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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Update on evidence-based clinical application of sodium-glucose cotransporter inhibitors: Insight to uncommon cardiovascular disease scenarios in diabetes

Shi-Bing Tao, Xi Lu, Zi-Wei Ye, Nan-Wei Tong

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Abstract

In this paper, we concentrate on updating the clinical research on sodium-glucose cotransporter inhibitors (SGLTis) for patients with type 2 diabetes who have heart failure with a preserved ejection fraction, acute heart failure, atrial fibrillation, primary prevention of atherosclerotic cardiovascular disease/cardiovascular disease, and acute myocardial infarction. We searched the data of randomized controlled trials and meta-analyses of SGLTis in patients with diabetes from PubMed between January 1, 2020 and April 6, 2024 for our review. According to our review, certain SGLTis (empagliflozin, dapagliflozin, canagliflozin, and tofogliflozin), but not sodium-glucose cotransporter 1 inhibitor (SGLT1i), exhibit relatively superior clinical safety and effectiveness for treating the abovementioned diseases. Proper utilization of SGLTis in these patients can foster clinical improvement and offer an alternative medication option. However, clinical trials involving SGLTis for certain diseases have relatively small sample sizes, brief intervention durations, and conclusions based on weak evidence, necessitating additional data. These findings are significant and valuable for providing a more comprehensive reference and new possibilities for the clinical utilization and scientific exploration of SGLTis.

Key Words: Sodium-glucose cotransporter inhibitors; Diabetes; Heart failure; Atrial fibrillation; Atherosclerosis; Cardiovascular disease; Acute myocardial infarction

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Core Tip: In this paper, we concentrate on updating the clinical research on sodium-glucose cotransporter inhibitors (SGLTis) for patients with type 2 diabetes who have heart failure with a preserved ejection fraction, acute heart failure, atrial fibrillation, primary prevention of atherosclerotic cardiovascular disease/cardiovascular disease, and acute myocardial infarction. We review the data from randomized controlled trials and meta-analyses of SGLTis in patients with diabetes from PubMed for our review. Previous studies have indicated that certain SGLTis (empagliflozin, dapagliflozin, canagliflozin, and tofogliflozin), but not sodium-glucose cotransporter 1 inhibitor (SGLT1i), exhibit relatively superior clinical safety and effectiveness for treating the abovementioned diseases. Proper utilization of SGLTis in these patients can foster clinical improvement and offer an alternative medication option for these conditions.

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INTRODUCTION

Diabetes has become a significant health issue that poses a grave threat to global health, with a remarkably high prevalence and incidence rate. To address the rapid increase in diabetes incidence and its widespread challenges globally, the treatment approach for diabetes is being updated and refined, and several novel medications and technologies are being integrated into clinical practice[1]. The sodium-glucose cotransporter (SGLT) family includes six members, SGLT1-SGLT6, which is highly related[2]. SGLT inhibitors (SGLTis) have been developed into various drugs, including SGLT1 inhibitors (SGLT1is), SGLT2 inhibitors (SGLT2is), and SGLT1/2 dual inhibitors (SGLT1/2is). SGLT1is include mizagliflozin; SGLT2is include dapagliflozin, empagliflozin, ertugliflozin, luseogliflozin, ipragliflozin, tofogliflozin, henagliflozin, remogliflozin, sergliflozin, janagliflozin, rongliflozin, and bexagliflozin; SGLT1/2is include canagliflozin, sotagliflozin, and licogliflozin. SGLT2is and SGLT1/2is are widely used in the clinic due to their efficacy and safety. Recent guidelines recommend SGLT2is and SGLT1/2is as first-line drugs for patients who have or are at high risk for heart failure (HF), atherosclerotic cardiovascular disease (ASCVD)/cardiovascular disease (CVD), and chronic kidney disease (CKD)[1,3]. However, we will not concentrate on the scenarios supported by clear evidence-based medical evidence and recommended by authoritative guidelines. In this paper, we mainly focus on the application of SGLTis in uncommon CVD scenarios in patients with type 2 diabetes (T2D), such as ejection fraction preserved HF (HFpEF), acute HF (AHF), atrial fibrillation (AF), primary prevention of ASCVD/CVD, and acute myocardial infarction (AMI). The review materials were sourced from PubMed between January 1, 2020 and April 6, 2024. Primary data were gathered from randomized controlled trials (RCTs) and meta-analyses of SGLTi trials. These trials were performed in patients with diabetes (age \geq 18 years), and the efficacy outcomes were related to HF with preserved ejection fraction, AHF, AF, primary prevention of ASCVD/CVD, and AMI.

HFPEF/HF WITH MILDLY REDUCED EJECTION FRACTION

Patients diagnosed with T2D are at significantly increased risk of developing CVD, with HF being one of the primary causes of morbidity and mortality. Despite the absence of traditional risk factors for HF, diabetes is still associated with a greater likelihood of developing HF. HF is currently classified into three types based on ejection fraction (EF) values: HF with reduced EF (EF value of \leq 40%), HFpEF/HF with mildly reduced EF (HFmrEF) (EF value between 41% and 49%), and HFpEF (EF value of \geq 50%)[4] (Figure 1).

Recently, several studies on the clinical application of SGLTis in patients with HFpEF/HFmrEF were performed.

In the Dapagliflozin Evaluation to Improve the LIVES of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, 6263 patients (with diabetes, $n = 2806$) with HF and left ventricular EF (LVEF) $> 40\%$ were randomly assigned to receive dapagliflozin (SGLT2i, 10 mg once daily) or matching placebo, in addition to conventional treatment. The primary outcome was a composite of either HF exacerbation (defined as unplanned hospitalization or emergency visit for HF) or cardiovascular death. Over a median of 2.3 years, the primary outcome occurred in 512 (16.4%) of 3131 patients in the dapagliflozin group and 610 (19.5%) patients in the placebo group [hazard ratio (HR): 0.82, 95% confidence interval [CI]: 0.73-0.92; $P < 0.001$]. Worsening HF occurred in 368 (11.8%) patients in the dapagliflozin group and 455 (14.5%) in the placebo group [HR: 0.79 (95%CI: 0.69-0.91)]. The incidence of cardiovascular death was 231 (7.4%) and 261 (8.3%) in the dapagliflozin and placebo groups, respectively. Overall, the results were similar in patients with LVEF $\geq 60\%$ and those with LVEF $< 60\%$. Hence, dapagliflozin has the potential to diminish the overall risk of HF progression or cardiovascular mortality in patients diagnosed with HFmrEF and HFpEF[5]. Furthermore, in the subgroup analysis of the DELIVER trial, researchers evaluated the benefits of dapagliflozin in HFpEF/HFmrEF patients based on various baseline characteristics. These studies revealed that the advantages of dapagliflozin in patients with HFpEF/HFmrEF and T2D were not associated with baseline blood glucose[6], age[7], N-terminal pro-brain natriuretic peptide (NT-proBNP) value [8], the existence of AF[9], or the degree of patient frailty[10], making it beneficial for a broad range of patients. A prespecified analysis of the DELIVER trial, investigated whether recent HF hospitalization modified the risk of clinical events or

