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REVIEW ARTICLE

Sodium–glucose cotransporter 2 inhibitors represent a paradigm shift in the prevention of heart failure in type 2 diabetes patients

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ABSTRACT

Recent major clinical trials of the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes have shown that they reduce three-point major adverse cardiovascular events, cardiovascular death, hospitalization for heart failure (HF) and a composite renal outcome. These beneficial effects of SGLT2 inhibitors are also evident in type 2 diabetes patients with a previous history of atherosclerotic cardiovascular disease or advanced renal disease. HF is a major determinant of the prognosis of diabetes patients. Although HF with low ejection fraction can be effectively treated with antihypertensive drugs, these treatments do not reduce mortality in HF patients with preserved ejection fraction (HFpEF). HFpEF is clinically characterized by left ventricular diastolic dysfunction, perivascular fibrosis and stiffness of cardiomyocytes, defined as "cardiomyopathy". Therefore, HFpEF is considered to be an entirely separate entity to HF with low ejection fraction. Recent studies have suggested that HFpEF might be treatable using SGLT2 inhibitors, which ameliorate visceral adiposity, insulin resistance, hyperglycemia, hyperlipidemia, volume overload, hypertension and cardiac inflammation. In the final part of the present review, we discuss the biochemical and molecular mechanisms of the effects of SGLT2 inhibitors in type 2 diabetes patients with HFpEF. These involve amelioration of the low nitric oxide production and oxidative stress, a reduction in cardiac inflammatory cytokine signaling, inhibition of Ca^{2+} overload, and an improvement in cardiac energy metabolism as a result of ketone body production. Investigations of the beneficial effects of SGLT2 inhibitors on cardiorenal outcomes, including hospitalization for HF, are now being carried out in preclinical and clinical studies.

INTRODUCTION

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a new class of oral glucose-lowering drug that inhibits renal glucose reabsorption, thereby increasing urinary glucose loss and causing osmotic diuresis in people with and without diabetes. SGLT2 inhibitor administration causes a urinary loss of 60–100 g glucose per day, which induces a negative energy balance, resulting in a significant change in whole-body energy metabolism[1–7]. Plasma glucose and insulin concentrations are significantly reduced in type 2 diabetes patients by treatment with SGLT2 inhibitors, and those are associated with significant improvements in both insulin resistance and insulin secretion[8–11]. In addition, SGLT2 inhibitors increase glucagon secretion through direct stimulation of pancreatic α-cells[12]. As a result, they reduce hepatic triglyceride synthesis, fat deposition in the liver and serum triglyceride concentration, and increase hepatic ketone body production[5–7,11]. Furthermore, the greater urinary glucose loss increases urinary uric acid excretion, resulting in a reduction in serum uric acid concentration[13]. Therefore, SGLT2 inhibitor treatment has beneficial effects on multiple atherogenic risk factors in patients with type 2 diabetes. SGLT2 inhibitors also have hemodynamic effects: they increase urinary water excretion and sodium loss, resulting in reductions in bodyweight, and both systolic and diastolic blood pressure[14–19]. These metabolic and hemodynamic effects of SGLT2 inhibitors have already been extensively reviewed[20].

Almost all the cardiovascular risk factors commonly found in patients with metabolic syndrome are significantly

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ameliorated by treatment with ipragliflozin, as shown in a pooled analysis of six Japanese phase II and III randomized controlled trials (RCTs)[21]. These beneficial effects on hemodynamic and metabolic parameters might also protect against the progression of atherogenic cardiovascular disease (CVD) in type 2 diabetes patients. Indeed, SGLT2 inhibitor treatment in type 2 diabetes patients with high cardiovascular risk consistently has reduced the incidence of hospitalization for heart failure (HHF), cardiovascular (CV) death and a renal composite outcome (RCO) in four multicenter RCTs[22–27].

Interestingly, major multicenter clinical RCTs found that glucagon-like peptide-1 receptor agonists also effectively protect against not only cardiovascular events, but also progression of renal disease, which is consistent with the results found in the use of SGLT2 inhibitors. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, liraglutide treatment for 3.8 years significantly reduced major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke with a hazard ratio (HR) of 0.87 ($P < 0.01$) compared with placebo[28]. In the Trial to Evaluate Cardiovascular and Other Long term Outcomes with semaglutide in patients with Type 2 Diabetes (SUSTAIN 6), semaglutide treatment for 2.1 years showed a HR of 0.74 for MACE ($P < 0.02$)[29]. However, the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) showed a HR for MACE that did not reach the threshold for demonstrated superiority versus placebo for the entire trial[30]. Taken together, it appears that among patients with established CVD, both liraglutide and semaglutide might provide cardiovascular benefits, but exenatide is less certain in regard to clinical benefits. Furthermore, protection against HHF has not been reported to be statistically significant with the use of any glucagon-like peptide-1 receptor agonists, which is entirely different from the results of treatment with SGLT2 inhibitors. The mechanisms to explain those differences between two types of drugs have not been extensively compared in the previous studies. Based on the evidence from recent major multicenter clinical RCTs, both SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists have been used as medicines to effectively protect not only cardiovascular events[28,29], but also progression of renal disease[29,31] in the 2019 European Society of Cardiology guidelines on diabetes, prediabetes and cardiovascular disease[32].

In the present review, we discuss several recent lines of evidence, which show that the use of SGLT2 inhibitors effectively prevents event rates of MACE, CV death, HHF and renal outcomes in type 2 diabetes patients with high CV risk or a history of advanced CVD or advanced renal disease. Finally, we represent a paradigm shift in the prevention of heart failure in type 2 diabetes patients to improve their life prognosis. We then summarize the subcellular biochemical and molecular mechanisms involved in the development of heart failure with preserved ejection fraction (HFpEF), and discuss the effectiveness of SGLT2 inhibitors for the treatment of HFpEF and HF with low ejection fraction (HFrEF) in diabetes patients.

LARGE MULTICENTER PLACEBO-CONTROLLED RCTS OF THE USE OF SGLT2 INHIBITORS FOR THE PREVENTION OF CARDIORENAL DISEASES

Reduction of the incidence of MACE

Four major multicenter RCTs of the use of SGLT2 inhibitors for the prevention of cardiorenal outcomes in diabetes patients were published between 2015 and 2019. Excellent reviews of the relationship between patient characteristics and cardiovascular outcomes in these four trials, and the mechanisms of these cardiovascular benefits have already been published[33–35], and the characteristics of the participants in the four trials are shown in Table 1. These trials were the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial[22–24], which involved the administration of 10 or 25 mg empagliflozin daily; the Canagliflozin Cardiovascular Assessment Study (CANVAS)[25], which involved the administration of 100 mg or 300 mg canagliflozin daily; the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial[26], which involved the administration of 10 mg dapagliflozin daily; and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial[27], which involved the administration of 100 mg canagliflozin daily.

