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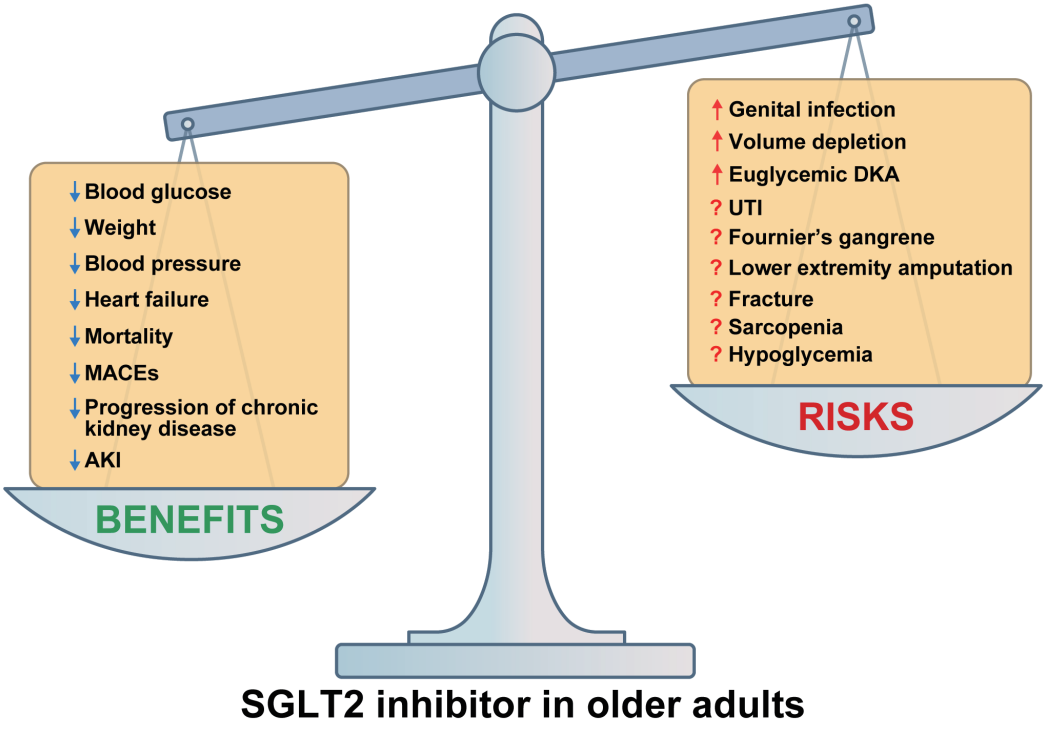

Highlights

- SGLT2 inhibitors provide similar cardio-renal benefits in older and younger adults.
- Adverse reactions to SGLT2 inhibitors are similar in younger patients.
- SGLT2 inhibitors are a favorable treatment option for older patients with T2DM.

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Benefit and Safety of Sodium-Glucose Co-Transporter 2 Inhibitors in Older Patients with Type 2 Diabetes Mellitus

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People with type 2 diabetes mellitus (T2DM) are at higher risk of developing cardiovascular disease, heart failure, chronic kidney disease, and premature death than people without diabetes. Therefore, treatment of diabetes aims to reduce these complications. Sodium-glucose co-transporter 2 (SGLT2) inhibitors have shown beneficial effects on cardiorenal and metabolic health beyond glucose control, making them a promising class of drugs for achieving the ultimate goals of diabetes treatment. However, despite their proven benefits, the use of SGLT2 inhibitors in eligible patients with T2DM remains suboptimal due to reports of adverse events. The use of SGLT2 inhibitors is particularly limited in older patients with T2DM because of the lack of treatment experience and insufficient long-term safety data. This article comprehensively reviews the risk-benefit profile of SGLT2 inhibitors in older patients with T2DM, drawing on data from prospective randomized controlled trials of cardiorenal outcomes, original studies, subgroup analyses across different age groups, and observational cohort studies.

Keywords: Aged; Diabetes mellitus, type 2; Risk assessment; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) continues to rise globally, and the number of elderly people is increasing with the aging of the population and longer life expectancy. As a result, the number of older adults with diabetes is also rising. In 2021, of the 530 million people with diabetes worldwide, those aged ≥65 years accounted for 25% [1]. By 2045, the number of older adults with diabetes is expected to double [1].