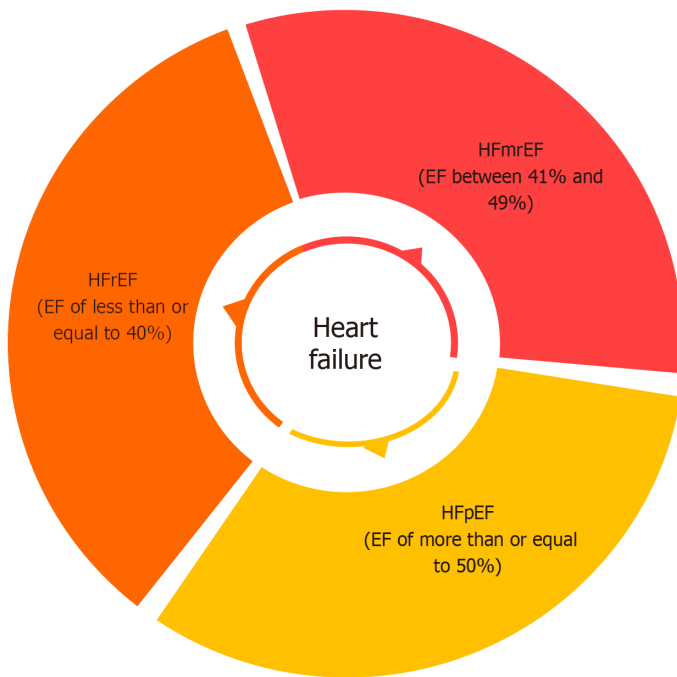


Figure 1 Classification of chronic heart failure. Adapted from McDonagh *et al*[4]. HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure and a mildly reduced or preserved ejection fraction; HFpEF: Ejection fraction preserved heart failure; EF: Ejection Fraction.

response to dapagliflozin, and attempted to explore the timing and benefits of dapagliflozin. The study suggested that dapagliflozin should be administered during or shortly after hospitalization for HF in patients with HFpEF/HFmrEF. Because the research found that dapagliflozin could reduce the primary outcome in patients who were recently hospitalized by 22% [HR: 0.78 (95% CI: 0.60-1.03); $P = 0.71$], and the primary outcome in patients without recent hospitalization was reduced by 18% [HR: 0.82 (95% CI: 0.72-0.94); $P = 0.71$], a safe and effective option for patients with HFpEF/HFmrEF is to begin taking dapagliflozin during or shortly after hospitalization for HF[11].

Similarly, a multicenter, randomized trial demonstrated that 12 wk of dapagliflozin treatment ($n = 324$, 56% with T2D) significantly improved patient-reported symptoms, physical limitations, and exercise function in patients with chronic HFpEF, with a good tolerability profile. Improvements in both the Kansas City Cardiomyopathy Questionnaire total symptom (KCCQ-TS) [5.8 points (95% CI: 2.0-9.6); $P = 0.003$] and physical limitations scores [5.3 points (95% CI: 0.7-10.0); $P = 0.026$] were observed. Furthermore, dapagliflozin also led to improvements in the 6-min walk test [mean effect size of 20.1 m (95% CI: 5.6-34.7); $P = 0.007$], KCCQ overall summary score (KCCQ-OSS) [4.5 points (95% CI: 1.1-7.8); $P = 0.009$], and proportion of participants with 5-point or greater improvements in the KCCQ-OSS [odds ratio (OR): 1.73 (95% CI: 1.05-2.85); $P = 0.03$] and reduced weight [mean effect size, 0.72 kg (95% CI: 0.01-1.42); $P = 0.046$][12]. Based on these research results, dapagliflozin substantially benefits patients with HFpEF/HFmrEF. Furthermore, the European Medicine Agency approved the use of dapagliflozin for HFpEF patients[13].

The EMPEROR-Preserved trial, including 5988 patients (with diabetes, $n = 2938$) with New York Heart Association class II-IV HF and EF > 40% that were randomly assigned to receive empagliflozin (SGLT2i, 10 mg, once daily) or placebo, in addition to conventional treatment, explored the effect of empagliflozin on patients with HFpEF. The primary outcome was a composite of cardiovascular death or hospitalization for HF. Over a median of 26.2 mo, 415 (13.8%) patients in the empagliflozin group and 511 (17.1%) in the placebo group experienced primary outcome events [HR: 0.79 (95% CI: 0.69-0.90); $P < 0.001$]. Furthermore, the total number of HF hospitalizations was lower in the empagliflozin group than in the placebo group [407 patients in the empagliflozin group *vs* 541 in the placebo group; HR: 0.73 (95% CI: 0.61-0.88); $P < 0.001$]. Therefore, empagliflozin can effectively reduce the combined risk of cardiovascular death or HF hospitalization in patients with HFpEF[14]. In the subgroup analysis, the results revealed that empagliflozin played a significant role in the treatment of patients with T2D and HFpEF/HFmrEF, regardless of blood glucose[15], age[16], sex[17], AF[18], mineralocorticoid receptor antagonists (MRAs) use[19], or underlying health conditions[20], with the same effect in improving patient prognosis.

Furthermore, empagliflozin decreased the likelihood of cardiovascular death, HF hospitalization, or emergency or urgent HF visits requiring intravenous treatment in HFpEF patients with escalating outpatient and inpatient conditions [432 and 546 (empagliflozin *vs* placebo), respectively; HR: 0.77 (95% CI: 0.67-0.87); $P < 0.0001$]. Specifically, empagliflozin decreased the overall number of HF hospitalizations requiring intensive care [HR: 0.71 (95% CI: 0.52-0.96); $P = 0.028$] and the total number of hospitalizations requiring vasopressors or inotropes [HR: 0.73 (95% CI: 0.55-0.97); $P = 0.033$]. Compared to the placebo group, fewer patients in the empagliflozin group reported using intensive diuretics for outpatient visits [482 *vs* 610; HR: 0.76 (95% CI: 0.67-0.86); $P < 0.0001$][21]. The United States Food and Drug Administration has approved the use of empagliflozin for HFpEF indications[22].

In the CHIEF-HF trial, 448 HF participants (28% with T2D and 60% with HFpEF) were randomly assigned to the canagliflozin (SGLT1/2i, 100 mg, once daily) or placebo group. The change in the KCCQ-TS over 12 wk was 4.3 points [(95%CI: 0.8-7.8); $P = 0.016$] greater with canagliflozin than with the placebo. Therefore, canagliflozin has the potential to significantly alleviate the symptom burden of HF[23]. A meta-analysis based on the DAPA HF, EMPEROR-Preserved, EMPEROR-Reduced, DECLARE-TIMI 58, SOLOIST-WHF, SCORED, and VERTIS-CV, also revealed that sotagliflozin and ertugliflozin can effectively decrease cardiovascular death and HF hospitalization in patients with HFpEF[24]. Moreover, an overview of systematic reviews, evaluated the effect of SGLT2is in patients with HFmrEF or HFpEF. Thirty-six systematic reviews synthesizing results from 18 RCTs were identified. The meta-analysis demonstrated that SGLT2is significantly improved health-related quality of life as assessed by the KCCQ-OSS [mean difference (MD) = 1.97, $P < 0.001$], KCCQ-TS score (KCCQ-TSS) (MD = 2.29, $P < 0.001$), KCCQ-clinical summary score (MD = 1.59, $P < 0.001$), and 6-min walking distance (MD = 10.78 m, $P = 0.032$). SGLT2is were associated with a significantly lower risk of serious adverse events (SAEs) compared to placebo [risk ratio (RR): 0.94, $P = 0.002$]. Therefore, the use of SGLT2is in patients with HFpEF is both efficient and safe[25].

These findings indicate that certain SGLTis (dapagliflozin and empagliflozin, but not SGLT1i) can effectively improve the prognosis of HFpEF/HFmrEF patients. Furthermore, the primary advantages were unaffected by factors such as blood glucose, age, sex, NT-proBNP level, presence of AF, use of MRAs, and general health status in patients with T2D. However, clinical studies on canagliflozin (SGLT1/2i), sotagliflozin (SGLT1/2i), ertugliflozin (SGLT2i), and luseogliflozin (SGLT2i) are limited (Table 1).

AHF

SGLTis can improve health status in patients with chronic HF, but its effect on these outcomes in patients with AHF has not been well established. In recent years, there have been several published studies on the application of SGLTis in T2D patients with AHF.