The primary end-points of each trial were evaluated after a mean follow-up period of 2.4–4.2 years. The baseline characteristics of the recruited patients are summarized in Table 1. They had a mean glycated hemoglobin of 8.1–8.3%, and renin–angiotensin–aldosterone system inhibitors and statins were used in >75% and 80% of patients, respectively. Reductions in glycated hemoglobin, bodyweight and systolic/diastolic blood pressure of 0.24–0.58%, 0.8–1.8 kg and 3–4 mmHg/0.36–1.39 mmHg were achieved, respectively. These drug effects were similar among the four trials of SGLT2 inhibitors, but there were clear differences in some of the baseline cardiorenal risk factors in the diabetes patients in these trials (Table 2).

Almost all the participants (99%) in the EMPA-REG OUTCOME trial had a previous history of CVD, 40% had a mean urinary albumin-to-creatinine ratio (UACR) above the microalbuminuric threshold, and 26% had an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. However, the participants in the CREDENCE trial had the most advanced renal disease of the four clinical trials, with 99.3% having a mean UACR above the microalbuminuric threshold, and 60% having an eGFR < 60 mL/min/1.73 m^2. In contrast, the participants in the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial had the lowest cardiorenal risk, with just 41% having a previous history of CVD, 30% having a mean UACR above the microalbuminuric threshold and 7% having an eGFR <60 mL/min/1.73 m^2.

Table 1 | Baseline characteristics of the type 2 diabetes patients in the four clinical trials in which the preventive effects of sodium–glucose cotransporter 2 inhibitors against cardiorenal events were investigated

Study	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58	CREDENCE
Patients enrolled (*n*)	7,020	10,142	17,160	4,401
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Dose	10 or 25 mg	100 or 300 mg	10 mg	100 mg
Median duration of follow up	3.1 years	2.4 years	4.2 years	2.62 years
Mean baseline HbA1c	8.1%	8.2%	8.3%	8.3%
Mean duration of diabetes	NA	13.5 years	11 years	15.8 years
Baseline RAASI use	81%	≥80%	81%	100%
Baseline statin use	77%	75%	75%	NA
HbA1c reduction	0.24%	0.58%	0.42%	0.25%
BW reduction	1.79 kg	1.6 kg	1.8 kg	0.8 kg
Blood pressure (mmHg) reduction (SBP/DBP)	2.96/0.36	3.93/1.39	2.7/0.7	3.30/0.95

BW, bodyweight; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DBP, diastolic blood pressure; DECLARE-TIMI 58; Dapagliflozin Effect of Cardiovascular Events-Thrombolysis in Myocardial Infarction 58, EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HbA1c, glycated hemoglobin; NA, not available; RAASI, renin–angiotensin–aldosterone system inhibitor; SBP, systolic blood pressure.

Table 2 | Previous history of cardiorenal risk factors and events in the type 2 diabetes patients enrolled in the four clinical trials of sodium–glucose cotransporter 2 inhibitors

Study	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58	CREDENCE
Mean eGFR (mL/min/1.73 m^2)	74	76.5	85.2	56.2
eGFR (mL/min/1.73 m^2)				
<60	25.9%	20.1%	7.4%	59.8%
≥60	74.1%	79.9%	92.6%	40.2%
UACR (mg/gCr)				
<30	59.4%	69.8%	67.9%	0.7%
30–300	28.7%	22.6%	23.4%	11.3%
>300	11.0%	7.6%	6.8%	88%
Micro- and macroalbuminuria	39.7%	30.2%	30.2%	99.3%
Previous history of CVD	99.2%	65.6%	41%	50%
Previous history of HF	10%	14.8%	10%	14.8%
Existence of multiple CVD risks	NA	Only two CVD risk factors (≥50 years)	59%	NA

CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CVD, cardiovascular disease; DECLARE-TIMI 58; Dapagliflozin Effect of Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HF, heart failure; NA, not available; UACR, urinary albumin-to-creatinine ratio.

A total of 66% of the participants in CANVAS had a previous history of CVD (65.6%), 30.2% had a mean UACR above the microalbuminuric threshold and 20.1% had an eGFR <60 mL/min/1.73 m^2, showing that they had a prevalence of cardiorenal comorbidities between the EMPA-REG OUTCOME and DECLARE-TIMI 58 trials.

The EMPA-REG OUTCOME trial of 7,020 type 2 diabetes patients showed that empagliflozin administration was associated with a 14% lower incidence ($P = 0.04$) of MACE after a mean of 3.1 years (Table 3). Similarly, in the CREDENCE trial, patients treated with 100 mg canagliflozin daily had a 20% lower incidence ($P = 0.01$) of MACE than those administering the placebo after a median of 2.62 years (Table 3). However, in the CANVAS study cohort, 10,142 type 2 diabetes patients were assigned to receive canagliflozin (100 mg, with the option to increase this to 300 mg, daily) or placebo for a median of 2.4 years (Table 3). The reduction in the incidence of MACE in the canagliflozin group versus the placebo group was not significant (HR 0.86, $P = 0.08$). Finally, the DECLARE-TIMI 58 trial included 17,160 type 2 diabetes patients who were followed for a median of 4.2 years. The patients in that trial had lower CVD risk and were at an earlier stage of CKD than those in the CREDENCE trial, the EMPA-REG OUTCOME trial and CANVAS, as shown in Table 2. Also in the DECLARE-TIMI 58 trial, the reduction in the incidence of MACE in the dapagliflozin group was not significantly different from that in the

placebo group (HR 0.93, $P = 0.17$; Table 3). Therefore, the findings of the major RCTs suggest that SGLT2 inhibitor treatment is more likely to prevent MACE in patients with a higher CVD risk, a previous history of CV events and/or advanced renal disease.

Reduction in the incidence of RCOs

As shown in Table 4, the RCOs were defined as: (i) a sustained reduction of ≥40% in eGFR to <60 mL/min/1.73 m^2; (ii) a diagnosis of end-stage renal disease and dialysis for ≥90 days; or (iii) kidney transplant or a sustained eGFR of <15 mL/min/1.73 m^2; with the addition of (iv) renal disease-related death in the DECLARE-TIMI 58 trial[26]. There was a HR for this RCO of 0.53 (95% confidence interval [CI] 0.43–0.66) in the dapagliflozin group versus the placebo group. In CANVAS[25], there was a HR of 0.60 (95% CI 0.47–0.77) for the RCO in the canagliflozin group versus the placebo group, in the EMPA-REG OUTCOME trial[23,24], the equivalent HR was 0.54 (95% CI 0.47–0.75) for the empagliflozin group versus the placebo group, and in the CREDENCE trial, it was 0.66 (95% CI 0.53–0.81) for the canagliflozin group versus the placebo group. These data showed that there were similar reductions in the risk of the RCO after treatment with various SGLT2 inhibitors, although there were some differences in the definitions of the RCO used among the four RCTs. However, we might add the following evidence that the absolute renal event rates were highest in the CREDENCE trial[27], probably because the participants had the highest prevalence of comorbidities associated with advanced renal dysfunction and micro-/macroalbuminuria at baseline among the four trials.

