher levels of NT-proBNP, a cleavage product of BNP, were significantly and independently associated with a decreased risk of incident diabetes.<sup>60</sup> Finally, bradykinins, which are inflammatory mediators with vasoactive effects, also seem to be involved in the regulation of blood glucose levels by improving systemic insulin sensitivity.<sup>61</sup>

Noteworthy, the PARAGON-HF (ID: NCT01920711) is an ongoing trial aimed at evaluating the effect of LCZ696 compared to valsartan in the reduction of CV death and HF hospitalizations in 4822 patients with HFrEF, of which 43% have T2D.<sup>62</sup>

### Nitrates

The African-American Heart Failure Trial (A-HeFT) reported that the fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride sig-

nificantly decreased the risk of all-cause death and first hospitalization for HF with a consistent beneficial effect in patients with and without T2D.<sup>63</sup>

### Ivabradine

A post hoc analysis on patients enrolled in the Systolic Heart failure treatment with the  $I_f$  inhibitor ivabradine Trial (SHIFT) examined the efficacy and safety of ivabradine in patients with HFrEF and T2D. As a result, ivabradine significantly reduced the primary composite endpoint of CV death and HF hospitalization with no difference between patients with and without T2D.<sup>64</sup>

### Diuretics

Diuretics are recommended to treat congestive symptoms. There are no trials examining their efficacy in persons with HF and T2D. Theoretically, thiazide diuretics can lead to increased insulin resistance and worsening of glycemic control.<sup>4</sup>

## Treatment of type 2 diabetes in patients with heart failure

### Glycemic control and target

Results from the UK Prospective Diabetes Study (UKPDS),<sup>65</sup> the Action to Control Cardiovascular risk in Diabetes (ACCORD)<sup>66</sup> study, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release controlled Evaluation (ADVANCE)<sup>67</sup> and the Veterans Affairs Diabetes trial (VADT)<sup>68</sup> agreed on the fact that intensive glycemic control in patients with T2D was associated with reduced incidence of microvascular complications (nephropathy, neuropathy and retinopathy). However, they did not consistently demonstrate benefits from intensive glycemic control on macrovascular risk, especially in the oldest and frail patients with long-standing T2D, multiple comorbidities, previous CV events or high CV risk and high risk of hypoglycemia. Therefore, whether an intensive glycemic control may affect the risk of CV events in patients with HF is uncertain. In particular, meta-analyses pooling data from the four studies together found that intensive glycemic control does not reduce cardiovascular mortality or HF hospitalization but it increases the risk of hypoglycemia.<sup>69,70</sup> Therefore, guidelines recommend individualized and patient-centered HbA1c targets, that should be tighter in younger patients with recent onset T2D and without complications/comorbidities (<6.5-7% HbA1c) and looser in older patients with long-standing T2D, short life expectancy, important comorbidities and/or established CV complications (<8-9 HbA1c).<sup>3,71</sup>

### Pharmacological treatment

Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological treatment in patients with T2D. In case of great metabolic imbalance, initiating with dual therapy is recommended. When monotherapy with metformin is not able to achieve an adequate glycemic control, a second oral glucose-lowering drug should be associated. When dual therapy is still not able to reach a satisfactory glycemic control, a third oral glucose-lowering drug should be added. If an insufficient glycemic control persists, a combination injectable therapy (adding insulin or GLP1-RA) should be considered.<sup>72</sup>

The choice of the drug/drugs to combine with metformin depends on the characteristics of the patients, including comorbidities. In congestive HF, metformin should be the first choice. Thiazolidinediones are contraindicated, while insulin/sulfonylureas/glinides should be used with caution. Regarding new oral antidiabetic drugs, safety data of DPP4 inhibitors and GLP1-RA in patients with HF are limited, while promising pieces of evidence are emerging for SGLT2 inhibitors, as detailed in the following paragraphs.

### Biguanides (metformin)

Metformin therapy has long been avoided in patients with HF, because of the fear of lactic acidosis in unstable patients.<sup>73</sup> However, observational studies demonstrated that metformin reduces mortality in patients with HF.<sup>74-76</sup> Therefore, the U.S. Food and Drug Administration (FDA) removed HF as a contraindication to metformin use in 2006, although acute or unstable HF remains a precaution.<sup>73</sup> Moreover, 2016 ESC guidelines for the management of HF patients established that metformin is safe and should be considered as a first-line treatment of glycemic control in patients with T2D and HF, unless contraindicated.<sup>1</sup> Of note, metformin is contraindicated in patients with severe renal impairment (estimated glomerular filtration rate, eGFR <30 mL/min).

### Insulin

Insulin is a powerful dose dependent sodium-retaining hormone, that when combined with reduced glycosuria may aggravate fluid retention and lead to HF worsening. Some observational studies found that insulin-treated T2D was associated with increased mortality in patients with HF.<sup>77-80</sup> However, insulin-treated patients are usually older, with long standing T2D, greater comorbidities and CV complications and this may represent a bias.<sup>81</sup> Of note, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial evaluated the effects of insulin glargine vs standard therapy in patients with impaired fasting glucose, or impaired glucose tolerance or T2D at high CV risk

(but without prevalent HF that was an exclusion criterion). As a result, it found no significant differences in CV death, non-fatal myocardial infarction, non-fatal stroke, CV revascularization procedures or HF hospitalization.<sup>82</sup> Moreover, one small, randomized clinical trial investigated the effect of insulin on cardiac function in 40 patients with T2D and HF<sub>rEF</sub>, finding no changes in left ventricular reserve capacity.<sup>83</sup> In conclusion, insulin should be used with caution in HF patients and monitoring signs and symptoms of fluid retention.

### Sulfonylureas

Sulfonylureas may cause hypoglycemia and weight gain and previous evidence showed that they have been associated with an increased risk of worsening HF.