Both T2DM and advanced age are major risk factors for developing cardiovascular disease (CVD), and older adults with T2DM have a markedly higher risk of cardiovascular complications [2]. Additionally, older adults with diabetes often have multiple comorbidities and are prone to aging-related syndromes such as cognitive impairment, urinary incontinence, falls, and depression. They are also more susceptible to developing adverse drug reactions.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have recently been developed as oral hypoglycemic agents. SGLT2 is responsible for reabsorption of filtered glucose in renal tubules. SGLT2 inhibitors block this process, promoting excretion of glucose through urine and thereby reducing blood glucose levels. Additionally, SGLT2 inhibitors lower blood pressure and cause weight loss by excreting sodium and water together with glucose. This unique mechanism of action, which differs from that of other antidiabetic medications, has allowed SGLT2 inhibitors to demonstrate beneficial effects in heart failure and chronic kidney disease (CKD) in large randomized controlled trials (RCTs) [3-12]. As a result, SGLT2 inhibitors are now approved for use in people with heart failure or CKD, even among those without diabetes [13].

Older adults with diabetes are at increased risk of both car-

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diovascular and renal events, or already have these diseases, implying that this group is particularly in need of SGLT2 inhibitors. However, because of safety concerns, older age contributes to a low prescription rate of SGLT2 inhibitors despite these medications being recommended in diabetes treatment guidelines [14-16]. In clinical practice, prescription of SGLT2 inhibitors is suboptimal in eligible patients at high cardiovascular risk [14,17,18]. Older adults are often poorly represented in clinical trials, and data on the efficacy and safety of SGLT2 inhibitors in this population are consequently insufficient; clinicians are thus hesitant to prescribe SGLT2 inhibitors to older adults with diabetes. Given the gradual increase in the number of older adults with diabetes, it is necessary to review the risk-benefit data regarding adequate use of SGLT2 inhibitors in this age group.

CARDIOVASCULAR EFFECTS OF SGLT2 INHIBITORS IN OLDER PATIENTS WITH T2DM

Several RCTs have been performed to evaluate the cardiovascular effects of SGLT2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin. The primary endpoints of these RCTs were mainly major athero-

Table 1. Summary of effects according to age in cardiorenal outcome trials of SGLT2 inhibitors

SGLT2 inhibitors	Trials	Total subjects	*P* value	<65 years	≥65 years	*P* interaction
MACEs						
Canagliflozin	CANVAS Program	0.86 (0.75–0.97)	<0.001	0.91 (0.76–1.10)	0.80 (0.67–0.95)	0.26
Dapagliflozin	DECLARE–TIMI 58	0.93 (0.84–1.03)	0.17	0.93 (0.81–1.08)	0.94 (0.82–1.07)	0.99
Empagliflozin	EMPA-REG OUTCOME	0.86 (0.74–0.99)	0.04	1.04 (0.84–1.29)	0.71 (0.59–0.87)	0.01
Ertugliflozin	VERTIS-CV	0.97 (0.85–1.11)	NS	0.90 (0.73–1.10)	1.03 (0.86–1.22)	NS
Sotagliflozin	SCORED	0.84 (0.72–0.99)	NA			
HHF+CV death						
Dapagliflozin	DECLARE–TIMI 58	0.83 (0.73–0.95)	0.005	0.88 (0.73–1.07)	0.80 (0.67–0.95)	0.50
	DAPA-HF	0.74 (0.65–0.85)	<0.001	0.78 (0.63–0.96)	0.72 (0.60–0.85)	NS
	DELIVER[a]	0.82 (0.73–0.92)	<0.001	0.82 (0.69–0.97)[a]	0.82 (0.69–0.96)[a]	NS
Empagliflozin	EMPEROR-Reduced	0.75 (0.65–0.86)	<0.001	0.71 (0.57–0.89)	0.78 (0.66–0.93)	NS
	EMPEROR-Preserved[b]	0.79 (0.69–0.90)	<0.001	0.88 (0.70–1.11)[b]	0.75 (0.64–0.87)[b]	NS
Sotagliflozin	SCORED	0.74 (0.63–0.88)	<0.001	0.60 (0.43–0.83)	0.79 (0.66–0.95)	NA
	SOLOIST-WHF	0.67 (0.52–0.85)	<0.001	0.79 (0.51–1.23)	0.62 (0.47–0.82)	NS
Renal events						
Canagliflozin	CREDENCE	0.70 (0.59–0.82)	<0.001	0.64 (0.51–0.79)	0.77 (0.60–1.00)	0.26
Dapagliflozin	DAPA-CKD	0.61 (0.51–0.72)	<0.001	0.64 (0.51–0.80)	0.58 (0.43–0.77)	NS
Empagliflozin	EMPA-KIDNEY[c]	0.72 (0.64–0.82)	<0.001	0.72 (0.59–0.88)[c] 0.81 (0.64–1.04)[c]	0.65 (0.52–0.81)[c]	NS