Reductions in the incidences of HHF and CV death

The absolute incidences per 1,000 patient-years of HHF and CV death were significantly less after treatment with each of the SGLT2 inhibitors (HR 0.66–0.83) than in the control groups. The reductions in relative risk and the absolute event rate for HHF and CV death were greater in the EMPA-REG OUTCOME and CREDENCE trials than in the DECLARE-TIMI 58 trial and CANVAS (Table 5). However, the reduction in the relative risk of HHF alone was similar among the four trials (HR 0.61–0.73). Surprisingly, the reduction in HHF was evident after approximately 6 months of treatment with empagliflozin, suggesting that this effect might be independent of long-term improvements in cardiovascular risk factors.

Comparison of the cardiorenal protection provided by SGLT2 inhibitors and other glucose-lowering drugs

The cardiorenal protective effects of SGLT2 inhibitor treatment have been studied in real-world clinical practice. In the large Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 inhibitors observational study (CVD-REAL)[36], the addition of an SGLT2 inhibitor was associated with reductions in the risks of all-cause death and HHF, regardless of the presence or absence of pre-existing CVD, compared with the use of other glucose-lowering drugs. Similarly, in the CVD-REAL2 study[37], which was carried out with a variety of patients across a number of countries, the initiation of a different SGLT2 inhibitor was associated with reductions in the risks of CV events, including CV death (HR 0.52), HHF (HR 0.60), myocardial infarction (HR 0.81) and stroke (HR 0.68). Finally, CVD-REAL3 study[38] aimed to determine the effects of SGLT2 inhibitors on the progression of renal dysfunction in type 2 diabetes patients with or without CKD, in routine clinical practice. The results showed that the initiation of SGLT2 inhibitor therapy in type 2 diabetes patients is associated with a smaller decline in kidney function and a lower incidence of a composite of renal events than the initiation of other glucose-lowering drugs.

PREVENTION OF HEART FAILURE IN DIABETES PATIENTS IN THE TREATMENT WITH SGLT2 INHIBITORS

Heart failure in diabetes

The current American College of Cardiology/American Heart Association guidelines define heart failure (HF) as a complex clinical syndrome[39]. HF is a major determinant of the prognosis of patients with diabetes mellitus. It is generally accepted that the prevalence of HF in diabetes is twice as high in men and fivefold as high in women with diabetes compared with

Table 3 | Reductions in the incidence of major adverse cardiovascular events in type 2 diabetic patients induced by sodium–glucose cotransporter 2 inhibitors

Study	MACEs (per 1,000 patient-years)			
	SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)	*P*-value
DECLARE-TIMI 58	22.6	24.2	0.93 (0.84–1.03)	0.17
CANVAS	26.9	31.5	0.86 (0.75–0.97)	0.08
EMPA-REG OUTCOME	37.4	43.9	0.86 (0.74–0.99)	0.04
CREDENCE	38.7	48.7	0.80 (0.67–0.95)	0.01

CANVAS, Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DECLARE-TIMI 58; Dapagliflozin Effect of Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MACEs, major adverse cardiovascular events; SGLT2, sodium–glucose cotransporter 2.

Table 4 | Reductions in the incidences of composite renal-specific outcomes in type 2 diabetic patients induced by sodium–glucose cotransporter 2 inhibitors

Study	Event rates of a composite renal outcome (per 1,000 person-years)			
	SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)	*P*-value
DECLARE-TIMI 58	3.7	7	0.53 (0.43–0.66)	<0.001
CANVAS	5.5	9	0.60 (0.47–0.77)	<0.001
EMPA-REG OUTCOME	6.3	11.5	0.54 (0.40–0.75)	<0.001
CREDENCE	28.7	43.7	0.66 (0.53–0.81)	$P < 0.001$

CANVAS, Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DECLARE-TIMI 58; Dapagliflozin Effect of Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; SGLT2, sodium–glucose cotransporter 2.

Table 5 | Reductions in the incidences of hospitalization for heart failure and cardiovascular death or hospitalization for heart failure in type 2 diabetes patients induced by sodium–glucose cotransporter 2 inhibitors

Study	Event rates for HHF and CV death (per 1,000 patient-years)				Event rates for HHF (per 1,000 patient-years)			
	SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)	*P*-value	SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)	*P*-value
DECLARE-TIMI 58	12.2	14.7	0.83 (0.73–0.95)	0.005	6.2	8.5	0.73 (0.61–0.88)	0.0008
CANVAS	16.3	20.8	0.78 (0.67–0.91)	0.0015	5.5	8.7	0.67 (0.52–0.87)	0.02
EMPA-REG OUTCOME	19.7	30.1	0.66 (0.55–0.79)	<0.001	9.4	14.5	0.65 (0.50–0.85)	0.002
CREDENCE	31.5	45.4	0.69 (0.57–0.83)	<0.001	15.7	25.3	0.61 (0.47–0.80)	0.00001

CANVAS, Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV, cardiovascular; DECLARE-TIMI 58; Dapagliflozin Effect of Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; HHF, hospitalization for heart failure; SGLT2, sodium–glucose cotransporter 2.

age-matched non-diabetic individuals. In addition, older adult type 2 diabetes patients have a 1.3-fold greater risk of developing HF than age-matched non-diabetic individuals[40,41]. Furthermore, it has been reported that patients with diabetic glomerulosclerosis, but without major coronary artery disease, cardiac hypertrophy or valvular heart disease develop HF, which has been defined as a novel type of cardiomyopathy[42,43]. Therefore, it is possible that poor long-term glycemic control puts patients at a higher risk of developing not only diabetic retinopathy and nephropathy, but also cardiac microvascular complications with interstitial and perivascular fibrosis, and myocardial cell death, which are significant risk factors for the development of HF in diabetes[44].

HF with preserved ejection fraction in diabetes

HF can be classified into three types, the first two of which are HFrEF (ejection fraction [EF] <40%) and HFpEF (EF ≥50%). Values of EF of 40–49% are defined as midrange. HFpEF is clinically characterized by poor diastolic function, and the wider clinical characteristics of patients with HFpEF are listed in Figure 1[39,45,46]. This type of HF is reported to be highly prevalent in patients with hypertension, diabetes, obesity, metabolic syndrome or chronic kidney disease[47]. It has also been shown that multiple parameters associated with high diastolic left ventricular stiffness negatively correlate with glycated hemoglobin in type 2 diabetes patients, without evidence of abnormal wall movement or systolic ejection fraction[46].

The significance of diabetic microvascular complications for the risk of HF in diabetes has also been studied. In the Candesartan in Heart Failure: Assessment of Resolution in Mortality and Morbidity (CHARM) trial[48], the risks of CV death and HHF were studied in a population containing patients with HFrEF or HFpEF and with or without diabetes. The results showed that diabetes patients had higher risks of CV death and HHF than patients without diabetes. Furthermore, the incidence of HHF in diabetes patients was reported to be almost twice that of non-diabetic patients, irrespective of the presence of either HFpEF or HFrEF. In addition, the prognosis of diabetes with or without microangiopathy was compared with that of non-diabetic patients, all of whom had HFpEF, in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT)[49]. The cumulative incidences of HHF and CV death were significantly higher in diabetes patients with any type of microvascular complication than in non-diabetic or diabetes patients without microangiopathy. These results suggest that the existence of microvascular complications in diabetes patients with HFpEF might increase the risks of both CV death and HHF.