For instance, a retrospective cohort study of T2D patients without HF newly treated with oral antidiabetic drugs found that incidence of HF was greater in those taking sulfonylureas than metformin and that higher doses of sulfonylureas were associated with higher risk.<sup>84</sup> In the UK General Practice Research Database, monotherapy with first- or second-generation sulfonylureas was associated with an 18-30% increased risk of HF as compared with metformin.<sup>85</sup> Moreover, a recent real-world study using data from the National Veterans Health Administration database found that the prescription of sulfonylureas as initial treatment of T2D was associated with a 32% increase in the risk of HF as compared with metformin.<sup>86</sup>

Therefore, sulfonylureas should be used with caution in patients with HF.<sup>1</sup>

Regarding the pathophysiological mechanisms through which sulfonylureas might worsen HF, a plausible explanation relates to hypoglycemia since it has been previously associated with an increased risk of severe ventricular arrhythmias, CV events and mortality.<sup>87-90</sup> Moreover, sulfonylureas non-selective for pancreatic receptors, such as glibenclamide, inhibit the adenosine triphosphate sensitive potassium ( $K_{ATP}$ ) channels located on the inner membrane of mitochondria and on the sarcolemma of cardiac, skeletal and smooth muscle cells.  $K_{ATP}$  channels are metabolic sensors that promote vasodilatation in response to specific signals, such as acidosis and hypoxia,<sup>91</sup> and are important for myocardial protection during ischemia/reperfusion (*i.e. ischemic preconditioning*). Experimental studies showed that, in the failing heart,  $K_{ATP}$  channels play a critical role in maintaining the balance between myocardial oxygen delivery and demand, and in mediating the response to stress.<sup>91</sup> Therefore, glibenclamide, blocking cardiovascular  $K_{ATP}$  channels, leads to vasoconstriction and decrease in coronary blood flow. Noteworthy, in animal models glibenclamide has been associated with reduced myocardial perfusion

and development of tissue hypoxia in congestive HF.<sup>91</sup> Moreover, in human patients with T2D and coronary artery disease, treatment with glibenclamide compared to insulin was associated with a more severe ischemia-induced left ventricular myocardial dysfunction due to the loss of the ischemic preconditioning cardioprotective mechanism.<sup>92</sup> Furthermore, a recent study showed that inhibition of vascular  $K_{ATP}$  channels by glibenclamide exacerbates skeletal muscle  $O_2$  delivery-utilization mismatch during contractions in rats with chronic HF, suggesting that the administration of non-selective sulfonylureas in patients T2D and congestive HF may severely compromise exercise tolerance.<sup>93</sup> Conversely, sulfonylureas selective for pancreatic receptors, such as gliclazide or glimepiride, seem to be safer as they cause fewer CV effects. In particular, lack of effect on ischemic preconditioning was found for glimepiride.<sup>94-96</sup> Moreover, data from the ADVANCE study showed no difference in the incidence of HF in T2D patients treated with gliclazide compared to placebo.<sup>67</sup>

### Thiazolidinediones

Thiazolidinediones (glitazones) cause sodium and water retention. Therefore, they increase the risk of HF worsening and hospitalization and are not recommended in patients with HF.<sup>97,98</sup>

### DPP4 inhibitors

The protease dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of anti-diabetic drugs that inhibits the protease DPP-4, which is responsible for the degradation of incretins with consequent increase in their circulating levels. Incretins, including the glucagon-like peptide-1 (GLP-1) and the gastric inhibitory polypeptide, are gut hormones synthesized and secreted by enteric endocrine cells in response to food intake that increase glucose-dependent insulin secretion and decrease glucagon secretion with consequent reduction of blood glucose levels with low hypoglycemia risk.

Therefore, DPP-4 inhibitors, including saxagliptin, alogliptin, sitagliptin, vildagliptin and linagliptin, reduce blood glucose levels with low hypoglycemia risk and with no relevant effect on body weight.

### Saxagliptin

The Saxagliptin Assessment of vascular outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in myocardial infarction 53 (SAVOR-TIMI 53) trial assessed the efficacy and safety of saxagliptin in 16,492 patients with T2D and a history of or at risk of CV events, randomized to receive saxagliptin or placebo and followed for a median of 2.1 years. A primary composite endpoint event (including CV death,

non-fatal myocardial infarction, or non-fatal ischemic stroke) occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively; HR 1.00, 95% CI 0.89 - 1.12;  $P=0.99$  for superiority;  $P<0.001$  for non-inferiority). However, more patients in the saxagliptin group than in the placebo group were hospitalized for HF (3.5% vs 2.8%; HR 1.27; 95%CI 1.07-1.51;  $P=0.007$ ).<sup>99</sup> In particular, the risk of HF hospitalization with saxagliptin was most evident in the first 12 months of therapy. Moreover, a subsequent analysis showed that this increase in risk was highest among patients with elevated levels of natriuretic peptides, previous HF, or CKD.<sup>100</sup> Of note, the increased risk of HF hospitalization was irrespective of age category.<sup>101</sup>

### Alogliptin

In the EXAMINE trial, 5380 patients with T2D and a recent acute coronary syndrome (ACS) event were randomized to receive alogliptin or placebo and followed for a median of 18 months. As a result, alogliptin was non-inferior to placebo in lowering the risk of the composite primary endpoint of CV death, myocardial infarction, or stroke (11.3% vs 11.8%, HR 0.96; upper boundary of the one-sided repeated CI 1.16;  $P<0.001$  for non-inferiority).<sup>102</sup> Moreover, first hospital admission for HF occurred in 85 (3.1%) patients taking alogliptin compared to 79 (2.9%) taking placebo (HR 1.07, 95%CI 0.79-1.46), showing a non-significant trend to an increase in HF hospitalization.<sup>103</sup>

### Sitagliptin

In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), 14,671 patients were randomized to add either sitagliptin or placebo to their existing therapy and followed for a median of 3 years. As a result, sitagliptin was non-inferior to placebo for the primary composite outcome of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina (HR 0.98; 95%CI 0.88-1.09;  $P<0.001$ ). Rates of hospitalization for HF did not differ between the two groups (HR 1.00; 95%CI 0.83-1.20;  $P=0.98$ ).<sup>104</sup> A subsequent analysis from TECOS confirmed that sitagliptin does not affect the risk of HF hospitalization in T2DM, both overall and among high-risk patient subgroups.<sup>105</sup>