In the EMPULSE trial, a total of 530 patients with a primary diagnosis of acute new-onset or decompensated chronic HF (regardless of LVEF) were randomly assigned to receive either empagliflozin (10 mg, once daily; with diabetes, $n = 124$) or placebo (with diabetes, $n = 116$). The primary outcome was defined as a hierarchical composite of death from any cause, number of HF events, and time to first HF event or a 5-point or greater difference in change from baseline in the KCCQ-TS at 90 d. Compared to placebo, a greater number of patients who received empagliflozin showed a clinical benefit [stratified win ratio, 1.36 (95%CI: 1.09-1.68); $P = 0.0054$], thus fulfilling the primary endpoint. At the conclusion of the trial, the impact of empagliflozin on the primary efficacy outcomes was uniformly similar in various prespecified subgroups, encompassing AHF status (both *de novo* and decompensated chronic HF), diabetes status, age, sex, geographic region, baseline NT-proBNP, renal function, AF status, and LVEF subgroups[26-28].

The EMPA-RESPONSE-AHF trial, included 80 patients with AHF (mean age 76 years, 33% female, 47% new-onset HF; with diabetes, $n = 66$) who were randomly assigned to receive empagliflozin (10 mg, once daily) or placebo for 30 d across multiple centers and examined the safety and clinical efficacy of empagliflozin in patients with AHF. No differences were observed between empagliflozin and the placebo in terms of the visual analogue scale (VAS) dyspnea score, diuretic response, length of hospital stay, or change in NT-proBNP (median 5236 pg/mL) at the end of the trial. Compared to the placebo, empagliflozin effectively reduced the composite endpoint of worsening in-hospital HF, rehospitalization for HF, or 60-d death [4 (10%) patients compared to 13 (33%) patients, $P = 0.014$]. The urine volume of the empagliflozin group was significantly greater than that of the placebo group until day 4 [difference: 3449 (95%CI: 578-6321) mL; $P < 0.01$]. This study revealed that empagliflozin treatment did not affect VAS dyspnea, diuretic response, NT-proBNP, or changes in hospital stay in AHF patients. However, it did reduce the composite endpoint of HF exacerbation, HF rehospitalization, or death within 60 d[29].

Dapagliflozin has also been studied to determine the effect of SGLT2is on renal function in patients with AHF. In a single-center RCT, patients ($n = 102$, 73.4 ± 11.7 years, 57.8% male; with diabetes, $n = 31$) were prescribed dapagliflozin in addition to standard treatment or standard treatment only. The mean LVEF was 44.9% ± 14.7%, the mean NT-proBNP was 4706 (1757-11244) pg/mL, and the mean estimated glomerular filtration rate (eGFR) was 51.6 ± 19.5 mL/min/1.73 m². The numbers of deaths within 30 d after discharge in the dapagliflozin group and control group were 9 (19%) and 12 (25%), respectively ($P = 0.55$); the numbers of rehospitalizations were 14 (29%) and 17 (35%), respectively ($P = 0.51$). Therefore, the use of dapagliflozin is associated with more pronounced weight loss and does not require increased diuretic treatment without significantly worsening renal function. However, dapagliflozin did not improve the prognosis 30 d after hospitalization and discharge[30].

A meta-analysis sought to compare cardiovascular outcomes, renal function, and diuresis in patients receiving standard diuretic therapy for AHF with or without the addition of SGLT2is (dapagliflozin, empagliflozin, and sotagliflozin). Nine eligible RCTs involving 2824 patients were enrolled. The results showed that the addition of SGLT2is to conventional therapy for AHF reduced all-cause death [OR: 0.75 (95%CI 0.56-0.99); $P = 0.049$], readmission for HF [OR: 0.54 (95%CI 0.44-0.66); $P < 0.001$], and the composite of cardiovascular death and readmission for HF [HR: 0.71 (95%CI 0.60-0.84); $P < 0.001$]. Therefore, SGLT2is combined with conventional diuretic therapy can improve all-cause mortality, readmission for HF, and the composite of cardiovascular death or readmission for HF in patients with AHF[31].

Collectively, the current findings indicate that empagliflozin (SGLT2i) has been examined in a comparatively larger sample size and exhibits positive evidence for AHF with diabetes. It may be a priority for the treatment of AHF and acute decompensated HF patients with diabetes in the future. However, dapagliflozin (SGLT2i) and sotagliflozin (SGLT1/2i) only showed a mild tendency to improve the prognosis of patients with AHF and diabetes. Higher-quality studies are

Table 1 Summary of clinical studies on sodium-glucose cotransporter inhibitors in ejection fraction preserved heart failure/heart failure with mildly reduced ejection fraction patients

Ref.	Type of article	Journal and published time	Drugs	Aim of study	Inclusive population	Intervention cycle	Number of cases	Main conclusion
Solomon <i>et al</i> [5]	RCT	<i>N Engl J Med</i> , 2022	Dapagliflozin (10 mg/d) or placebo	To evaluate whether SGLT2is are effective in patients with a higher LVEF	Patients with HFpEF/HFmrEF	2.3 years	6263	Dapagliflozin reduced the combined risk of worsening HF or cardiovascular death among patients with HFpEF/HFmrEF
Inzucchi <i>et al</i> [6]	RCT	<i>Lancet Diabetes Endocrinol</i> , 2022	Dapagliflozin (10 mg/d) or placebo	To assess the efficacy and safety of oral dapagliflozin in these patients by their baseline glycaemia categories	Patients with HFpEF/HFmrEF	2.3 years	6263	Dapagliflozin improved HF outcomes to a similar extent in normoglycaemia, prediabetes, and T2D
Peikert <i>et al</i> [7]	RCT	<i>Circ Heart Fail</i> , 2022	Dapagliflozin (10 mg/d) or placebo	To assess the efficacy and safety of oral dapagliflozin in these HFpEF patients with New York Heart Association functional class II-IV and LVEF > 40%	Patients with HFpEF/HFmrEF	2.3 years	6263	Dapagliflozin reduced the combined risk of cardiovascular death or worsening HF events across the spectrum of age
Myhre <i>et al</i> [8]	RCT	<i>JACC Heart Fail</i> , 2022	Dapagliflozin (10 mg/d) or placebo	To assess the treatment effect of dapagliflozin across baseline levels of NT-proBNP among patients with HFmrEF or HFpEF	Patients with HFpEF/HFmrEF	2.3 years	6263	Dapagliflozin is safe and improves outcomes irrespective of baseline NT-proBNP concentrations in HFmrEF or HFpEF
Butt <i>et al</i> [9]	RCT	<i>J Am Coll Cardiol</i> , 2022	Dapagliflozin (10 mg/d) or placebo	To examine the effects of dapagliflozin according to the presence or not of AF in the DELIVER trial	Patients with HFpEF/HFmrEF	2.3 years	6263	Dapagliflozin improved HF outcomes to a similar extent irrespective of type of AF at baseline
Butt <i>et al</i> [10]	RCT	<i>Circulation</i> , 2022	Dapagliflozin (10 mg/d) or placebo	To investigate the efficacy and tolerability of dapagliflozin according to frailty status in patients with HFpEF/HFmrEF randomized in DELIVER	Patients with HFpEF/HFmrEF	2.3 years	6263	The benefit of dapagliflozin was consistent across the range of frailty studied
Cunningham <i>et al</i> [11]	RCT	<i>J Am Coll Cardiol</i> , 2022	Dapagliflozin (10 mg/d) or placebo	To investigate clinical outcomes and response to dapagliflozin in patients with HFpEF/HFmrEF who were enrolled during or following hospitalization	Patients with HFpEF/HFmrEF	2.3 years	6263	Dapagliflozin safely reduced risk of worsening HF or cardiovascular death similarly in patients with and without history of recent HF hospitalization
Nassif <i>et al</i> [12]	RCT	<i>Nat Med</i> , 2021	Dapagliflozin (10 mg/d) or placebo	To evaluate whether the SGLT2i dapagliflozin improves the primary endpoint of Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, a measure of HF-related health status, at 12 wk after treatment initiation	Patients with HFpEF	12 wk	324	Dapagliflozin significantly improved patient-reported symptoms, physical limitations, and exercise function in chronic HFpEF
Anker <i>et al</i> [14]	RCT	<i>N Engl J Med</i> , 2021	Empagliflozin (10 mg/d) or placebo	To investigate effects of empagliflozin in patients with HFpEF	Patients with HFpEF/HFmrEF	26.2 mo	5988	Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF in patients with HFpEF, regardless of the presence of diabetes or not
Filippatos <i>et al</i> [15]	RCT	<i>Circulation</i> , 2022	Empagliflozin (10 mg/d) or placebo	To evaluate whether the effects of empagliflozin are consistent in patients with and without	Patients with HFpEF/HFmrEF	26.2 mo	5988	Empagliflozin significantly reduced the risk of HF outcomes irrespective of