1. HF is classified into three types, on the basis of left ventricular ejection fraction: HFrEF: LVEF <40%, HFmrEF: LVEF 40–49%, and HFpEF: LVEF ≥50%.
2. Patients with HFpEF exhibit signs of heart failure, namely dyspnea, fatigue, fluid retention, and excercise intolerance.
3. Patients with HFpEF have high circulating BNP (≥35 pg/mL) and NT-proBNP (≥125 pg/mL) concentrations.
4. At least one additional criterion: either relevent structrual heart disease (left ventricular hypertrophy and/or left arterial enlargement) or diastolic dysfunction
5. Characteristics of impaired left ventricular dysfunction, identified using CMR or TTE
   - ① Early-to-late transmitral flow ratio (E/A): low
   - ② Deceleration time (DecT): high
   - ③ End-diastolic volume (EDV)/body surface area: low
   - ④ Normalized peak LV filling rate (pLVFR)/body surface area: low
   - ⑤ Early transmitral flow velocity to septal velocity ratio (E/e'): high
   - ⑥ Isovolumetric relaxation time (IVRT): high

Figure 1 | Classification of 3 type of heart failure and clinical diagnosis of HFpEF Characteristics of patients with heart failure with preserved ejection fraction(HFpEF) were shown in this figure. BNP, brain natriuretic peptide; CMRI, cardiac magnetic resonance imaging; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TTE, transthoracic echocardiography[39,45,46].

Mechanisms of progression of HFpEF in diabetes

As shown in Figure 2, type 2 diabetes patients mostly fit into two categories with regard to their progression to HF. One category comprises type 2 diabetes patients with visceral obesity, and insulin resistance, hyperinsulinemia, lipid abnormalities and/or hypertension, who are at higher risk of developing acute coronary syndrome. Once these patients develop acute coronary syndrome, they might also develop acute or chronic left ventricular systolic dysfunction, which is classified as HFrEF[45]. However, obesity and type 2 diabetes might also lead to HFpEF, which is induced by an increase in cardiac pre-load, developing because of volume overload due to plasma volume expansion. Furthermore, in such patients, insulin resistance and pro-inflammatory cytokines released from hypertrophied visceral adipocytes cause arterial stiffness, endothelial dysfunction in arterioles, and a reduction in capillary density systemically and in the heart, which results in an increase in cardiac afterload[50–52]. These pathophysiological states are highly prevalent in obese type 2 diabetes patients. The obesity-induced accumulation of cardiovascular risk factors has been studied in pigs fed a high-fat diet and in which hypertension was induced by renal artery embolization, over a 6-month period. These animals showed systemic inflammation, greater myocardial superoxide production, greater endothelial nitric oxide synthase (eNOS) uncoupling and lower nitric oxide production, and an impairment in endothelial-dependent vasodilatation in small coronary arteries[53,54].

The second category includes patients with long-standing type 2 diabetes complicated by the presence of severe diabetic nephropathy and/or retinopathy, and type 1 diabetes patients with poor long-term glycemic control. This second group of patients are characterized by diffuse narrowing and heavy sclerosis of distal coronary arteries, perivascular fibrosis, the deposition of a large amount of extracellular matrix, and the formation of advanced glycation end-products in cardiac muscle and intracardiac vascular walls, without major coronary artery stenosis. These changes are characteristic of "diabetic cardiomyopathy"[42–44].

A new strategy for the treatment of HFrEF using SGLT2 inhibitors

Studies of a number of drugs, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, diuretics and sacubitril/valsartan (a combination of a neprilysin inhibitor and an angiotensin receptor blocker) have shown that they reduce the risk of mortality in patients with HFrEF[32,55,56]. Neprilysin is a zinc-dependent metalloprotease that cleaves peptides at the amino side of hydrophobic residues, thereby inactivating several peptide hormones, including glucagon, brain natriuretic peptide and bradykinin. Therefore, the beneficial clinical effects of the neprilysin inhibitor, sacubitril, might relate to its inhibition of vasoactive peptide degradation. In addition, the efficacy of SGLT2 inhibitors for the prevention of HHF has been studied in 4,744 patients with symptoms of HF, New York Heart Association (NYHA) stage II–IV and EF ≤40%. The participants were treated with 10 mg dapagliflozin or placebo once daily for a median of 18.2 months[57], and deterioration in HF occurred in 16.3% of those in the dapagliflozin group, but 21.2% of those in the placebo group (HR 0.74, 95% CI 0.65–0.85; $P < 0.001$). This protective effect of dapagliflozin was similar in patients with or without diabetes.

The use of SGLT2 inhibitors for the treatment of patients with type 2 diabetes and HFpEF

HFpEF is considered to be an entirely separate entity to HFrEF and is present in nearly 50% of patients with HHF. Multicenter RCTs have not shown a reduction in the incidence of mortality