Consistently a meta-analysis of 10 studies including 340,747 patients demonstrated that sitagliptin exposure was not associated with the incidence of HF.<sup>106</sup>

Of note, a population-based retrospective cohort study using data from a national commercially insured U.S. claims database showed that sitagliptin was associated with an increased risk of HF hospitalization among patients with T2D with pre-existing HF.<sup>107</sup>

### Vildagliptin

The Vildagliptin in Ventricular Dysfunction Diabetes (VIVID) trial enrolled 254 patients with T2D and HFrEF randomized to 52 weeks treatment with vildagliptin 50 mg twice daily (50 mg once daily if treated with a sulfonylurea) vs placebo in addition to standard therapy. The primary endpoint was between-treatment change from baseline in echocardiographic LVEF. As a result, compared with placebo, vildagliptin had no major effect on LVEF but did lead to an increase in left ventricular volumes, the cause and clinical significance of which is unknown.<sup>108</sup>

A meta-analysis did not find a significant increased risk of HF in vildagliptin-treated patients.<sup>109</sup>

### Linagliptin

The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) trial enrolled 6979 participants with T2D and atherosclerotic CV disease and/or kidney disease randomized to receive once daily oral linagliptin 5 mg or placebo. During a median follow-up of 2.2 years, the primary outcome (*i.e.* time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or non-fatal stroke) occurred in 434 of 3494 (12.4%) and 420 of 3485 (12.1%) in the linagliptin and placebo groups respectively (HR 1.02; 95%CI, 0.89-1.17;  $P<0.001$  for non-inferiority).<sup>110</sup> In addition, linagliptin *versus* placebo did not affect the incidence of HF hospitalization (HR 0.90; 95%CI 0.74-1.08), the composite of CV death/HF hospitalization (HR 0.94; 95%CI, 0.82-1.08), or risk of recurrent HF hospitalization (HR 0.94; 95%CI, 0.75-1.20).<sup>111</sup>

Finally, the Cardiovascular Outcome Study of Linagliptin *Versus* Glimpiride in Patients with Type 2 Diabetes (CAROLINA) is an ongoing study aimed at investigating the long-term impact of linagliptin, as compared with glimepiride, on CV morbidity and mortality, relevant efficacy parameters (*e.g.*, glycemic parameters) and safety (*e.g.*, weight and hypoglycemia) in patients with T2D at elevated CV risk (ClinicalTrials.gov, ID: NCT01243424).<sup>112</sup>

### GLP-1 receptor agonists

GLP-1 receptor agonists (GLP1-RA), including short acting (exenatide and lixisenatide) and long acting (liraglutide, semaglutide, extended-release exenatide and dulaglutide) agents, are a new class of antidiabetic drugs, that improves glycemic control with a low risk of hypoglycemia and the additional benefit of clinically relevant weight loss.

Data from experimental studies suggested a cardio protective effect of GLP1 RA<sup>113,114</sup> and a small pilot study proposed that they might improve cardiac function in patients with advanced HF.<sup>115</sup> However,

some evidence from randomized and observational studies demonstrated only a modest effect on left ventricular EF.<sup>116</sup>

### Lixisenatide

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial enrolled 6068 patients with T2D who recently had ACS randomized to receive lixisenatide or placebo in addition to locally determined standards of care. As a result, no significant difference was found in the occurrence of the primary composite endpoint of CV death, myocardial infarction, stroke, or hospitalization for unstable angina between lixisenatide and placebo (HR 1.02; 95%CI 0.89-1.17, P for non-inferiority <0.001 but P for superiority =0.81). Moreover, there was no significant between-group difference in the rate of hospitalization for HF (HR 0.96; 95%CI 0.75-1.23).<sup>117</sup>

A further analysis showed that in patients with T2DM and recent ACS, a history of retinopathy and/or neuropathy and longer T2DM duration could be considered clinical markers for high risk of recurrent CV events.<sup>118</sup>

### Liraglutide

The Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial assessed the cardiovascular safety of liraglutide in 9340 patients with T2D, randomized to receive either 1.8 mg (or the maximum tolerated dose) of liraglutide or matching placebo once daily as a subcutaneous injection in addition to standard care.<sup>119</sup> As a result, the primary composite outcome, consisting of the first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke, occurred in significantly fewer patients in the liraglutide group than in the placebo (HR 0.87; 95%CI 0.78-0.97; P<0.001 for non-inferiority; P=0.01 for superiority). In addition, fewer patients died from CV causes in the liraglutide group than in the placebo group (HR 0.78; 95%CI 0.66-0.93; P=0.007). Moreover, the rate of death from any cause was lower in the liraglutide group than in the placebo group (HR 0.85; 95%CI 0.74-0.97; P=0.02). However, no significant difference was found in the rate of hospitalization for HF between the two groups (HR 0.87, 95%CI 0.73-1.05).<sup>120</sup> Furthermore, a subsequent analysis from the LEADER showed that liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo.<sup>121</sup>

Besides, two further studies specifically investigated the effect of liraglutide in patients with T2D and HFrEF.

The FIGHT trial enrolled 300 patients with established HF and reduced LVEF who were recently hospitalized, randomized to liraglutide 1.8 mg daily

versus placebo and followed for a mean of 210 days. As a result, regardless of T2D status, liraglutide had no significant effect on the primary endpoint, a hierarchical global rank score including time to death, time to re-hospitalization for HF and time-averaged proportional change in NT-proBNP level from baseline to 180 days (P=0.31). In particular, no significant between-group difference was found in HF hospitalization (HR 1.30, 95%CI 0.89-1.88; P=0.17).<sup>122</sup>

The LIVE Study enrolled 241 patients with chronic HF and reduced LVEF ( $\leq 45\%$ ) with and without T2D, randomized to liraglutide 1.8 mg once daily VS placebo for 24 weeks.<sup>123</sup> As a result, no significant difference in change in LVEF was found between the liraglutide and the placebo group (P=0.24). In addition, no significant change in LV dimensions, NYHA class or quality of life were reported. The results were consistent in patients with and without T2D. It is worth mentioning that due to its positive chronotropic effect, treatment with liraglutide was associated with an increase in heart rate and more serious cardiac adverse events.<sup>124</sup>