Values are presented as hazard ratio (95% confidence interval).
SGLT2, sodium-glucose co-transporter 2; MACE, major atherosclerotic cardiovascular event; CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removal of Excess Glucose; VERTIS-CV, Evaluation of Ertugliflozin EffIcacy and Safety Cardiovascular Outcomes; NS, non-significant; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; NA, not applicable; HHF, hospitalization for heart failure; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; SOLOISTWHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; EMPA-KIDNEY, Study of Heart and Kidney Protection with Empagliflozin.
[a]The cut-off age was 72 years in the DELIVER trial, [b]The cut-off age was 70 years in the EMPEROR-Preserved trial, [c]The stratified age groups were <60, 60–69, and ≥70 years in the EMPA-KIDNEY trial.

sclerotic cardiovascular events (MACEs) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) and hospitalization for heart failure (HHF) plus cardiovascular death. Canagliflozin, empagliflozin, and sotagliflozin significantly reduced the incidence of MACEs by 16%, 14%, and 16% in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removal of Excess Glucose (EMPA-REG OUTCOME), and Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial, respectively (Table 1) [8,19,20]. In subgroup analyses of the EMPA-REG OUTCOME trial, patients aged ≥65 years showed a cardiovascular benefit (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.59 to 0.87) compared with patients aged <65 years (HR, 1.04; 95% CI, 0.84 to 1.29; *P* value for interaction=0.01) [20]. Another subgroup study of the EMPA-REG OUTCOME trial, in which patients were stratified into three age groups (<65, 65–74, and ≥75 years), also confirmed the heterogeneity of three-point MACE outcomes by age (<65 years: HR, 1.04; 95% CI, 0.84 to 1.29; 65–74 years: HR, 0.74; 95% CI, 0.58 to 0.93; ≥75 years: HR, 0.68; 95% CI, 0.46 to 1.00; *P* value for interaction=0.047) [21]. By contrast, the CANVAS Program with canagliflozin, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), and Evaluation of Ertugliflozin EffIcacy and Safety Cardiovascular Outcomes (VERTIS-CV) trial with ertugliflozin revealed no differences in the effects of these therapies on MACEs between patients aged <65 and ≥65 years [3,19,22]. A meta-analysis of three RCTs (EMPA-REG OUTCOME, CANVAS Program, and DECLARE–TIMI 58) also showed that the effect of SGLT2 inhibitors on MACEs was not significantly different (*P* value for interaction=0.15) between patients aged <65 years (HR, 0.95; 95% CI, 0.86 to 1.05) and those aged ≥65 years (HR, 0.83; 95% CI, 0.71 to 0.96) [23]. Seven RCTs evaluated risk reduction in HHF plus cardiovascular death, as the primary outcome, with treatment with SGLT2 inhibitors (Table 1) [3-9]. Dapagliflozin, empagliflozin, and sotagliflozin consistently reduced the risk of HHF plus cardiovascular death by 18% to 33% [3-9]. In three studies, the beneficial effects of SGLT2 inhibitors on HHF plus cardiovascular death were similar in older and younger adults, although the cut-off age in each study differed (65, 70, and 72 years, respectively) [5,6,9]. A meta-analysis of four studies was performed to examine the age-associated risk of HHF plus cardiovascular death with SGLT2 inhibitors [24]. SGLT2 inhibitor therapy was associated with a decreased risk of HHF plus cardiovascular death in patients aged ≥65 years, with a reduction in risk similar to that in patients aged <65 years [24]. The effect of cardiovascular risk reduction with SGLT2 inhibitors in older patients was confirmed through an RCT subanalysis.