Böhm <i>et al</i> [16]	RCT	<i>J Am Coll Cardiol</i> , 2022	Empagliflozin (10 mg/d) or placebo	diabetes To evaluate the interplay of age and empagliflozin effects in EMPEROR-Preserved	Patients with HFpEF/HFmrEF	26.2 mo	5988	diabetes status Empagliflozin reduced primary outcomes and first and recurrent HF hospitalization and improved symptoms across a broad age spectrum
Butler <i>et al</i> [17]	RCT	<i>Circulation</i> , 2022	Empagliflozin (10 mg/d) or placebo	To evaluate the influence of sex on the effects of empagliflozin in patients with HFpEF enrolled in the EMPEROR-Preserved trial	Patients with HFpEF/HFmrEF	26.2 mo	5988	Empagliflozin produced similar benefits on outcomes and health status in women and men with HFpEF
Ferreira <i>et al</i> [18]	RCT	<i>J Am Coll Cardiol</i> , 2022	Empagliflozin (10 mg/d) or placebo	To examine the effect of empagliflozin in mineralocorticoid receptor antagonists users and nonusers in the EMPEROR-Preserved trial	Patients with HFpEF/HFmrEF	26.2 mo	5988	Empagliflozin reduced the primary outcome, which is not related to the use of mineralocorticoid receptor antagonists or not
Butler <i>et al</i> [19]	RCT	<i>Circulation</i> , 2022	Empagliflozin (10 mg/d) or placebo	To evaluate the efficacy of empagliflozin on health-related quality of life in patients with HFpEF and whether the clinical benefit observed with empagliflozin varies according to baseline health status	Patients with HFpEF/HFmrEF	26.2 mo	5988	Empagliflozin reduced the risk for major HF outcomes across the range of baseline Kansas City Cardiomyopathy Questionnaire Clinical Summary scores
Savarese <i>et al</i> [20]	RCT	<i>J Card Fail</i> , 2021	Empagliflozin (10 or 25 mg/d) or placebo	To determine the effects of empagliflozin in HF with predicted HFrEF vs HFpEF vs non-HF	Patients with T2D and established cardiovascular disease and an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m ²	31.0 mo	7001	The benefits of empagliflozin on HF and mortality outcomes were consistent in non-HF, predicted HFpEF, and HFmrEF/HFrEF
Packer <i>et al</i> [21]	RCT	<i>Circulation</i> , 2021	Empagliflozin (10 mg/d) or placebo	To evaluate the efficacy of empagliflozin on inpatient and outpatient HF events	Patients with HFpEF/HFmrEF	26.2 mo	5988	Empagliflozin produced a reduction in the risk and severity of inpatient and outpatient worsening HF events
Spertus <i>et al</i> [23]	RCT	<i>Nat Med</i> , 2022	Canagliflozin (100 mg/d) or placebo	To confirm benefits of canagliflozin in a new type of trial that was patient centered and conducted in a completely remote fashion	Patients with HF	12 wk	476	Canagliflozin significantly improves symptom burden in HF, regardless of EF or diabetes status
Pandey <i>et al</i> [24]	Meta-analysis	<i>ESC Heart Fail</i> , 2022	Dapagliflozin (10 mg/d), empagliflozin (10 mg/d), sotagliflozin (200 mg/d, with a possible dose increase to 400 mg) or placebo	To evaluate the efficacy of SGLT2is in HF patients with HFpEF/HFmrEF	Patients with HFpEF/HFmrEF	9-26 mo	15684	SGLT2is reduce cardiovascular death and HF hospitalization among patients with HF, regardless of left ventricular ejection fraction status
Karakasis <i>et al</i> [25]	Meta-analysis (overview)	<i>Heart Fail Rev</i> , 2023	Dapagliflozin, empagliflozin, canagliflozin, sotagliflozin, ertugliflozin, lusogliflozin, or placebo	To evaluate the effect of SGLT2is in HFmrEF or HFpEF	Patients with HFpEF/HFmrEF	3-50.4 mo	42224	The use of SGLT2i in HFpEF is both efficient and safe

AF: Atrial fibrillation; EF: Ejection fraction; EMPEROR-Preserved: Empagliflozin in Heart Failure with a Preserved Ejection Fraction; DELIVER: Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure.

needed to clarify their effects (Table 2).

AF/ATRIAL FLUTTER AND OTHER ARRHYTHMIAS

Diabetes is an independent risk factor for AF. Patients with diabetes and AF have a substantially increased risk of death and serious cardiovascular complications compared with those in normal sinus rhythm[32].

For new-onset AF, a meta-analysis ($n = 66685$) was conducted to investigate whether the use of SGLTis (canagliflozin, empagliflozin, ertugliflozin, and sotagliflozin, but not SGLT1i) is associated with a lower risk of AF/atrial flutter (AFL). SAEs (defined as AF/AFL incidents) of AF/AFL occurrence were significantly lower in the SGLTis group than in the placebo group [0.96% vs 1.19%; RR: 0.83 (95%CI: 0.71-0.96); $P = 0.01$; $I^2 = 25.5\%$]. However, subgroup analysis showed that the reduction in AF/AFL was significant only for dapagliflozin and not for canagliflozin, empagliflozin, ertugliflozin, and sotagliflozin. Therefore, the use of SGLTis (possibly dapagliflozin) was associated with a lower rate of SAEs of AF/AFL compared with placebo. However, further studies are needed to determine whether canagliflozin, empagliflozin, ertugliflozin, and sotagliflozin similarly protect against the development of AF/AFL[33]. One real-world study in Taiwan, China analyzed the comparative risk of new-onset AF between SGLTis and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in Asian patients with T2D. In this study, 54%, 45%, and 1% of patients in the SGLTis group received empagliflozin, dapagliflozin, and canagliflozin, respectively, while 65% and 35% of patients in the GLP-1RAs group received liraglutide and dulaglutide, respectively. After treatment, for which the inverse probability was weighted, the risk of new-onset AF was lower in the SGLTis group than in the GLP-1RAs group [subdistribution HR: 0.72 (95%CI: 0.54-0.97); $P = 0.028$]. Subgroup analysis revealed that these findings were consistent in the following high-risk subgroups: Older patients, female patients, and patients with CVD or CKD. In this real-world practice, SGLTis were associated with a lower risk of new-onset AF in patients with T2D compared with GLP-1RAs[34]. There are also data for incident AF with the initiation of one SGLTi (empagliflozin, dapagliflozin, and canagliflozin, but not SGLT1i) compared with the initiation of a dipeptidyl peptidase-4 inhibitor (DPP-4i) or a GLP-1RA among older adults (aged ≥ 66 years) with T2D in routine clinical practice. New users of SGLTis were 1:1 propensity score-matched to new users of a DPP-4i ($n = 74868$) or GLP-1RA ($n = 80475$). The risk of incident AF was lower in the SGLTis group than in the matched DPP-4i group [HR: 0.82 (95%CI: 0.76-0.89)] or the matched GLP-1RA group [HR: 0.90 (95%CI: 0.83-0.98)]. The findings of this study showed that the initiation of SGLTis is associated with a reduced risk of incident AF compared with DPP-4i or GLP-1RA[35].