Finally, in a large Scandinavian register-based cohort study, the use of liraglutide, as compared with the use of DPP-4 inhibitors, was associated with significantly reduced risk of major cardiovascular events, but no significant differences were identified for risk of HF.<sup>125</sup>

### Semaglutide

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) enrolled 3927 patients with T2D with established CV disease or at high CV risk, randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary outcome of CV death, nonfatal myocardial infarction or nonfatal stroke was significantly reduced in the semaglutide group (HR 0.74; 95%CI 0.58-0.95; P<0.001 for non-inferiority). No difference was found between the two groups regarding HF hospitalization (HR 1.11; 95%CI 0.77-1.61; P=0.56).<sup>126</sup>

### Exenatide

The Exenatide Study of Cardiovascular Event Lowering (EXSCCEL) trial enrolled 14,752 patients with T2D, of whom more than 70% had a previous established CV disease, randomized to once weekly, injectable, extended-release formulation of exenatide at a dose of 2 mg or placebo and followed for a median of 3.2 years.<sup>127</sup> As a result, no difference was found between exenatide and placebo in the primary composite outcome of CV death, nonfatal myocardial infarction and nonfatal stroke (3.7 versus 4.0 events per 100 patient-years), as well as in the secondary end-



point of HF hospitalization (0.9 *versus* 1 events per 100 patient-years).<sup>128</sup>

However, exenatide was found to improve hemodynamic function in patients with T2D and congestive HF.<sup>129-131</sup> Moreover, a retrospective observational study showed that treatment with exenatide twice daily, in addition to oral antidiabetic drugs, was associated with a reduced risk of CV events, including HF, compared to insulin.<sup>132</sup>

Noteworthy, the FREEDOM-CVO is an ongoing trial aimed at evaluating CV outcomes in patients with T2D treated with continuous subcutaneous delivery of exenatide *versus* placebo (ClinicalTrials.gov ID: NCT01455896).

### Albiglutide

The Harmony Outcomes Trial assessed the safety and efficacy of albiglutide in 9463 patients with T2D and established CV disease randomized to a subcutaneous injection of albiglutide (30-50 mg, based on glycemic response and tolerability) or of a matched volume of placebo once a week, in addition to their standard care. The median duration of the follow up was 1.6 years. The primary composite outcome (*i.e.* first occurrence of CV death, myocardial infarction, or stroke) occurred at an incidence rate of 4.6 events per 100 person-years in the albiglutide group and at an incidence rate of 5.9 events per 100 person-years in the placebo group (HR 0.78, 95%CI 0.68-0.90;  $P < 0.001$  for non-inferiority;  $P = 0.0006$  for superiority). The composite secondary outcome of death from CV causes or hospital admission for HF did not significantly differ between the two groups (HR 0.85, 95%CI 0.70-1.04).<sup>133</sup> Moreover, a randomized, placebo-controlled study in 82 patients with NYHA class II or III and LVEF  $< 40\%$  found no difference between albiglutide *versus* placebo in change in LVEF.<sup>134</sup>

### Dulaglutide

The Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial evaluated the CV safety of dulaglutide in 9901 patients with T2D with or at risk of CV disease.<sup>135</sup>

As a result, during a median follow-up of 5.4 years, the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or CV death occurred in 594 (12.0%) participants in the dulaglutide group and in 663 (13.4%) in the placebo group (HR 0.88, 95%CI 0.79-0.99;  $P = 0.026$ ). However, dulaglutide did not significantly affect the incidence of hospitalization for HF (HR 0.93, 95%CI 0.77-1.12).<sup>136</sup> In addition, an exploratory analysis from the REWIND found that long-term use of dulaglutide was associated with a decreased composite renal outcome defined as the first occurrence of new macroalbuminuria, a sus-

tained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy (HR 0.85, 95%CI 0.77-0.93;  $P = 0.0004$ ).<sup>137</sup>

### SGLT2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of antidiabetic drugs that block the SGLT2 receptor, which is located in the proximal tubule of the kidney and it is responsible for 90% of renal glucose reabsorption, with consequent increase in renal glucose excretion. They include four oral agents (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) approved for the treatment of T2D by FDA and the European Medicines Agency, either as monotherapy or in combination with other glucose-lowering drug classes. They are effective in lowering fasting blood glucose and HbA<sub>1c</sub> levels; moreover, they induce loss of weight. In general, they are well tolerated and have a low hypoglycemia risk in patients not using sulfonylureas or insulin.<sup>138</sup> Adverse effects include hypotension, dehydration, increased risk of urinary and genital infections and euglycemic ketoacidosis.

### Empagliflozin

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - Removing Excess Glucose (EMPA-REG OUTCOME) explored the effects of empagliflozin in addition to standard care on CV morbidity and mortality in 7020 patients with T2D at high CV risk. As compared with placebo, empagliflozin resulted in a significantly lower risk of death from CV causes (HR 0.62; 95%CI 0.49-0.77;  $P < 0.001$ ), death from any causes (HR 0.68; 95%CI 0.57-0.82;  $P < 0.001$ ) and hospitalization for HF (HR 0.65; 95%CI 0.50-0.85;  $P = 0.002$ ),<sup>139</sup> with a consistent benefit observed in patients with and without HF at baseline.<sup>140</sup> In addition, a subsequent analysis regarding long-term renal effects showed that empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events compared to placebo.<sup>141</sup> Further analyses confirmed that the reduction in CV outcome and mortality with empagliflozin *vs* placebo was consistent across the spectrum of HF and CV risk.<sup>142,143</sup> Moreover, empagliflozin was found to reduce the risk of additional HF-related outcomes (specifically, first introduction of loop diuretic, the composite outcome of first introduction of loop diuretic or first HF hospitalization, first mention of edema, and first investigator-reported HF) regardless of HF status at baseline.<sup>144</sup> Furthermore, a *post-hoc* analysis including 221 patients hospitalized for HF at least once, found that empagliflozin was associated with a lower risk of post-acute HF re-hospitalization and mortality as compared with placebo.<sup>145</sup>