Observational studies can complement the results of RCTs because they present findings from real-world clinical practice, including for people with T2DM from the general population and not just the specific populations included in RCTs. Several observational studies involving large populations from different countries have been conducted, such as the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) and Empagliflozin Comparative Effectiveness and Safety (EMPRISE) trials, among others [25-28]. In several observational studies, favorable effects of SGLT2 inhibitors were similarly observed across all age groups [29-32]. Like the EMPA-REG OUTCOME trial, some studies found that the benefit of SGLT2 inhibitors for cardiovascular outcomes was greater in patients aged ≥65 years versus <65 years [26,33,34]. However, protective effects of SGLT2 inhibitors with respect to all-cause mortality, HHF, and HHF combined with all-cause mortality were not found in patients aged ≥75 years but were seen in those aged <75 years. These inconsistent results imply heterogeneity among observational studies [35].

A recent meta-analysis focused on 20 RCTs and observational studies that examined the efficacy and safety of SGLT2 inhibitors in patients aged ≥65 years with heart failure and T2DM [36]. Relative-risk reductions of 19% and 20% were found in patients using SGLT2 inhibitors in terms of all-cause mortality and cardiac death, respectively. Notably, these benefits were more pronounced in the real-world observational studies than in the RCTs. The researchers considered that the clinical condition of real-world patients may often be worse than those enrolled in RCTs, and that this baseline condition may contribute to SGLT2 inhibitors providing greater benefit.

RENOPROTECTIVE EFFECTS OF SGLT2 INHIBITORS IN OLDER PATIENTS WITH T2DM

In addition to their beneficial effects on CVD, several studies also found that SGLT2 inhibitors were renoprotective. The Evaluation of the Effects of Canagliflozin on Renal and The

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was an RCT that focused on the efficacy of the SGLT2 inhibitor canagliflozin with respect to kidney-related primary outcomes in patients with T2DM and CKD (Table 1) [10]. Canagliflozin significantly lowered overall kidney-related adverse outcomes by 30%, and this effect did not differ between patients aged <65 and ≥65 years (*P* value for interaction=0.91) [10]. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial and the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trial involved patients who had CKD with versus without diabetes, and these trials also showed consistent beneficial effects of SGLT2 inhibitors on primary kidney-related outcomes in older patients (DAPA-CKD: HR, 0.58; 95% CI, 0.43 to 0.77 in patients aged >65 years; EMPA-KIDNEY: HR, 0.65; 95% CI, 0.52 to 0.81 in patients aged ≥70 years) (Table 1) [11,12]. A meta-analysis of nine RCTs involving patients with diabetes focused on renal composite outcomes (doubling of serum creatinine, renal impairment/failure, renal death, and end-stage kidney disease) [37]. A subgroup analysis of this study showed that SGLT2 inhibitors significantly reduced renal events by 29% in patients with diabetes aged ≥60 years [37]. This result is consistent with those of previous meta-analyses of several RCTs involving both young and old patients with diabetes [38,39].

The patients in most observational studies analyzing the effect of SGLT2 inhibitors on renal outcomes were primarily older patients with a mean age of >60 years. Some cohort studies specifically compared renal outcomes between elderly patients (≥65 years) and younger patients with T2DM [40-43]. These studies used nationwide cohort or hospital-based data and mainly involved Asian populations. Although the renal composite outcomes were defined differently across studies, they commonly included end-stage kidney disease as a hard endpoint. SGLT2 inhibitors reduced adverse renal composite outcomes by 23% to 60% [40-43]. Subgroup analyses in each study revealed no significant interaction according to age (*P* value for interaction >0.05). These observational studies have reinforced the renal-protective effect of SGLT2 inhibitors in elderly patients with T2DM, confirming findings from the general population in observational studies and large prospective RCTs.