Whether a history of AF will affect the clinical benefits of SGLTis is also an area of interest to clinicians. A meta-analysis was performed to explore whether SGLTis (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin, but not SGLT1i) can reduce AF incidence and whether a history of AF will change the effect of SGLTis on HF hospitalization or cardiovascular death. Thirty-one eligible RCTs reporting AF events (75279 participants, mean age 62 years, 35.0% female) were included. In patients with a history of AF, SGLTis were associated with a lower risk in the composite of HF hospitalization or cardiovascular death [HR: 0.70 (95%CI: 0.57-0.85)][36]. According to the presence of AF, in the DELIVER trial ($n = 6261$), 18.0% had paroxysmal AF, and 38.7% had persistent/permanent AF. The benefit of dapagliflozin on the primary outcome was consistent across AF types. Consistent effects on HF hospitalization, cardiovascular death, all-cause mortality, and KCCQ-TSS improvement were observed[9]. Moreover, in a systematic review, a total of 5018 patients with AF were treated with SGLTis (canagliflozin, dapagliflozin, and empagliflozin, but not SGLT1i). The follow-up period ranged from 2.3 to 3.3 years. SGLTis treatment was significantly associated with a reduction in the risk of the primary endpoint (the composite outcome of HF hospitalization and cardiovascular death) in patients with AF [RR: 0.81 (95%CI: 0.74-0.88); $P < 0.001$]. SGLTis were strongly associated with a consistent reduction in the risk of HF hospitalization in patients with AF [RR: 0.76 (95%CI 0.69-0.84); $P < 0.001$]. Thus, the treatment effects of SGLTis were associated with a lower incidence of cardiovascular events, especially HF hospitalization, in patients with a history of AF[37].

Compared with healthy people, diabetes patients have a significantly increased risk of sudden cardiac death (SCD). A meta-analysis aimed to evaluate the association between SGLTis (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, but not SGLT1i) and arrhythmia in patients with T2D or HF. Primary outcomes were incident atrial arrhythmias, ventricular arrhythmias, and SCD. Compared with those in the control group, the risk of atrial arrhythmia [OR: 0.81 (95%CI: 0.69-0.95); $P = 0.008$] and the incidence of SCD [OR: 0.72 (95%CI: 0.54-0.97); $P = 0.03$] were significantly lower in the SGLTis treatment group. Therefore, SGLTis (but not SGLT1i) were associated with a significantly reduced risk of incident atrial arrhythmias and SCD in patients with T2D[38].

According to the above research results, SGLT2i (dapagliflozin and empagliflozin) and SGLT1/2i (canagliflozin) agents are significantly beneficial for reducing new-onset AF and AF-related adverse cardiovascular outcomes (HF hospitalization, cardiovascular death, and all-cause mortality). Moreover, studies have shown that a history of AF does not affect the clinical efficacy of SGLTis (but not SGLT1i). SGLTis (but not SGLT1i) may be a potential treatment option for T2D patients with AF (Table 3). However, the effect of SGLTis on arrhythmias other than AF, such as ventricular arrhythmia and SCD, only shows a certain tendency. Future research should focus on confirming these data and exploring potential underlying mechanisms.

PRIMARY PREVENTION OF ASCVD/CVD

SGLTis have significant benefits in the secondary prevention of CVD (mainly because of the improvement in HF), but research on the primary prevention of ASCVD has not been reviewed very well. In this review, we explain the role of

Table 2 Summary of clinical studies on sodium-glucose cotransporter inhibitors in acute heart failure patients

Ref.	Type of article	Journal and published time	Drugs	Aim of study	Inclusive population	Intervention cycle	Number of cases	Main conclusion
Voors <i>et al</i> [26]	RCT	<i>Nat Med</i> , 2022	Empagliflozin (10 mg/d) or placebo	To evaluate whether empagliflozin can improve clinical outcomes when initiated in patients who are hospitalized for AHF	Patients with AHF or decompensated chronic HF	90 d	530	Empagliflozin results in significant clinical benefit in patients hospitalized for AHF
Biegus <i>et al</i> [27]	RCT	<i>Eur Heart J</i> , 2023	Empagliflozin (10 mg/d) or placebo	To evaluate effects of the SGLT2i empagliflozin on decongestion-related endpoints in the EMPULSE trial	Patients with AHF or decompensated chronic HF	90 d	530	Empagliflozin in patients hospitalized for AHF resulted in an early, effective, and sustained decongestion
Kosiborod <i>et al</i> [28]	RCT	<i>Circulation</i> , 2022	Empagliflozin (10 mg/d) or placebo	To investigate the effects of the SGLT2i empagliflozin on symptoms, physical limitations, and quality of life, using the KCCQ in the EMPULSE trial	Patients with AHF or decompensated chronic HF	90 d	530	Empagliflozin improved symptoms, physical limitations, and quality of life in patients hospitalized for AHF
Damman <i>et al</i> [29]	RCT	<i>Eur J Heart Fail</i> , 2020	Empagliflozin (10 mg/d) or placebo	To evaluate safety and clinical efficacy of SGLT2is in patients with acute decompensated HF	AHF patients with and without diabetes	30 d	80	Empagliflozin increased urinary output and reduced a combined endpoint of worsening HF, rehospitalization for HF, or death at 60 d
Charaya <i>et al</i> [30]	RCT	<i>Open Heart</i> , 2022	Dapagliflozin (10 mg/d in addition to standard therapy)	To evaluate safety and clinical efficacy of the SGLT2i dapagliflozin in patients with acute decompensated HF	Patients with AHF	30 d	102	Dapagliflozin did not improve the in-hospital and 30-d prognosis after discharge
Carvalho <i>et al</i> [31]	Meta-Analysis	<i>Clin Res Cardiol</i> , 2023	Dapagliflozin (10 mg/d), empagliflozin (10/25 mg/d), sotagliflozin (200-400 mg/d), or placebo	To compare cardiovascular outcomes, renal function, and diuresis in patients receiving standard diuretic therapy for AHF with or without the addition of SGLT2i	Patients with AHF	30 d to 2.3 years	2824	SGLT2i combined conventional diuretic therapy can reduce all-cause death, readmissions for HF, and the composite results

AHF: Acute heart failure; EMPULSE: Empagliflozin in Patients Hospitalized with Acute Heart Failure Who Have Been Stabilized; HF: Heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; NT-proBNP: N-terminal pro B-type natriuretic peptide; SGLT2i: Sodium-glucose co-transporter-2 inhibitors; AHF: Acute heart failure.

SGLTis in the primary prevention of ASCVD/CVD.

In the UTOPIA study, patients with T2D ($n = 340$) recruited from 24 clinical units without a history of significant ASCVD were enrolled to investigate the preventive effect of tofogliflozin (SGLT2i) on the progression of atherosclerosis in patients with T2D without apparent ASCVD by monitoring carotid intima-media thickness (IMT). The mean IMT of the common carotid artery and the maximum IMT of the left and right common carotid arteries were significantly decreased in both the tofogliflozin group and the control group. This study suggested that tofogliflozin might be a safe and effective treatment regimen for management of the major risk factors of ASCVD in this population[39].