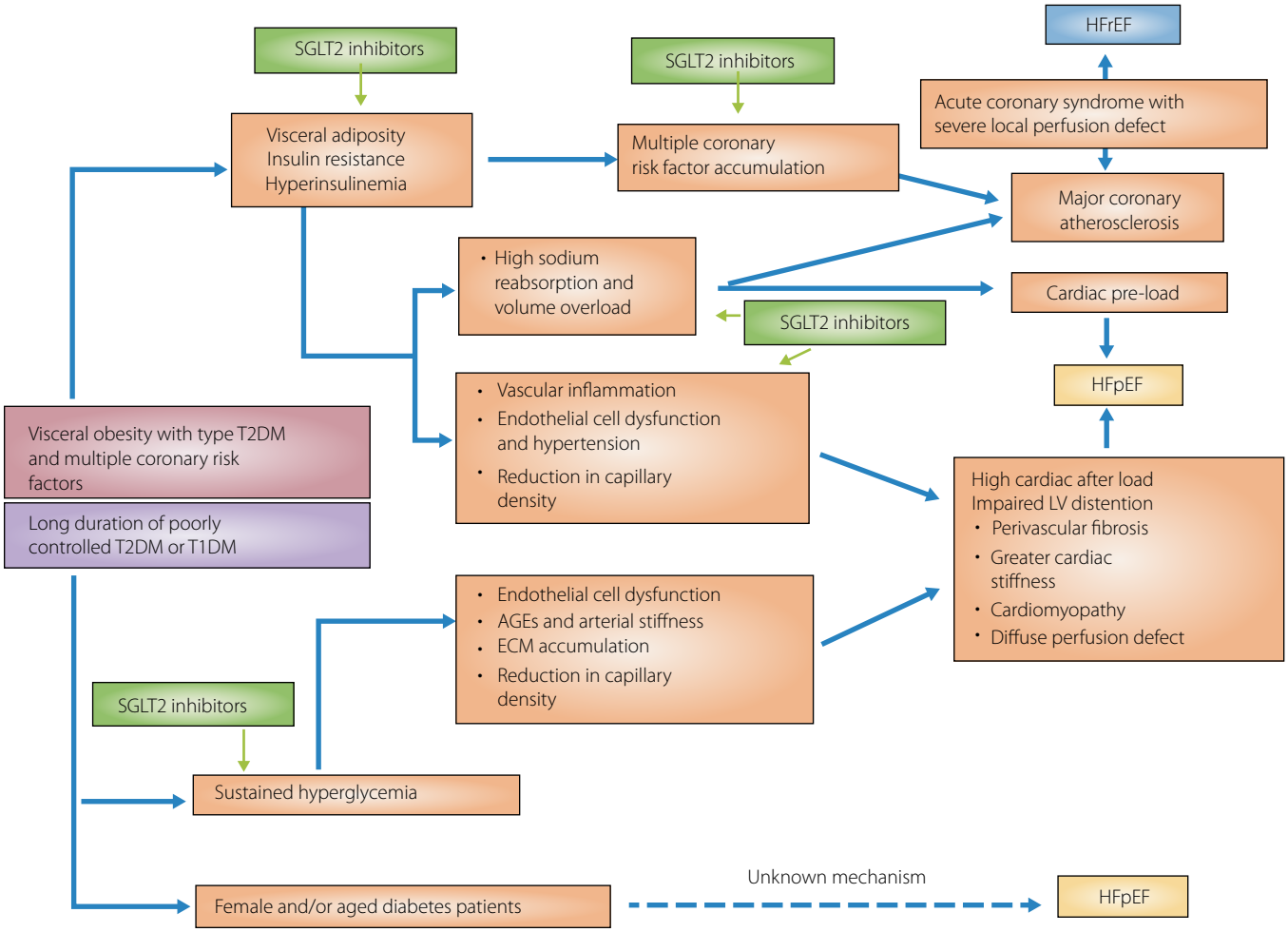

Figure 2 | Potential mechanisms for the progression of heart failure. Patients with diabetes can be placed into two categories: those who have visceral obesity and type 2 diabetes mellitus (T2DM), with multiple coronary risk factors; and those who are lean, and have long-standing, poorly controlled type 2 or type 1 diabetes mellitus (T1DM). The former category is characterized by the progression of coronary atherosclerosis, resulting in acute coronary syndrome and severe local perfusion defects, then progression to heart failure with reduced ejection fraction (HFrEF). In addition, insulin resistance and hyperinsulinemia induce volume overload, resulting in high cardiac preload. Furthermore, insulin resistance and visceral adiposity are associated with vascular inflammation, endothelial cell dysfunction and a reduction in capillary density, which lead to higher cardiac afterload and an impairment in left ventricular distension, resulting in the progression of heart failure with preserved ejection fraction (HFpEF). The latter category comprises patients with prolonged hyperglycemia, and hyperglycemia-induced vascular and cardiac tissue abnormalities, which impair left ventricular distension and cause the progression of HFpEF. Although HFpEF is considered to be an entirely separate entity to HFrEF as an etiological background, it is undeniable possibility that HFpEF progresses further into reduced ejection fraction in the advanced stage. Finally, female and older diabetes patients are more likely to develop HFpEF. The potential sites of sodium–glucose cotransporter 2 (SGLT2) inhibitor action are shown in green. AGEs, advanced glycation end-products; ECM, extracellular matrix.

in patients with HFpEF that were treated with RASs, angiotensin-converting enzyme inhibitors, β-blockers[58] or sacubitril/valsartan[59]. Although TOPCAT[60] showed that spironolactone treatment reduced the incidence of HHF (HR 0.83, 95% CI 0.69–0.99, $P = 0.04$) in patinets with HFpEF, it did not reduce the incidences of total death or hospitalization for any reason. Furthermore, this treatment was associated with an increase in serum creatinine concentration and hyperkalemia. Therefore, the use of mineralocorticoid receptor antagonists has not been recommended for the treatment of patients with HFpEF. As a result, a new approach to the diagnosis and treatment of HFpEF in diabetes has been sought[61].

Recently, there have been many studies that show that SGLT2 inhibitors improve ventricular diastolic function and the micro- and macrovascular circulation in diabetes patients with HF. A prospective multicenter study of type 2 diabetes patients with stable HF was carried out, in which patients with HFpEF (69%) and HFrEF + HF with midrange EF (31%) were administered with 5 mg/day dapagliflozin for 6 months. This showed a significant reduction in the ratio of mitral inflow E to mitral

e′ annular velocity (E/e') from 9.3 to 8.5 cm/s ($P < 0.02$) in response to dapagliflozin treatment[62]. Although this was an observational, follow-up study without a control group, the findings suggested that SGLT2 inhibitors might be beneficial for treatment of left ventricular diastolic dysfunction in diabetes. In another study[63], empagliflozin was shown to significantly reduce diastolic tension, without affecting systolic function, which was assessed *in vitro* using ventricular trabeculae isolated from patients with end-stage systolic HF. In addition, empagliflozin had a beneficial effect to reduce passive myofilament stiffness by increasing the phosphorylation of myofilament regulatory proteins.

In CANVAS[64], EF was measured by echocardiography as part of the routine clinical care of the participants, and the incidence of HF was compared between participants with HFpEF (EF ≥50%) and HFrEF (EF <50%). This analysis showed that the protective effects of canagliflozin against HF did not significantly differ between patients in these two categories and, thus, provided some hope that HFpEF might be ameliorated by SGLT2 inhibitor treatment in diabetes patients. Furthermore, in a subanalysis of the DECLARE-TIMI 58 data[65], the ability of dapagliflozin to prevent CV death and HHF was compared in participants with low ventricular EF (EF <45%) and those without HFrEF. Of the 17,160 participants, 671 (3.9%) had HFrEF, 1,316 (7.7%) had HF without a known reduction in EF and 15,173 (88.4%) had no history of HF at baseline. The results showed that dapagliflozin reduced the incidences of CV death more significantly in patients with HFrEF (HR 0.62, 95% CI 0.45–0.86) than in those without HFrEF (HR 0.88, 95% CI 0.76–1.02). However, it significantly reduced HHF to a similar extent in patients with (HR 0.64) and without (HR 0.76) HFrEF. Further clinical trials of the efficacy of SGLT2 inhibitors for the prevention of cardiovascular events in patients with HFpEF and HFrEF are now ongoing[66–68].

SUBCELLULAR, BIOCHEMICAL AND MOLECULAR MECHANISMS OF THE BENEFICIAL EFFECTS OF SGLT2 INHIBITORS ON HFPEF IN DIABETES PATIENTS

The molecular mechanisms of the development of HFpEF in diabetes have been analyzed in a number of studies. The delineation of some of these mechanisms has suggested promising targets for the amelioration of HFpEF in patients with type 2 diabetes, and below we discuss the subcellular biochemical and molecular mechanisms whereby SGLT2 inhibitors might prevent HFpEF in diabetes (Figures 3,4).