Although concerns have been raised regarding acute kidney injury in association with SGLT2 inhibitors, a series of published studies found that SGLT2 inhibitors actually reduced the risk of acute kidney injury. A meta-analysis of RCTs showed that SGLT2 inhibitors reduced the incidence of acute kidney injury by 16% to 25% [44,45], and this finding was replicated in a large observational cohort [46]. Among older adults aged ≥66 years with T2DM, the risk of acute kidney injury was lower in the SGLT2 inhibitor group than in the dipeptidyl peptidase-4 (DPP4) inhibitor group (HR, 0.71; 95% CI, 0.65 to 0.76) and the glucagon-like peptide 1 receptor agonist group (HR, 0.81; 95% CI, 0.75 to 0.87) [47].

SAFETY OF SGLT2 INHIBITORS IN OLDER PATIENTS WITH T2DM

Numerous clinical studies have provided insights into the effectiveness and adverse drug reactions of SGLT2 inhibitors. The most common side effects are genital infections and volume depletion. Clinical trials have shown that SGLT2 inhibitors increase the risk of genital infections by two- to four-fold, affecting 5% to 10% of women [48]. These infections occur more frequently in females than in males, with similar incidence rates in both younger and older groups [49-53]. Serious genital infections or those leading to drug discontinuation are uncommon and typically mild to moderate [50,51,53]. These infections generally respond well to oral and topical antifungal agents. Volume depletion-related adverse events (AEs) increase with age, with participants aged ≥75 years being more susceptible [49-51]. Some studies have shown a higher incidence of volume depletion-related AEs in this age group [51,52], whereas others have revealed similar frequencies across different age groups [49,50,53].

Hypoglycemia, euglycemic diabetic ketoacidosis, urinary tract infections, necrotizing fasciitis of the perineum, lower-extremity amputation, bone fractures, and sarcopenia have also been reported in patients treated with SGLT2 inhibitors [45,54]. Considering their mechanism of action and reports from clinical trials, SGLT2 inhibitors are associated with a lower risk of hypoglycemia than are sulfonylureas or insulin. However, caution is required when prescribing SGLT2 inhibitors in combination with sulfonylureas or insulin to elderly patients because of the risk of hypoglycemia. A risk of fractures and lower-extremity amputations was observed in the CANVAS Program but not in the CREDENCE trial using the same agent, canagliflozin [10,19], nor was such a risk seen in clinical studies of other SGLT2 inhibitors. There was no difference in the risk of fracture or lower-extremity amputation with SGLT2 inhibitors

between participants aged <65 and ≥65 years in the CANVAS Program (*P* value for interaction=0.65 and 0.37) [55,56]. Furthermore, observational studies did not show an increased risk of fractures or amputations across different age groups [57,58], nor any specific etiological mechanism or definitive explanation for either the fracture risk or amputation risk. SGLT2 inhibitors might lead to skeletal muscle loss alongside reductions in body weight and fat mass, impacting skeletal muscle both positively and negatively [59]. A recent meta-analysis has demonstrated that these inhibitors significantly reduce body weight, body mass index, waist circumference, visceral fat area, fat mass, percentage body fat, lean mass, and skeletal muscle mass [60]. The potential of SGLT2 inhibitors to cause sarcopenia remains unconfirmed; however, caution is advised, particularly in older patients with T2DM, to prevent sarcopenia. Ongoing clinical studies aim to further explore this issue [61]. SGLT2-inhibitor-associated diabetic ketoacidosis has been reported as a rare complication, occurring in 0.6–2.2 per 1,000 person-years of treatment [4,10,12,19]. This condition is characterized by an absence of elevated blood glucose (blood glucose concentration <250 mg/dL) and acute onset of weakness, nausea, and vomiting, which should alert the clinician to the possibility of ketoacidosis. Despite conflicting results, SGLT2 inhibitors are considered associated with a small but higher risk of ketoacidosis relative to placebo and other drugs [62-65], and this risk also exists in older adults with T2DM [66]. SGLT2-inhibitor-associated ketoacidosis is a rare but life-threatening complication, making proper patient selection and education crucial.