According to an international study of patients with T2D from the Asia Pacific region, the Middle East, and North America, the initiation of SGLTis (but not SGLT1i) was associated with a lower risk of cardiovascular events, involving a broad range of outcomes and patient characteristics, including patients without CVD. This study included new users of SGLTis and other glucose-lowering drugs (metformin, sulfonylureas, DPP-4 inhibitors, thiazolidinediones, GLP-1 receptor agonists, and insulin) identified through claims and medical records. HRs for death, HF hospitalization, death or HF hospitalization, myocardial infarction (MI), and stroke were assessed by country and pooled using weighted meta-

Table 3 Summary of clinical studies on sodium-glucose co-transporter inhibitors in atrial fibrillation/atrial flutter and other arrhythmias patients

Ref.	Type of article	Journal and published time	Drugs	Aim of study	Inclusive population	Intervention cycle	Number of cases	Main conclusion
Li <i>et al</i> [33]	Meta-Analysis	<i>Front Endocrinol (Lausanne)</i> , 2021	Dapagliflozin (10 mg/d), canagliflozin (100/300 mg/d), empagliflozin (10/25 mg/d), ertugliflozin (5/15 mg/d), sotagliflozin (200/400 mg/d), or placebo	To investigate whether SGLT2i use is associated with lower risks of AF/AFL	Patients with randomized placebo-controlled trials registered in comparing SGLT2is with matching placebo including recorded AF/AFL outcomes	60 d to 5.2 years	66685	SGLT2i use is associated with a 19.33% lower rate of SAEs of AF/AFL compared with the placebo
Hsiao <i>et al</i> [34]	Multicenter Study	<i>J Clin Endocrinol Metab</i> , 2022	Dapagliflozin (10 mg/d), empagliflozin (10 mg/d), canagliflozin (100 mg/d), or liraglutide or dulaglutide	To determine the comparative risk of new-onset AF with SGLT2is <i>vs</i> GLP-1RAs in Asian patients with T2D in a real-world setting	New-onset AF in patients with T2D	3.0 years	16566	SGLT2is were associated with lower risk of new-onset AF compared with GLP-1RAs among patients with T2D in a real-world practice
Zhuo <i>et al</i> [35]	Cohort study	<i>JAMA Netw Open</i> , 2022	Dapagliflozin (10 mg/d), empagliflozin (10 mg/d), canagliflozin (100 mg/d), or DPP-4i/GLP-1RA	To examine incident AF with initiation of an SGLT2i compared with initiation of a DPP-4i or a GLP-1RA among older adults (age \geq 66 years) with T2D in routine clinical practice	Older adults with T2D who had no history of AF	April 1, 2013 to December 31, 2018	165984	SGLT2is reduced risk of incident AF compared with a DPP-4i or GLP-1RA
Pandey <i>et al</i> [36]	Meta-analysis	<i>J Am Heart Assoc</i> , 2021	Empagliflozin (10/20 mg/d), dapagliflozin (2.5/5/10 mg/d), canagliflozin (100/300 mg/d), ertugliflozin (5/15 mg/d), sotagliflozin (200/400 mg/d), or placebo	To determine whether SGLTis reduce AF and whether a history of AF modifies the effect of SGLTis on the composite of HF hospitalization or cardiovascular death	Patients regardless of prior AF history or other comorbidities	24-304 wk	75279	SGLTis may reduce AF events and likely reduce HF hospitalization/cardiovascular death to a similar extent in patients with and without AF
Zheng <i>et al</i> [37]	Meta-analysis	<i>Pacing Clin Electrophysiol</i> , 2024	Canagliflozin (100/300 mg/d), dapagliflozin (10 mg/d), empagliflozin (10/25 mg/d), or placebo	To investigate the effect of SGLT2is on the incidence of cardiovascular disease events in patients with AF	Patients with AF	2.3 to 3.3 years	38529	SGLT2is were associated with a lower incidence of cardiovascular disease events, especially HF hospitalization, in patients with AF
Fernandes <i>et al</i> [38]	Meta-analysis	<i>Heart Rhythm</i> , 2021	Dapagliflozin (2.5/5/10 mg/d), canagliflozin (100/300 mg/d), empagliflozin (10/25 mg/d), ertugliflozin (5/15 mg/d), or placebo	To evaluate the association of SGLT2is with arrhythmias in patients with T2D or HF	Patients with T2D or HF	24 wk to 5.7 years	63166	SGLT2is are associated with significantly reduced risks of incident atrial arrhythmias and sudden cardiac death in patients with T2D

AF: Atrial fibrillation; AFL: Atrial flutter; CREDENCE: Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation; DELIVER: Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure; DPP-4i: Dipeptidyl peptidase-4 inhibitor; GLP-1RA: Glucagonlike peptide-1 receptor agonist; HF: Heart failure; SAEs: Serious adverse events; SGLT1/2i: Sodium-glucose co-transporter-1/2 inhibitors; SGLT2i: Sodium-glucose co-transporter-2 inhibitors.

analysis. Dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, and luseogliflozin accounted for 75%, 9%, 8%, 4%, 3%, and 1% of the exposure time in the SGLTis group, respectively. The use of SGLTis *vs* other glucose-lowering drugs was associated with a lower risk of death [HR: 0.51 (95%CI: 0.37-0.70); $P < 0.001$], HF hospitalization [HR: 0.64

(95%CI: 0.50-0.82); $P = 0.001$], death or HF hospitalization [HR: 0.60 (95%CI: 0.47-0.76); $P < 0.001$], MI [HR: 0.81 (95%CI: 0.74-0.88); $P < 0.001$], and stroke [HR: 0.68 (95%CI: 0.55-0.84); $P < 0.001$]. Therefore, the results were consistent across both countries and patient subgroups with and without CVD. Overall, the use of SGLTis (especially dapagliflozin) in patients without CVD can reduce the risk of cardiovascular events, with a certain degree of primary prevention of cardiovascular events[40].

In patients with multiple risk factors for T2D, according to a systematic review and meta-analysis of EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, SGLTis (canagliflozin and dapagliflozin, but not SGLT1i) can reduce the risk of cardiovascular death or HF hospitalization by 23% [HR: 0.77 (95%CI: 0.71-0.84), $P < 0.0001$], with a similar benefit in patients regardless of whether they had existing ASCVD or a history of HF. This study showed that SGLTis (canagliflozin and dapagliflozin) may reduce the risk of cardiovascular death or HF hospitalization for patients with T2D without ASCVD or a history of HF. Therefore, the use of canagliflozin and dapagliflozin in patients with T2D without CVD may have a partial primary preventive effect on CVD[41]. In a meta-analysis, patients without established ASCVD with T2D ($n = 23987$) were enrolled in five RCTs with a mean follow-up duration of 135 wk. SGLTis (dapagliflozin, canagliflozin, and sotagliflozin, but not SGLT1i) significantly improved all-cause mortality [RR: 0.85 (95%CI: 0.72-1.0); $P = 0.04$; $I^2 = 23$]. Subgroup analyses of patients with chronic kidney disease and T2D demonstrated that the use of SGLTis led to significant reductions in major adverse cardiovascular events (MACEs) [RR: 0.74 (95%CI: 0.61-0.89); $P = 0.001$], MI [RR: 0.67 (95%CI: 0.47-0.97); $P = 0.03$], and stroke [RR: 0.61 (95%CI: 0.41-0.91); $P = 0.01$][42]. Similarly, in another meta-analysis of SGLTis ($n = 65587$, empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin, but not SGLT1i), the benefits of SGLTis were assessed in T2D patients without ASCVD. SGLTis were associated with a 12% reduction in the risk of MACEs [HR: 0.88 (95%CI: 0.83-0.93); $P = 0.19$], with no significant heterogeneity ($P = 0.465$) between subgroups of patients with or without ASCVD. Among patients without preexisting ASCVD (in CANVAS, DECLARE-TIMI58, and CREDENCE), treatment with SGLTis reduced the risk of MACEs by 7% [HR: 0.93 (95%CI: 0.83-1.07)]. This study demonstrated that SGLTis (canagliflozin and dapagliflozin) have moderate benefits on MACEs in patients without ASCVD[43].

In conclusion, the above evidence shows that in patients with T2D without established CVD, SGLTis (but not SGLT1i), including SGLT1/2i (canagliflozin) and SGLT2i (dapagliflozin and tofogliflozin), may improve the primary prevention of ASCVD/CVD with regard to carotid IMT, HF hospitalization, and MACEs. However, other drugs, such as empagliflozin, ertugliflozin, sotagliflozin, ipragliflozin, and luseogliflozin, did not show a primary preventive effect on CVD in patients with T2D (Table 4).