Consistently, several translational studies over the past couple of years showed that empagliflozin improves cardiorespiratory fitness in patients with T2D.<sup>146,147</sup> In addition, empagliflozin was found to cause pleiotropic effect on the myocardium by improving diastolic stiffness and function in experiments with *in toto*-isolated human systolic end-stage HF ventricular trabeculae.<sup>148</sup> Moreover, in a pilot study enrolling T2D patients with symptomatic HF, empagliflozin was found to improve 1-month exercise capacity.<sup>149</sup> Furthermore, using two commercial and one federal (Medicare) US claims data sources, empagliflozin was recently found to significantly reduce the risk of HF hospitalization compared to sitagliptin (the EMPRISE STUDY).<sup>150</sup>

Noteworthy, the following trials are ongoing:

- Renal and Cardiovascular Effects of SGLT2 inhibition in combination with loop Diuretics in diabetic patients with Chronic Heart Failure (RECEDE-CHF): to assess the effect of empagliflozin used in combination with a loop diuretic on urine output, glomerular filtration rate, cystatin C, urinary sodium excretion, urinary protein/creatinine ratio and urinary albumin/creatinine ratio when compared with placebo in 34 participants with stable T2D and congestive HF (ClinicalTrials.gov, ID: NCT03226457);<sup>151</sup>
- EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure with Reduced Ejection Fraction (EMPEROR-Reduced): to evaluate efficacy and safety of empagliflozin *versus* placebo on top of guideline-directed medical therapy in patients with HF<sub>r</sub>EF (ClinicalTrials.gov, ID: NCT03057977);
- EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure with Preserved Ejection Fraction (EMPEROR-Preserved): to evaluate efficacy and safety of empagliflozin *versus* placebo on top of guideline-directed medical therapy in patients with HF<sub>p</sub>EF (ClinicalTrials.gov, ID: NCT03057951).<sup>152</sup>

### Canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS)<sup>153</sup> and the CANVAS-Renal (CANVAS-R)<sup>154</sup> are two sister trials designed to assess the cardiovascular safety and efficacy of canagliflozin. In an integrated analysis of the two trials as CANVAS Program,<sup>155</sup> involving 10,142 patients with T2D and at high CV risk, canagliflozin was associated with a lower risk of CV events as composite outcome including death from CV causes, nonfatal myocardial infarction and nonfatal stroke (HR 0.86, 95%CI 0.75-9.97,  $P < 0.001$  for non-inferiority and  $P = 0.002$  for superiority). Moreover, it was also significantly associated with a lower risk of HF hospitalization (HR 0.67,

95%CI 0.52-0.87).<sup>156</sup> Subsequent analyses demonstrated that the results were consistent across a broad range of different patient subgroups<sup>157</sup> and that canagliflozin significantly reduced the risk of HF with no clear difference in effect on HF<sub>r</sub>EF *versus* EF<sub>p</sub>HF events.<sup>158</sup>

Noteworthy, results from the CANVAS Program also showed a possible benefit of canagliflozin on the progression of albuminuria (HR 0.73; 95%CI, 0.67-0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95%CI, 0.47 to 0.77).<sup>156</sup> Recently, a pre-specified exploratory analysis from the CANVAS on the long-term renal effect of canagliflozin showed that the composite outcome of sustained doubled creatinine, end-stage kidney disease or renal death occurred less frequently in the canagliflozin group compared to placebo (HR 0.53, 95%CI 0.33-0.84). In addition, annual eGFR decline was slower (slope difference 1.2 mL/min/1.73 m<sup>2</sup>/year, 95% CI 1.0-1.4) and mean urinary albumin:creatinine ratio was 18% lower (95% CI 16%-20%) in participants treated with canagliflozin compared to placebo. Overall, these results support a possible renoprotective effect in people with T2D.<sup>159</sup> Besides, a further analysis from the CANVAS demonstrated that the beneficial effects of canagliflozin on CV and renal outcomes were independent of baseline renal function.<sup>160</sup>

Furthermore, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study compared the efficacy and safety of canagliflozin *versus* placebo at preventing clinically important kidney and CV outcomes in 4,401 patients with T2D and albuminuric CKD. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL per minute per 1.73 m<sup>2</sup>), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR 0.70; 95%CI 0.59-0.82;  $P = 0.00001$ ). The relative risk of the renal-specific composite of end-stage kidney disease (ESKD), a doubling of the creatinine level, or death from renal causes was 34% lower (HR 0.66; 95%CI 0.53-0.81;  $P < 0.001$ ), and the relative risk of end-stage kidney disease was 32% lower (HR 0.68; 95%CI 0.54 to 0.86;  $P = 0.002$ ). The canagliflozin group also had a lower risk of CV death, myocardial infarction, or stroke (hazard ratio, 0.80; 95%CI, 0.67 to 0.95;  $P = 0.01$ ) and hospitalization for HF (HR 0.61; 95%CI 0.47 to 0.80;  $P < 0.001$ ).<sup>161</sup>

Evidence from observational trials substantially

confirmed the results from randomized control trials (RCTs). In particular, a meta-analysis of four observational databases (OBSERVE 4 D) found that canagliflozin and other SGLT2i significantly reduce the risk of HF hospitalization for HF.<sup>162</sup> Also, a large retrospective cohort study found that canagliflozin was associated with a lower risk of HF admission to hospital and with a similar risk of stroke or myocardial infarction compared to other antidiabetic drugs (DPP4 I, GLP-1a and sulfonylureas).<sup>163</sup> Finally, canagliflozin was found to improve left ventricular diastolic function in patients with T2D.<sup>164</sup>

Of note, the CANDLE is an ongoing study aimed at evaluating the safety and non-inferiority of canagliflozin as compared with glimepiride in patients with T2D with chronic HF.<sup>165</sup>