Effects of SGLT2 inhibitors on nitric oxide production and oxidative stress

We have reported that insulin resistance is associated with poor endothelium-dependent vascular relaxation because of impairment in eNOS activity and greater production of the superoxide anion[69–71]. In insulin resistance, eNOS uncoupling is principally induced by a deficiency of tetrahydrobiopterin (BH_4; an active cofactor of eNOS) in vascular endothelial cells, which develops because of a reduction in BH_4 biosynthesis secondary to lower activity of guanosine-triphosphate cyclohydrolase I. Furthermore, 7,8-dihydropteridine (BH_2; the inactive form) concentration markedly increases because of a reduction in the activity of dihydropteridine reductase, the enzyme that catalyzes the conversion of BH_2 to BH_4. The resulting reduction in the BH_4/BH_2 ratio significantly reduces eNOS activity and increases peroxynitrite production in endothelial cells of insulin-resistant rats (Figure 3). The resulting increase in oxidative stress might cause higher expression of pro-inflammatory cytokines in cardiomyocytes. This exposure to pro-inflammatory cytokines and oxidative stress activates the Janus kinase-signal transduction and activator of transcription, nuclear factor-kappa B and Smad signaling pathways in cardiomyocytes[72]. Interestingly, ipragliflozin administration significantly improves acetylcholine-dependent vasodilation in mice with streptozotocin-induced diabetes, potentially by ameliorating the impairment of eNOS, and reducing both reactive oxygen species generation in the endothelial cells of the abdominal aorta and inflammatory cytokine expression[73].

SGLT2 inhibitors reduce pro-inflammatory cytokine secretion and the activation of downstream signaling pathways

Inflammatory cytokines that are released from hypertrophic adipocytes activate cytokine signaling in cardiac tissue (the Janus kinase-signal transduction and activator of transcription, nuclear factor-kappa B, and Smad signaling pathways; Figure 3)[72,74]. Furthermore, transforming growth factor-β is released by activated macrophages and binds to its receptor on fibroblasts in cardiac tissue, which activates Smad signaling, resulting in greater synthesis of extracellular matrix proteins[74]. Hyperglycemia-induced cardiac damage is also caused by an increase in reactive oxygen species, inflammation and apoptosis[75,76]. Furthermore, it has been shown that greater release of pro-inflammatory cytokines by hypertrophic adipocytes stimulates the expression of inducible NOS in cardiomyocytes secondary to the activation of nuclear factor-kappa B[77,78]. Thus, the oxidative stress that is induced by insulin resistance and hyperglycemia activates inflammatory cytokine signaling in cardiomyocytes.

Interestingly, the SGLT2 inhibitor ipragliflozin ameliorates diabetes and obesity-associated metabolic abnormalities in type 2 diabetes mice[79]. In addition, 8 weeks of empagliflozin treatment significantly improves diabetic myocardial structure and function, and ameliorates fibrosis through inhibition of the transforming growth factor-β/Smad signaling pathway in diabetic KK-Ay mice[80]. Furthermore, canagliflozin is superior to glimepiride with respect to its beneficial effects on adipose tissue function and serum leptin, adiponectin, and interleukin-6 concentrations, which are related to the reduction in CV risk[81].

Recently, further interesting work regarding the molecular mechanisms of the progression of HFpEF has been published[82]. Overexpression of nitric oxide synthase (iNOS) induces reductions in the activities of two proteins: an isoform of X-box