AMI

The clinical application of SGLTis in patients with T2D with AMI is limited, and the major guidelines have not yet been well recommended. Therefore, we collected relevant published data in recent years to provide some clues for the study of SGLTis in patients with T2D and AMI.

In an academic, multicenter, double-blind trial, patients [$n = 476$; with diabetes, $n = 63$ (13%)] with AMI and elevated creatine kinase (> 800 IU/L) were randomly assigned to the empagliflozin (10 mg, once daily) or matching placebo group for percutaneous coronary intervention within 72 h. Compared with the placebo group, the reduction in NT-proBNP in the empagliflozin group was significantly greater (15%) [(95%CI: -4.4% to -23.6%); $P = 0.026$] after adjusting for baseline NT-proBNP, sex, and diabetes status. The absolute LVEF improvement was significantly greater [1.5% (95%CI: 0.2%-2.9%); $P = 0.029$], the mean E/e' reduction was greater [6.8% (95%CI: 1.3%-11.3%); $P = 0.015$], and the left ventricular end-systolic and end-diastolic volumes decreased by 7.5 mL [(95%CI: 3.4-11.5 mL); $P = 0.0003$] and 9.7 mL [(95%CI: 3.7-15.7 mL); $P = 0.0015$], respectively. In general, the effect of empagliflozin was superior to that of the placebo. In patients with recent MI, empagliflozin was associated with a significant reduction in NT-proBNP within 26 wk, and echocardiographic functional and structural parameters were significantly improved[44].

One study showed that intensive standard therapy (insulin, DPP-4is, and alpha-glucosidase inhibitors) plus empagliflozin (10 mg, once daily) can attenuate neointimal progression after drug-eluting stent implantation in patients with T2D. In the present study, the primary endpoint was the thickness of neointimal hyperplasia (NIH) assessed by optical coherence tomography 12 mo after stent placement. A total of 28 patients with T2D (15 in the empagliflozin group and 13 in the control group) were analyzed. According to optical coherence tomography analysis, there were significantly less NIH in the empagliflozin group than in the control group (mean NIH thickness: 137 ± 32 vs 168 ± 39 μm , $P = 0.02$)[45].

In the EMBODY trial, 105 patients with T2D were randomly (1:1) treated with empagliflozin (10 mg, once daily) or placebo within 2 wk after the onset of AMI. The eGFR in the placebo group decreased from 66.14 mL/min/1.73 m² at baseline to 62.77 mL/min/1.73 m² at week 24 ($P = 0.023$), whereas eGFR in the empagliflozin group remained unchanged (from 64.60 to 64.36 mL/min/1.73 m², $P = 0.843$). From baseline to 24 wk, compared to the placebo group, the eGFR and serum creatinine of patients (eGFR ≥ 60 mL/min/1.73 m²) were significantly improved in the empagliflozin group (+0.22 vs -6.61 mL/min/1.73 m², $P = 0.008$ and -0.001 vs +0.063 mg/dL, $P = 0.030$). Therefore, in patients with AMI and T2D, empagliflozin can prevent a decline in renal function[46].

A double-blind RCT revealed the effect of empagliflozin (10 mg, once daily) on cardiovascular outcomes, including all-cause mortality, coronary revascularization, rehospitalization for unstable angina, HF hospitalization, cardiovascular death, nonfatal MI, and nonfatal stroke. The trial included 93 patients (mean age 56.55 years, 37 female) with T2D complicated with acute coronary syndrome who underwent percutaneous coronary intervention. After percutaneous coronary intervention, the patients were randomly assigned to receive a similar dose of empagliflozin (10 mg, once daily) or placebo for 6 mo. There was no significant difference between the empagliflozin group and the placebo group in terms

Table 4 Summary of clinical studies on sodium-glucose co-transporter inhibitors in primary prevention of atherosclerotic cardiovascular disease/cardiovascular disease patients

Ref.	Type of article	Journal and published time	Drugs	Aim of study	Inclusive population	Intervention cycle	Number of cases	Main conclusion
Katakami <i>et al</i> [39]	RCT	<i>Cardiovasc Diabetol</i> , 2020	Tofogliflozin (20 mg/d in addition to an alternative antidiabetic agent), or placebo	To investigate the preventive effects of tofogliflozin on atherosclerosis in T2D patients without apparent cardiovascular disease by monitoring carotid intima-media thickness	Patients with T2D and no history of apparent cardiovascular disease	104 wk	340	Tofogliflozin is a safe and effective treatment option for managing primary cardiovascular disease risk factors in this population
Kosiborod <i>et al</i> [40]	RCT	<i>J Am Coll Cardiol</i> , 2018	Dapagliflozin (2.5/5/10 mg/d), canagliflozin (100/300 mg/d), empagliflozin (10/25 mg/d), ipragliflozin (50 mg/d), tofogliflozin (20 mg/d), luseogliflozin (2.5 mg/d), or oGLD	To examine a broad range of cardiovascular outcomes in patients initiated on SGLT2is <i>vs</i> oGLD across 6 countries in the Asia Pacific, the Middle East, and North American regions	Patients initiated on SGLT2is <i>vs</i> oGLD	Start date ranged from December 2013 in Australia to April 2015 in Israel, last date of data collection from June 2016 in Australia to November 2017 in Singapore ¹	235064	SGLT2is were associated with a lower risk of cardiovascular events across a broad range of outcomes and patient characteristics
Zelniker <i>et al</i> [41]	Meta-analysis	<i>Lancet</i> , 2019	Empagliflozin (10/25 mg/d), canagliflozin (100/300 mg/d), dapagliflozin (10 mg/d), or placebo	To evaluate the magnitude of effect of SGLT2is on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics	Patients with T2D	2.4-4.2 years	34322	SGLT2is have moderate benefits on atherosclerotic MACEs that seem confined to patients with established atherosclerotic cardiovascular disease
Rahman <i>et al</i> [42]	Meta-analysis	<i>J Am Heart Assoc</i> , 2023	Dapagliflozin (10 mg/d), canagliflozin (100 mg/d), sotagliflozin (400 mg/d), or placebo	To explore the benefit in patients without established ASCVD	Patients with prior ASCVD and T2D	69-218 wk	23987	SGLT2is significantly reduced atherosclerotic MACEs in both CKD and T2D without established ASCVD
Giugliano <i>et al</i> [43]	Meta-analysis	<i>Diabetes Obes Metab</i> , 2021	Dapagliflozin (2.5/5/10 mg/d), canagliflozin (100/300 mg/d), empagliflozin (10/25 mg/d), ertugliflozin (5/15 mg/d), sotagliflozin (200/400 mg/d), or placebo	To present a meta-analysis of cardiorenal outcomes of SGLT2is available in Europe or the United States in patients with T2D	Patients with T2D	1.5-4.2 years	65587	SGLT2is have moderate benefits on MACEs and major benefits on the progression of diabetic kidney disease

¹Patients were followed from index date (initiation of either sodium-glucose co-transporter-2 inhibitors or other glucose-lowering drugs) until end of the index treatment (on-treatment analysis only), migration/leaving the practice/database, last date of data collection, outcome date, or censoring date.

CKD: Chronic kidney disease; MACEs: Major adverse cardiovascular events; oGLD: Other glucose-lowering drugs; SGLT2i: Sodium-glucose co-transporter-2 inhibitors; T2D: Type 2 diabetes.

of post-treatment cardiovascular mortality (2.2% *vs* 4.2%; $P = 0.598$), rehospitalization for unstable angina (4.5% *vs* 8.7%; $P = 0.433$), or coronary revascularization (2.2% *vs* 0%; $P = 0.312$). The results of this study showed that the addition of empagliflozin to standard care after percutaneous coronary intervention in patients with T2D complicated with acute coronary syndrome did not significantly reduce cardiovascular outcomes within 6 mo[47].