### Dapagliflozin

The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis In Myocardial Infarction Study Group 58 (DECLARE-TIMI 58) evaluated the safety and efficacy of dapagliflozin in 17,160 patients with T2D and established CV diseases or at high CV risk. Dapagliflozin resulted non-inferior to placebo regarding the primary composite outcome (*i.e.*, time to the first event of CV death, myocardial infarction, or ischemic stroke; HF 0.93; 95%CI 0.84-1.03; P=0.17 for superiority; P<0.001 for non-inferiority) and it was associated with a lower rate of hospitalization for HF (HR 0.73; 95%CI 0.61-0.88).<sup>166</sup> Moreover, the incidence of a secondary renal composite outcome ( $\geq 40\%$  decrease in eGFR to <60 mL per minute per 1.73 m<sup>2</sup> of body-surface area, new ESKD, or death from renal or CV causes) was 4.3% in the dapagliflozin group and 5.6% in the placebo group (HF 0.76; 95%CI 0.67-0.87).

In addition, subsequent analyses found that the risk reduction of CV death and HF hospitalization were even greater benefits in patients with T2D and prior myocardial infarction<sup>167</sup> and in patients with HFpEF than in those without.<sup>168</sup>

Consistently, in a real-world population similar to the one included in the DECLARE-TIMI 58 study, dapagliflozin showed CV safety and resulted in lower event rates of HF hospitalization and CV mortality *versus* other glucose-lowering drugs.<sup>169</sup> Moreover, in another study dapagliflozin was associated with a lower risk of MACE, HF hospitalization and all-cause mortality compared with DPP-4 inhibitors.<sup>170</sup> Finally, dapagliflozin was found to significantly improve the left ventricular diastolic function in patients with T2D and HF after 6 months of treatment.<sup>171</sup>

Noteworthy, the following trials are ongoing:

- An Exploratory Study of Dapagliflozin for the Attenuation of Albuminuria in Patients with Heart Failure and Type 2 Diabetes Mellitus (DAPPER):

to evaluate whether dapagliflozin decreases albuminuria and exerts cardioprotective effects in Patients with T2D and HF.<sup>172</sup>

- Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure (DAPA-HF): to evaluate the effect of dapagliflozin on the incidence of worsening HF or CV death in patients with HFpEF (ClinicalTrials.gov, ID: NCT03036124).<sup>173</sup>
- Dapagliflozin Evaluation to Improve the LIVES of Patients with PReserved Ejection Fraction Heart Failure (DELIVER): to evaluate the effect of dapagliflozin 10 mg *versus* placebo once daily in reducing the composite of CV death or heart failure events in patients with HFpEF (hospitalizations for HF or urgent HF visits) (ClinicalTrials.gov, ID: NCT03619213).

### Ertugliflozin

VERTIS-CV is an ongoing trial to assess the cardiovascular safety of ertugliflozin in patients with T2D and established CVD (ClinicalTrials.gov, ID: NCT01986881).<sup>174</sup>

### Sotagliflozin

The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) Trial is an ongoing study aimed at demonstrating that:

- sotagliflozin reduces CV mortality and morbidity (composite of CV death or HF hospitalization) compared to placebo in hemodynamically stable patients with T2D and LVEF <50% after admission for worsening heart failure (WHF);
- sotagliflozin reduces CV mortality and morbidity (composite of CV death or HF hospitalization) compared to placebo in hemodynamically stable patients with T2D and HF irrespective of LVEF after admission for WHF (ClinicalTrials.gov, ID: NCT03521934).

## Discussion

The main innovation concerning the treatment of patients with T2D and HF comes from studies on new glucose-lowering drugs. In particular, some robust and consistent evidence suggests a beneficial effect of all SGLT2 inhibitors in reducing the risk of hospitalization for HF in patients with T2D (Table 1<sup>99,102-104,110-112,117,119,120,126-128,133,135,136,139,155,156,161,166,174</sup>). Consistently, in the Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL) Study examining real-world data (medical claims, primary care/hospital

**Table 1. Randomized controlled trials testing cardiovascular safety of novel anti-diabetic drugs (DPP4 inhibitors, GLP-1 agonists and SGLT2 inhibitors).**