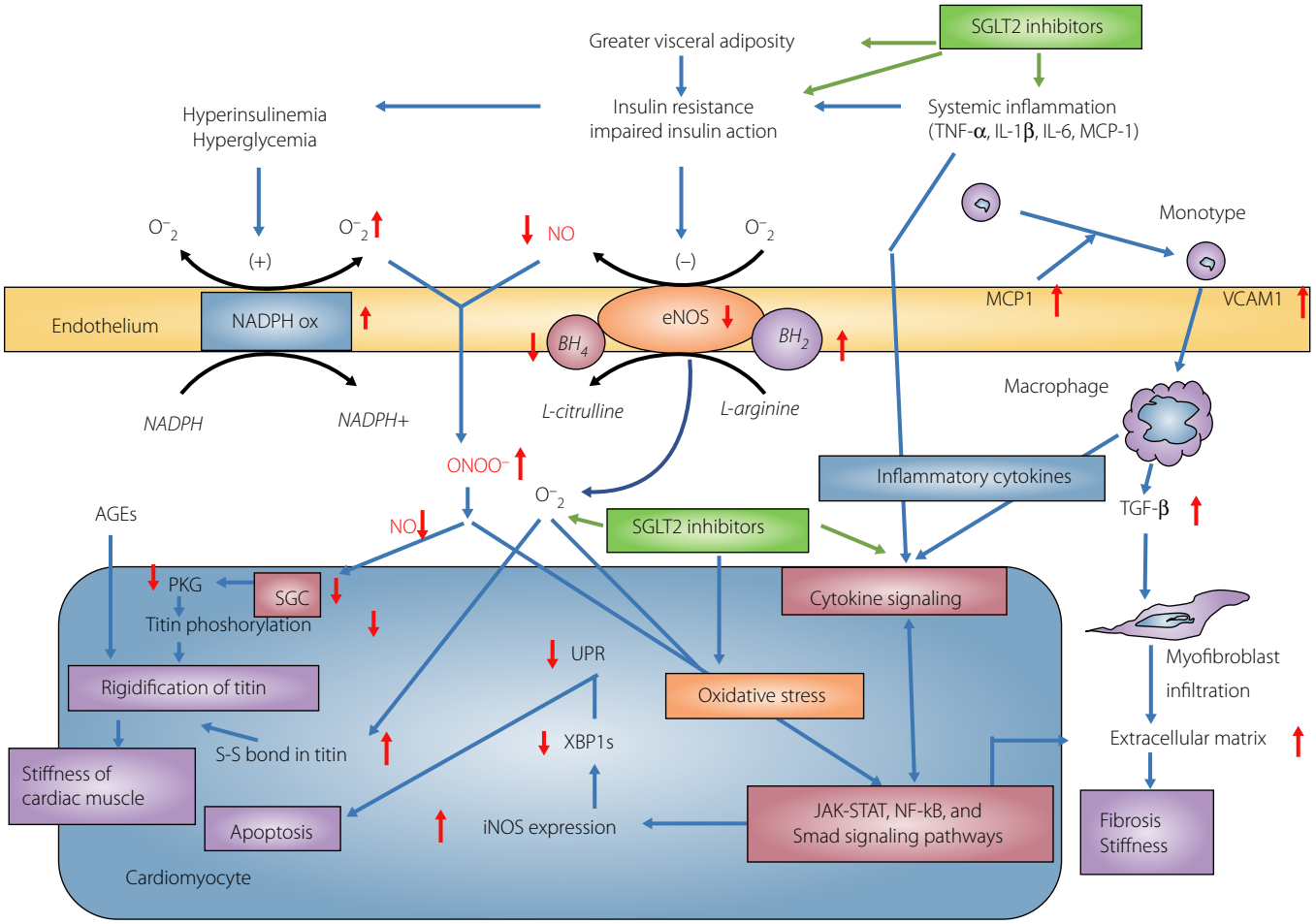

Figure 3 | Oxidative stress and effects of inflammatory cytokines in the cardiac tissue in obese type 2 diabetes patients and the sites of sodium–glucose cotransporter 2 (SGLT2) inhibitor action. Systemic low-grade inflammation is a characteristic of patients with visceral obesity and insulin resistance. Plasma inflammatory cytokine concentrations are high in these patients, and activate intracellular cytokine signaling in cardiomyocytes. Impaired activation of endothelial nitric oxide synthase (eNOS) and higher nicotinamide dinucleotide phosphate (NADPH) oxidase activity in endothelial cells are also characteristics of patients with insulin resistance. Oxidative stress in cardiac tissues also induces intracellular inflammatory cytokine signaling in cardiomyocytes, which results in higher nitric oxide synthase (iNOS) expression, cell death, accumulation of extracellular matrix (ECM) proteins, and an increase in the rigidity of proteins in cardiac muscle cells. Furthermore, systemic inflammation and the activation of endothelial cells stimulates monocyte infiltration and transformation into macrophages. Activated macrophages produce transforming growth factor-β (TGF-β), which in turn activates myofibroblast infiltration and ECM overproduction. All these molecular mechanisms increase diastolic left ventricular stiffness, predisposing toward heart failure with preserved ejection fraction (HFpEF). The possible sites of SGLT2 inhibitor action are shown in green. Red arrows: ↑ increase, ↓ decrease. BH_2, 7,8-dihydropteridine; BH_4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; IL-6, interleukin-6; JAK-STAT, Janus kinase-signal transduction and activator of transcription; MCP-1, monocyte chemotactic protein-1; NADPH, nicotinamide dinucleotide phosphate; NADPHox, nicotinamide dinucleotide phosphate oxidase; NF-κB, nuclear factor-kappa B; NO, nitric oxide; PKG, cyclic GMP-dependent protein kinase G; sGC, soluble guanylate cyclase; TNF-α, tumor necrosis factor-α; UPR, unfolded protein response; XBP1s, spliced form of X-box binding protein 1.

binding protein 1 (XBP1) and inositol-requiring enzyme 1α. Inositol-requiring enzyme 1α is responsible for the splicing of XBP1 messenger ribonucleic acid to yield XBP1s, and only this spliced form of XBP1 can efficiently activate the unfolded protein response. Thus, a reduction in XBP1s expression inhibits the unfolded protein response, which causes the myocardial accumulation of destabilized proteins and greater apoptosis of cardiomyocytes[82]. In fact, Schiattarella *et al.* induced HFpEF in mice by feeding a high-fat diet, which involved the cardiac activation of iNOS, causing inflammation, and successfully induced hypertension with the use of N^{ω}-nitro-L-arginine methyl ester, an inhibitor of eNOS. In addition, they also showed that a deficiency in iNOS expression or overexpression of XBP1s ameliorated the HFpEF phenotype in those mice, which was

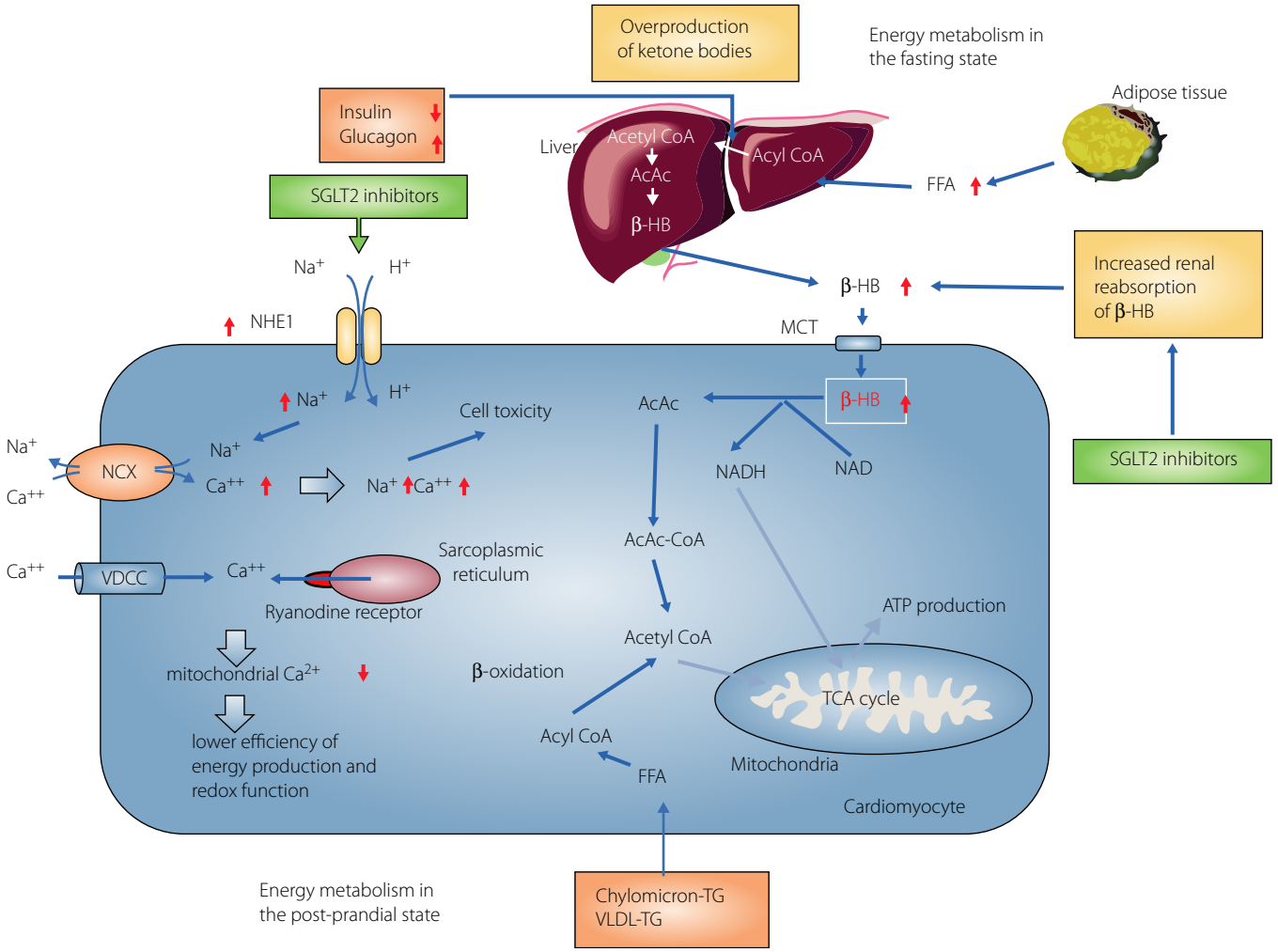

Figure 4 | Sodium–glucose cotransporter 2 (SGLT2) inhibitors inhibit Na^+-H^+ exchanger 1 (NHE1) and increase ketone body production, which ameliorate cardiac dysfunction in type 2 diabetes. The NHE1 is directly inhibited by SGLT2 inhibitors. The activation of NHE1 increases cytosolic [Na^+] and [Ca^{2+}], and reduces mitochondrial [C^{2+}]. These ionic derangements result in impaired efficiency of mitochondrial adenosine triphosphate (ATP) production, Ca^{2+} overload and cell death. Treatment with SGLT2 inhibitors ameliorates these abnormalities in intracellular ion concentrations. Plasma ketone body concentrations are high in diabetes patients because of insulin deficiency, higher counter-regulatory hormone activity and a deficiency in dietary carbohydrate intake. Although ketone body production in diabetes is high in both the fasting and postprandial states, SGLT2 inhibitors also increase serum ketone concentrations. Red arrows: ↑ increase, ↓ decrease. β-HB, β-hydroxybutyrate; AcAc CoA, acetoacetyl coenzyme A; AcAc, acetoacetate; MCT, monocarboxylate transporter; NCX, Na^+-Ca^{2+} exchanger; VDCC, voltage-dependent calcium channel.