BALANCE OF RISKS AND BENEFITS OF SGLT2 INHIBITORS IN OLDER PATIENTS WITH T2DM

SGLT2 inhibitors have been shown to reduce the risk of CVD, heart failure, death, and progression of CKD (which are the ultimate goals of diabetes treatment) beyond their primary function of lowering blood glucose in many RCTs and observational studies (Fig. 1). However, SGLT2 inhibitors increase the risk of several AEs, including genital infections and volume-depletion-related AEs (Fig. 1). They have also been associated with urinary tract infections, Fournier's gangrene, lower-extremity amputations, fractures, sarcopenia, and hypoglycemia, although clear evidence of an increased risk is lacking (Fig. 1). Given the benefits and risks of SGLT2 inhibitor therapy, recent diabetes treatment guidelines recommend choosing SGLT2 inhibitors over other agents in patients with diabetes, especial-

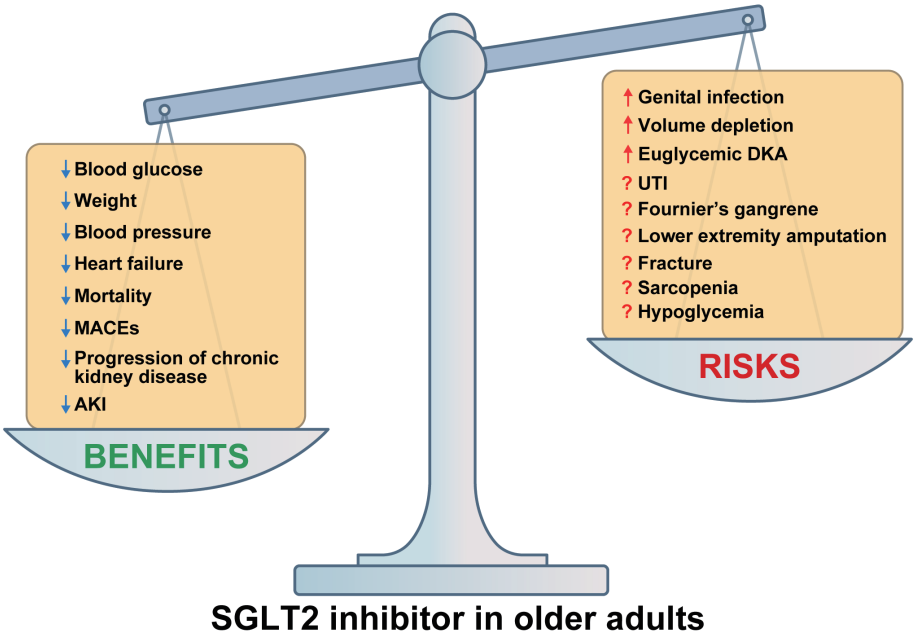

Fig. 1. Risk-benefit balance of sodium-glucose co-transporter 2 (SGLT2) inhibitors in older adults with type 2 diabetes mellitus. MACE, major atherosclerotic cardiovascular disease; AKI, acute kidney injury; DKA, diabetic ketoacidosis; UTI, urinary tract infection.