Trial's name and year	Drug	Control	No.	Age (years)	T2DM duration (years)	Previous CVD	Previous HF	Median follow up (years)	MACE (HR, 95% CI)	All-cause death (HR, 95% CI)	CV death (HR, 95% CI)	Non-fatal stroke (HR, 95% CI)	MI (HR, 95% CI)	HF hospitalization (HR, 95% CI)
<i>DPP4 inhibitors</i>														
SAVOR TIMI 532013 <sup>99</sup>	Saxagliptin 5 mg daily (or 2.5 mg daily if GFR≤50 mL/min)	Placebo	16,492	65.0 (±8.6)	11.9 (±8.9)	78.3%	12.8%	2.1	1 (0.89-1.12)	1.11 (0.96-1.27)	1.03 (0.87-1.22)	0.95 (0.80-1.11)	1.12 (1.07-1.19)	1.27 (1.07-1.51)
EXAMINE 2013 <sup>102,103</sup>	Alogliptin 25 mg daily (GFR≥60 mL/min), 12.5 mg daily (30≤GFR<60), or 6.25 mg (GFR<30)	Placebo	5380	60.8 (±9.9)	9.1 (±8.1)	100% (recent ACS)	27.9%	1.5	0.96 (≤1.16)	0.88 (0.71-1.09)	0.79 (0.60-1.04)	1.08 (0.88-1.33)	0.91 (0.55-1.50)	1.07 (0.79-1.46)
TECOS 2015 <sup>104</sup>	Sitagliptin 100 mg daily (or 50 mg daily if 30≤GFR<50)	Placebo	14,671	65.5 (±8.0)	11.6 (±8.1)	74.0%	18%	3.0	0.98 (0.88-1.09)	1.06 (0.91-1.24)	1.04 (0.87-1.24)	-	-	0.98 (0.81-1.19)
CARMELINA2019 <sup>110,111</sup>	Linagliptin 5 mg daily	Placebo	6979	65.8 (±9.1)	14.7 (±9.4)	57%	26.8%	2.2	1.02 (0.89-1.17)	0.98 (0.84-1.13)	0.96 (0.81-1.14)	1.15 (0.91-1.45)	1.23 (1.08-1.38)	0.90 (0.74-1.08)
CAROLINA (ongoing) <sup>112</sup>	Linagliptin 5 mg daily	Glimepiride 1-4 mg daily	6041	64.0±9.5	6.2 (2.9-11.0)	34.5%	-	-	-	-	-	-	-	-
<i>GLP-1 agonists</i>														
ELIXA 2015 <sup>117</sup>	Lixisenatide 10 to 20 µg daily	Placebo	6068	60.25 (±9.6)	9.3 (±8.2)	100% (recent ACS)	22.4%	2.1	1.02 (0.89-1.17)*	0.94 (0.78-1.13)	0.98 (0.78-1.22)	1.03 (0.87-1.22)	1.12 (1.07-1.18)	0.96 (0.75-1.23)
LEADER 2016 <sup>119,120</sup>	Liraglutide 1.8 mg daily	Placebo	9340	64.3 (±7.2)	12.8 (±8.0)	81.3%	14%	3.8	0.87 (0.78-0.97)	0.85 (0.74-0.97)	0.78 (0.66-0.93)	0.88 (0.75-1.03)	0.89 (0.72-1.11)	0.87 (0.73-1.05)
SUSTAIN-62016 <sup>126</sup>	Semaglutide 0.5 to 1 mg weekly	Placebo	3297	64.6 (±6.7)	13.9 (±8.1)	83.0%	23.6%	2.1	0.74 (0.58-0.95)	1.05 (0.74-1.50)	0.98 (0.65-1.48)	0.74 (0.51-1.08)	0.61 (0.38-0.99)	1.11 (0.77-1.61)
EXSCEL 2017 <sup>127,128</sup>	Exenatide 2 mg once weekly	Placebo	14,752	62 (56-68)	12 (7-18)	73.1%	16.2%	3.2	0.91 (0.83-1.00)	0.86 (0.77-0.97)	0.88 (0.76-1.02)	-	-	0.94 (0.78-1.13)
HARMONY 2018 <sup>133</sup>	Albiglutide 30-50 mg weekly	Placebo	9463	64.1 (±8.7)	14.1 (±8.7)	100%	20.3%	1.6	0.78 (0.68-0.90)	0.95 (0.79-1.16)	0.93 (0.73-1.19)	0.75 (0.61-0.90)	0.86 (0.66-1.14)	-
REWIND 2019 <sup>135,136</sup>	Dulaglutide 1.5 mg weekly	Placebo	9901	66.2 (±6.5)	10.5 (7.2)	31.5%	8.6%	5.4	0.88 (0.79-0.99)	0.90 (0.80-1.01)	0.91 (0.78-1.06)	0.96 (0.79-1.16)	0.76 (0.61-0.95)	0.93 (0.77-1.12)

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Table 1. Continued from previous page.

Trial's name and year	Drug	Control	No.	Age (years)	T2DM duration (years)	Previous CVD	Previous HF	Median follow up (years)	MACE (HR, 95% CI)	All-cause death (HR, 95% CI)	CV death (HR, 95% CI)	Non-fatal MI (HR, 95% CI)	Non-fatal stroke (HR, 95% CI)	HF hospitalization (HR, 95% CI)
<i>SGLT2 inhibitors</i>														
EMPA-REGOUTCOME 2015 <sup>139</sup>	Empagliflozin 10 or 25 mg daily	Placebo	7020	63 (±8.6)	>10 in more than 50%	More than 99%	10.1%	3.1	0.86 (0.74-0.99)	0.68 (0.57-0.82)	0.62 (0.49-0.77)	0.87 (0.70-1.09)	1.24 (0.92-1.67)	0.65 (0.50-0.85)
CANVAS Program 2017 <sup>155,156</sup>	Canagliflozin 100 or 300 mg daily	Placebo	10,142	63.3 (±8.3)	13.5 (±7.8)	65.6%	14.4%	2.4	0.86 (0.75-0.97)	0.87 (0.74-1.01)	0.87 (0.72-1.06)	0.85 (0.69-1.05)	1.15 (0.87-1.50)	0.67 (0.52-0.87)
DECLARE-TIMI-58 2018 <sup>166</sup>	Dapagliflozin 10 mg daily	Placebo	17,160	63.8 (±6.8)	11 (6-16)	40.6%	10%	4.2	0.93 (0.84-1.03)	0.93 (0.82-1.04)	0.98 (0.82-1.17)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.73 (0.61-0.88)
CREDESCENCE 2019 <sup>161</sup>	Canagliflozin 100 mg daily	Placebo	4401	63.0 (±9.2)	15.8 (±8.6)	50.4%	14.8	2.6	0.80 (0.67-0.95)	0.83 (0.68-1.02)	0.78 (0.61-1.00)	-	-	0.61 (0.47-0.80)
VERTIS-CV (ongoing) <sup>174</sup>	Ertugliflozin 5 mg or 15 mg	Placebo	8238	64.4 (±8.1)	12.9 (±8.3)	99.9%	23.1%	-	-	-	-	-	-	-

T2D; type 2 diabetes; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; GRF, glomerular rate filtration. \*Including also unstable angina.

records, and national registries) from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom, SGLT2 inhibitors were associated with a lower risk of death and HF hospitalization compared to other glucose-lowering drugs.<sup>175</sup> The subsequent CVD-REAL 2 study, enrolling T2D patients from Asia Pacific, Middle East and North America, confirmed this finding.<sup>176</sup>

The plausible underlying mechanism seems to relate to their natriuretic effect with consequent decrease in fluid overload and improvement of congestive symptoms.<sup>177</sup> Over the past decade, several trials have been developed to test the efficacy and safety of SGLT2 inhibitors. Four of them, including EMPAREG-OUTCOME (empagliflozin), CANVAS Program (canagliflozin), DECLARE-TIMI 58 (dapagliflozin) and CREDESCENCE (canagliflozin) have been completed and they consistently showed a significant reduction in HF hospitalization, suggesting the existence of a possible class effect. Ongoing trials specifically enrolling patients with HF (Table 2<sup>165,172,173</sup>) will provide further information, especially whether these drugs may be used also in patients without T2D and with acute HF decompensation.<sup>178</sup>