associated with lower left ventricular filling pressure and less pulmonary congestion[83]. Furthermore, inflammatory cytokines inhibit eNOS production, and reduce the activities of both soluble guanylate cyclase and protein kinase G in endothelial cells, which reduces the phosphorylation of titin[84], and overproduction of reactive oxygen might cause disulfide bonds to be established in titin molecules. Both of these changes alter the rigidity of titin, and lead to cardiac muscle stiffening. Therefore, SGLT2 inhibitors might be able to inhibit iNOS expression and activate eNOS, causing an increase in XBP1s expression and greater titin phosphorylation in cardiac muscle[63]. This possibility is further tested in animal models of diabetes in future studies.

Clinical significance of the inhibition of Na^+-H^+ exchanger 1 in the diabetic myocardium by SGLT2 inhibitor treatment

The Na^+-H^+ exchanger (NHE1; the predominant isoform of NHE in cardiomyocytes) plays an important role in maintaining intracellular pH during myocardial ischemia, when the high intracellular H^+ concentration activates NHE1, which reduces the cytosolic [H^+] by increasing cytosolic [Na^+], which activates

the Na^+-Ca^{2+} exchanger, leading to an increase in cytosolic $[Ca^{2+}]$[85].

Interestingly, it has been reported that SGLT2 inhibitors might directly inhibit NHE1 in the myocardium (Figure 4)[86]. Dapagliflozin reduces the amplitude of cell shortening and the L-type Ca^{2+} current in ventricular cardiomyocytes from streptozotocin-treated rats, which implies that SGLT2 inhibitors have an acute negative inotropic effect in diabetic cardiomyocytes[87]. Consistent with this, empagliflozin reduces both cytosolic $[Na^+]$ and $[Ca^{2+}]$ during both systole and diastole, and increases mitochondrial $[Ca^{2+}]$ in rat cardiomyocytes[88]. These findings might reflect a greater mitochondrial capacity to synthesize adenosine triphosphate (ATP), restoring the energetic state of cardiomyocytes (Figure 4). Both dapagliflozin and canagliflozin also inhibit NHE1, and reduce cytosolic $[Na^+]$ in mouse cardiomyocytes and hearts[89]. Interestingly, SGLT2 inhibitors have high binding affinities for the extracellular Na^+-binding site of NHE[89]. These data show that SGLT2 inhibitors might have an off-target effect on NHE1. In addition, it has been suggested that SGLT2 inhibitors promote natriuresis by inhibiting NHE3 activity in the proximal tubule[90], which might represent an additional mechanism by which they reduce the incidence of HHF in diabetes patients.

Role of ketone bodies in amelioration of the cardiac energy crisis in diabetes patients with a failing heart by SGLT2 inhibitor treatment

Diabetes patients with cardiomyopathy and a failing heart often develop a cardiac energy crisis. Therefore, interventions that improve cardiac energy metabolism might be effective treatments for cardiac dysfunction in patients with diabetes. It is generally accepted that glucose utilization is significantly impaired in the diabetic heart, and ATP generation in cardiomyocytes is highly dependent on free fatty acid metabolism, which can adversely affect cardiomyocytes[91]. Furthermore, it has been reported that the myocardial uptake of glucose, lactate and pyruvate are lower, whereas that of ketone bodies is higher in individuals with diabetes than non-diabetic individuals[92].

The use of ketone bodies is more energetically efficient than fatty acid oxidation, because it yields more energy for ATP synthesis per molecule of oxygen[93]. Furthermore, the use of ketone bodies is associated with less mitochondrial uncoupling and oxidative stress[94–96]. During the development of cardiac hypertrophy and HF in mouse models, ketone oxidation increases in the heart, and ketone bodies become a key fuel source in the context of a lower capacity to oxidize fatty acids[97]. A vast quantity of evidence shows that the hepatic rate of ketogenesis is finely regulated by an orchestrated series of metabolic interactions between adipose tissue and the liver (Figure 4). Plasma ketone body concentrations increase in patients with diabetes treated with SGLT2 inhibitors because of greater ketogenesis in the liver and an increase in renal tubular reabsorption of ketone bodies[98,99]. In this way, SGLT2 inhibitors increase circulating ketone body concentrations[100–102]. Therefore, the effect of SGLT2 inhibitors to prevent HHF might be partly attributable to increases in plasma ketone body concentrations. Interestingly, a 3-h infusion of 3-hydroxybutyrate increased the plasma concentration of this ketone from 0.4 to 3.3 mmol/L ($P < 0.001$), which was accompanied by an 8% increase in cardiac output ($P < 0.001$). Furthermore, there was a dose-dependent relationship between the increase in plasma 3-hydroxybutyrate and cardiac output[103]. Therefore, therapeutic approaches aimed at increasing circulating ketone body concentrations in HF patients are currently under investigation in preclinical and clinical studies.

CONCLUSION

SGLT2 inhibitors effectively protect against major adverse cardiovascular events, especially in type 2 diabetes patients with a previous history of atherosclerotic cardiovascular disease and advanced renal disease. Furthermore, similar reductions in both HHP and RCOs occur in type 2 diabetes patients, regardless of the level of cardiorenal risks. HF is a major clinical problem that determines the life expectancy of diabetes patients. One particular challenge is to protect diabetes patients against the development of HFpEF and HErEF. HFpEF is clinically characterized by diastolic dysfunction, which is highly prevalent in diabetes patients with multiple CV risks. It is generally accepted that SGLT2 inhibitors ameliorate visceral adiposity, insulin resistance, hyperglycemia, hyperlipidemia, volume overload and hypertension. Furthermore, it has also been suggested that SGLT2 inhibitor treatment ameliorates endothelial dysfunction, inflammatory cytokine signaling, the inhibition of Ca^{2+} overload as a result of the inhibition of NHE1 activity and mitochondrial dysfunction; and increases serum ketone body concentrations, which have been shown to ameliorate HFpEF in preclinical and clinical studies. In summary, we suggest that the use of SGLT2 inhibitors represents an effective new approach for the prevention of HFpEF in patients with diabetes.

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