In the EMPACT-MI trial, patients with T2D who had been hospitalized for AMI were assigned to receive empagliflozin ($n = 3260$; 10 mg, once daily) and placebo ($n = 3262$) in addition to standard care within 14 d after admission. During a median follow-up of 17.9 mo, among patients at increased risk for HF after AMI, treatment with empagliflozin did not lead to a significantly lower risk of the first hospitalization for HF or death from any cause than treatment with a placebo [48]. However, a prespecified secondary analysis of the EMPACT-MI trial aimed to evaluate the impact of empagliflozin

Table 5 Summary of clinical studies on sodium-glucose co-transporter inhibitors in acute myocardial infarction patients

Ref.	Type of article	Journal and published time	Drugs	Aim of study	Inclusive population	Intervention cycle	Number of cases	Main conclusion
von Lewinski <i>et al</i> [44]	RCT	<i>Eur Heart J</i> , 2022	Empagliflozin (10 mg/d) or placebo	To investigate the effects of this drug class in patients with AMI	Patients with AMI accompanied by a large creatine kinase elevation (> 800 IU/L)	26 wk	476	Empagliflozin was associated with a significantly greater NT-proBNP reduction over 26 wk, accompanied by a significant improvement in echocardiographic functional and structural parameters
Hashikata <i>et al</i> [45]	RCT	<i>Heart Vessels</i> , 2020	Empagliflozin (10 mg/d) or insulin, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor	To evaluate the effects of empagliflozin on neointimal response after drug-eluting stent implantation	T2D with coronary artery disease planned for drug-eluting stent placement	12 mo	28	Data possibly support a beneficial effect of empagliflozin in T2D required for coronary revascularization therapy
Mozawa <i>et al</i> [46]	RCT	<i>ESC Heart Fail</i> , 2021	Empagliflozin (10 mg/d) or placebo	To evaluate the reno-protective effects of SGLT2i in patients with AMI	Patients with AMI and T2D	24 wk	96	Early administration of SGLT2i in these patients is considered desirable for renal protection
Adel <i>et al</i> [47]	RCT	<i>Saudi Med J</i> , 2022	Empagliflozin (10 mg/d) or placebo	To study the effects of low dose empagliflozin in improving outcomes in diabetic patients with acute coronary syndrome after percutaneous coronary intervention	Diabetic patients with acute coronary syndrome after percutaneous coronary intervention	6 mo	93	Low dose empagliflozin to standard care of acute coronary syndrome diabetic patients after percutaneous coronary intervention was associated with no significant reduction in negative cardiovascular outcomes during 6 mo
Butler <i>et al</i> [48]	RCT	<i>N Engl J Med</i> , 2024	Empagliflozin (10 mg/d) or placebo	To evaluate the safety and efficacy of empagliflozin in patients with AMI	Patients with AMI and T2D	17.9 mo	6522	Empagliflozin did not lead to a significantly lower risk of a first hospitalization for HF or death from any cause than placebo
Hernandez <i>et al</i> [49]	RCT	<i>Circulation</i> , 2024	Empagliflozin (10 mg/d) or placebo	To evaluate the effects of empagliflozin on first and recurrent heart failure events in patients after myocardial infarction	Patients with AMI and T2D	17.9 mo	6522	Empagliflozin reduced the risk of heart failure in patients after acute myocardial infarction with left ventricular dysfunction or congestion

AMI: Acute myocardial infarction; NT-proBNP: N-terminal pro B-type natriuretic peptide; SGLT2i: Sodium-glucose co-transporter-2 inhibitors; T2D: Type 2 diabetes.

on first and recurrent HF events in patients after MI. The analysis revealed that the risk for first HF hospitalization [HR: 0.77 (95%CI: 0.60-0.98), $P = 0.031$] and total HF hospitalizations [RR: 0.67 (95%CI: 0.51-0.89), $P = 0.006$] was significantly lower in the empagliflozin group than in the placebo group. Post-discharge need for new diuretics, renin-angiotensin modulators, and MRAs were less in patients randomized to empagliflozin than in those randomized to placebo ($P < 0.05$) [49].

In general, these preliminary explorations suggested that empagliflozin may improve cardiac function (NT-proBNP), neointimal progression after drug-eluting stent implantation, renal function (eGFR and serum creatinine), and HF hospitalizations in T2D patients with AMI. However, conclusions cannot be drawn based on the current evidence completely, because the sample sizes and intervention durations were not enough, and the effect of the drug was not well explained (Table 5).

LIMITATIONS

In this review, most of the studies were subgroup analyses or meta-analyses. RCT studies directly targeting these diseases are rare. Moreover, there is heterogeneity in the matching group, with the majority being placebo and a few being insulin or other oral hypoglycemic drugs, which can confuse readers as to whether these CV improvements are because of blood glycemia reduction or hypoglycemic drugs. However, according to a previous meta-analysis on hypoglycemic drugs, only SGLT2is and GLP1-1RA were found to reduce cardiovascular risk. Moreover, SGLTis (but not SGLT1i) drugs have a wide range of cardiovascular risk reductions (HHF, the composite of HHF with CV mortality, CV and overall mortality, and MI), with a group effect of the drugs[50]. According to our previous research, for ASCVD primary prevention in T2D, a reduction in HbA1c < 0.9% and a cardiovascular benefit within ten years were considered nonglycemic effects; for ASCVD secondary prevention or in a very high-risk population, a reduction in HbA1c < 1.0% and a cardiovascular benefit within approximately five years were also considered nonglycemic effects[51]. Therefore, concerns about interference caused by reduced blood sugar can be partially ruled out. Furthermore, the diversity of patient populations in the included studies impacted the generalizability of the conclusions. Although subgroup analysis of some studies showed that baseline diversity did not significantly affect the results, these studies only included a few large RCTs and cannot be fully extrapolated. In addition, our review tends to focus on narratives, and the conclusions drawn are biased.

CONCLUSION

In conclusion, previous studies indicate that certain SGLTis (empagliflozin, dapagliflozin, canagliflozin, and tofogliflozin, but not SGLT1i) exhibit relatively superior clinical safety and effectiveness for treating the above-mentioned diseases. Our review revealed the following conclusions: (1) Dapagliflozin and empagliflozin can improve the prognosis of patients with HFpEF/HFmrEF; (2) Empagliflozin can improve the prognosis of patients with AHF; (3) Dapagliflozin, empagliflozin, and canagliflozin can improve the development of adverse cardiovascular outcomes in patients with AF/AFL; (4) Dapagliflozin, canagliflozin, and tofogliflozin are beneficial for the primary prevention of patients with ASCVD/CVD; and (5) The application of empagliflozin in patients with AMI has shown conflicting results. Large-sample RCTs have not shown that empagliflozin improves the prognosis of patients with AMI, while subgroup analysis and small-sample studies have shown a trend toward improving prognosis. Therefore, further research is needed. The significance of these conclusions lies in these facts: (1) These cardiovascular diseases seriously endanger the health and life of patients, often making treatment difficult. It would be very meaningful if a new approach could be provided; and (2) There are few reports on the use of SGLTis in these cardiovascular diseases, and a comprehensive review is beneficial for attracting academic attention. These findings are significant and valuable in providing a more comprehensive reference and new possibilities for the clinical utilization and scientific exploration of SGLTis. However, based on the limitations mentioned above, further research should concentrate on: (1) Conducting RCTs with larger sample sizes and longer periods; (2) clarifying the specificity of different categories of SGLTis, especially whether strict distinctions should be made between SGLT1/2i and SGLT2i in clinical applications (many studies classify canagliflozin as an SGLT2i, which is not accurate); and (3) exploring the mechanism of SGLTis in these CVDs.

FOOTNOTES

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