Interestingly, a renal-protective effect of SGLT2 inhibitors was also suggested. In fact, RCTs (EMAPREG-OUTCOME, CANVAS Program and DECLARE-TIMI 58) consistently demonstrated that SGLT2 inhibitors significantly reduce renal events in patients with T2D when compared to placebo (Table 3<sup>139,155,156,161,166</sup>). This was also recently confirmed by the CREDESCENCE trial, which was specifically designed to test renal outcomes in patients with T2D and nephropathy and, therefore, included only participants with impaired renal function (eGFR of 30 to <90 mL per minute per 1.73 m<sup>2</sup> of body-surface area). However, we need to mention that patients with severe or end-stage CKD were excluded from RCTs. Specifically, the exclusion criteria were CrCl <60 mL/min (estimated using the Cockcroft-Gault equation) for the DECLARE-TIMI 58; eGFR <30 mL/min/1.73 m<sup>2</sup> (estimated using the MDRD formula) for the other trials (Table 3).

Noteworthy, in a recent meta-analysis including data from the EMPAREG-OUTCOME, CANVAS Program and DECLARE-TIMI 58, Zelniker and colleagues confirmed that SGLT2i reduced the risk of hospitalization for HF and progression of renal disease regardless of existing atherosclerotic CV disease or a history of HF. However, an interaction between baseline renal function and the clinical benefit of SGLT2 inhibition was observed. In particular, they found a lesser reduction in progression of renal disease but a greater reduction in hospitalization for HF with SGLT2 inhibition in patients with worse baseline renal function.<sup>179</sup> Although the exact mechanisms underlying this interaction are not fully understood, the

**Table 2. Ongoing trials of SGLT2 inhibitors in patients with heart failure.**<sup>165,172,173</sup>

Drug	Control	No.	NYHA class	LVEF	Diabetes status	Inpatient/outpatient	Primary endpoint
EMPEROR-REDUCED	Placebo	2850	II-IV	≤40%	Diabetes/no diabetes	Outpatient	CV death or HF hospitalization
EMPEROR-PRESERVED	Placebo	6000	II-IV	>40%	Diabetes/no diabetes	Outpatient	CV death or HF hospitalization
CANDLE <sup>165</sup>	Glimepiride	250	I-III	Any	Diabetes	Outpatient	% change from baseline in NT-proBNP
DAPPER <sup>172</sup>	Placebo	446	II-IV	Any	Diabetes	Outpatient	% change from baseline in urine albumin-to-creatinine ratio
DAPA-HF <sup>173</sup>	Placebo	4695	II-IV	≤40%	Diabetes/no diabetes	Outpatient	CV death, HF hospitalization or urgent HF visit
DELIVER	Placebo	8000	II-IV	>40%	Diabetes/no diabetes	Inpatient/outpatient	CV death, HF hospitalization or urgent HF visit
SOLOIST-WHF	Placebo	4000	Admitted to the hospital, or urgent HF visit for worsening HF	Any	Diabetes only	Inpatient/outpatient	CV death or HF hospitalization (in patients with LVEF<50% and in all patients)

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CV, cardiovascular; HF, heart failure.

**Table 3. Randomized controlled trials testing renal effects of SGLT2 inhibitors.**

Trial name	Exclusion criteria based on renal function	eGFR mL/min/1.73 m <sup>2</sup> mean (SD)	eGFR >60 mL/min/1.73 m <sup>2</sup>	Composite outcome (doubling serum creatinine, ESKD, or renal death or CV death) HR (95%CI)	Composite outcome (doubling serum creatinine, ESKD, or renal death) HR (95%CI)	Composite outcome (progression to macroalbuminuria, doubling serum creatinine, ESRD, or renal death) HR (95%CI)	Doubling serum creatinine HR (95%CI)	≥40% decrease in eGFRHR (95%CI)	ESKD HR (95%CI)	ESKD or renal death HR (95%CI)
EMPAREG OUTCOME <sup>139</sup>	eGFR <30 mL/min/1.73 m <sup>2</sup> (MDRD)	74.03 (±21.4)	25.9%	-	0.54 (0.40-0.75)	0.61 (0.53-0.70)	-	-	-	-
CANVAS Program <sup>155,156</sup>	eGFR <30 mL/min/1.73 m <sup>2</sup> (MDR)	76.5 (±20.5)	20.1%	-	0.53 (0.33-0.78)	-	0.50 (0.30-0.84)	0.60 (0.57-0.68)	0.77 (0.30-0.1.97)	0.56 (0.23-1.132)
DECLARE TIMI 58 <sup>166</sup>	CrCl <60 mL/min (Cockcroft-Gault)	85.2 (±15.9)	7.4%	-	-	0.53 (0.43-0.66)	-	-	-	-
CREDESCENCE <sup>61</sup>	eGFR <30 mL/min/1.73 m <sup>2</sup> (MDRD)	56.2 (±18.2)	59.8% (0-59-0.82)	0.70 (0.53-0.81)	0.66	-	0.60 (0.48-0.76)	-	0.68 (0.54-0.86)	0.72 (0.54-0.97)

eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; CV, cardiovascular; HR, hazard ratio; CI, confidence interval; MDRD, modification of diet in renal disease; CrCl, creatinine clearance.

authors suggest that patients with worse baseline renal function are at higher risk of HF hospitalization and therefore this susceptible population may have a particular benefit from SGLT2' renoprotective effect and natriuresis, that largely explain their association with the reduction in HF hospitalization.

## Conclusions

In conclusion, SGLT2 inhibitors appear to be a promising drug to treat patients with T2D and HF. Ongoing RCTs specifically enrolling patients with HF treated with SGLT2 inhibitors will provide more insights on the underlying mechanisms and further information about their indications and safety.

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