ly those with comorbidities such as CVD, heart failure, and CKD [67-69]. But are the recommendations for SGLT2 inhibitor therapy in older patients with diabetes the same as those in younger patients? Although there is a lack of comprehensive prospective studies comparing the effectiveness and safety of SGLT2 inhibitors in younger versus older patients with a primary endpoint of effectiveness and safety, ongoing studies may provide some answers (ClinicalTrials.gov Identifiers NCT05975528, NCT04796428, NCT05477017) [61]. Based on previous studies of the efficacy and safety of SGLT2 inhibitors in older adults compared with younger patients, the effectiveness of SGLT2 inhibitors in reducing CVD, heart failure, mortality, and adverse kidney outcomes in older adults is likely to be similar to or better than that in younger patients [20,21]. Given that older adults with T2DM often have CVD or multiple risk factors for CVD, the benefits of SGLT2 inhibitors may be particularly significant in this group [16]. Although the exact mechanisms are not fully understood, SGLT2 inhibitors may improve age-related CVD progression in experimental models by suppressing inflammation, reducing oxidative stress, and restoring endothelial dysfunction [70]. Notably, due to their rapid impact on cardiovascular conditions such as heart failure, the benefits of SGLT2 inhibitors may appear within the shorter lifespans typical of elderly patients, supporting their use in this population [71,72]. In older adults without CVD, heart failure, or CKD, SGLT2 inhibitors can also safely and effectively manage blood glucose levels [61,73]. Diabetes treatment guidelines recommend SGLT2 inhibitors as highly effective antidiabetic medications for glucose lowering, superior to DPP4 inhibitors [69]. Observational studies have found that the glucose-lowering efficacy of SGLT2 inhibitors is similar to that of DPP4 inhibitors in older people, but is more effective in younger adults [74]. Moreover, significant and comparable reductions in glycosylated hemoglobin with SGLT2 inhibitors have been observed across all age groups [50]. Additionally, the safety of SGLT2 inhibitors appears to be similar in younger and older patients [71,75], although older patients may be at higher risk of certain AEs such as volume-depletion-related AEs. Elderly patients with T2DM represent a diverse group, and the benefits and risks of SGLT2 inhibitors can be comparable among those with reduced renal function. Three RCTs, primarily involving patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, demonstrated benefits in elderly patients in terms of HHF plus cardiovascular death and renal outcomes [8,11,12]. An observational study of elderly patients aged ≥66 years with T2DM indicated a benefit in HHF plus cardiovascular death, independent of serum creatinine levels [76]. However, concerns regarding the safety of SGLT2 inhibitors are higher in elderly patients with T2DM with low renal function. A recent meta-analysis demonstrated varying outcomes based on eGFR levels in elderly patients with T2DM and CKD, defined as age ≥60 years [37]. In a subgroup with an eGFR <60 mL/min/1.73 m^2, both the safety profile and the renal-protective effects, such as a reduced risk of acute kidney injury, were reduced [37]. Therefore, while the cardiovascular benefits of SGLT2 inhibitors are evident in elderly patients with low renal function, these medications should be used cautiously with regard to safety. However, it is difficult to draw conclusions about the benefits and risks of using SGLT2 inhibitors in frail elderly or very old adults aged >75 and 80 years because data regarding the efficacy and safety of SGLT2 inhibitors are often lacking for this population. Notably, *post hoc* analyses of the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trials showed that the beneficial effects of SGLT2 inhibitors on cardiovascular outcomes were consistent across different levels of frailty [36]. The relative-risk reduction in CVD, heart failure, mortality, and adverse renal outcomes with SGLT2 inhibitors is consistent across age groups. Similarly, the safety profile of SGLT2 inhibitors is comparable or slightly higher in older adults with T2DM than in younger adults, but the drugs are mostly well tolerated. Therefore, SGLT2 inhibitors are a favorable treatment option in older adults with T2DM considering the risk-benefit balance. Older adults, especially those at high risk of CVD, heart failure, and renal failure, may prefer SGLT2 inhibitors over other antidiabetic medications; however, they must balance this preference against individual safety considerations, and education regarding AEs is required.

CONCLUSIONS

Older adults with diabetes may have high priority for SGLT2 inhibitors because they are at increased risk of developing CVD, heart failure, and CKD. However, in practice, clinicians often hesitate to prescribe SGLT2 inhibitors to elderly patients with diabetes because of safety concerns. In clinical practice, safety is considered more important than effectiveness when selecting a diabetes treatment. This is because the expected car-

diovascular and renal-protective effects for patients will appear in the distant future, while dehydration and genital infections can cause immediate discomfort. This also explains why DPP4 inhibitors are often preferred over SGLT2 inhibitors. Extensive research has elucidated the AEs associated with SGLT2 inhibitors. This knowledge allows us to clearly recognize the risks and side effects of administering SGLT2 inhibitors rather than having only vague concerns about their safety. Therefore, information on known side effects can be effectively utilized when prescribing SGLT2 inhibitors. Age should not be an absolute criterion when deciding whether to use an SGLT2 inhibitor. Instead of using 65 or 75 years as an absolute standard, the overall health status, comorbidities, and degree of frailty of elderly patients should also be taken into consideration. The efficacy and safety of SGLT2 inhibitors should be fully evaluated before deciding on drug use. As the elderly population and the number of elderly patients with diabetes increase, the prescription rate of SGLT2 inhibitors for elderly patients with diabetes is expected to rise. Therefore, it is necessary to understand the characteristics of elderly patients and carefully consider the effectiveness and safety of drugs before they are prescribed.

CONFLICTS OF INTEREST

Dae Jung Kim has been associate editor of the *Diabetes & Metabolism Journal* since 2020. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

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