Efficacy and safety of sodium-glucose co-transporter 2 inhibitors in the elderly versus non-elderly patients with type 2 diabetes mellitus: a meta-analysis

Yao Wang1) *, Xian Shao2) * and Zewen Liu3) 

1) Department of Endocrinology and Metabolism, Clinical Medical College & Affiliated Hospital of Chengdu University, Chengdu University, 610081, P.R. China
2) NHC Key Laboratory of Hormones and Development (Tianjin Medical University), Tianjin Key Laboratory of Metabolic Diseases, Tianjin Medical University Chu Hsien-I Memorial Hospital & Tianjin Institute of Endocrinology, Tianjin 300134, P.R. China
3) Tianjin First Central Hospital, Tianjin 300134, P.R. China

Abstract. This meta-analysis was performed to compare the influence of sodium-glucose co-transporter 2 inhibitors (SGLT2i) on the efficacy and safety of elderly patients with type 2 diabetes with the young ones. PubMed, Medline, Web of Science, EMBase, and Cochrane Library were searched for literature published before March 2020 to identify studies comparing efficacy and safety of SGLT2i in elderly diabetes patients (≥65 years) and young controls (<65 years). A fixed or random-effect model was used to calculate the summary standard means difference and odds ratios. A total of 13 articles with data for 86,433 participants were included. Old patients receiving SGLT2i had a smaller reduction in hemoglobin A1c (SMD = –0.07, 95% CI –0.14 to –0.00, p = 0.044) than young ones. They had higher incidence of serious adverse events (SAEs) (OR 1.78, 95% CI 1.25–2.55, p = 0.001), AE leading to discontinuation (OR 2.34, 95% CI 1.53–3.59, p = 0.000), volume depletion (OR 2.80, 95% CI 1.82–4.32, p = 0.000), and urinary tract infections (OR 1.37, 95% CI 1.18–1.60, p = 0.000), and renal function impairment (OR 2.61, 95% CI 1.78–3.81, p = 0.000) than young patients, and there was a opposite result in genital mycotic infections (OR 0.69, 95% CI 0.55–0.87, p = 0.002). No significant differences were recorded in the reduction of fasting blood glucose, blood pressure, body weight, and in incidence of overall AEs and fracture. In summary, relatively satisfying efficacy was observed in the elderly patients receiving SGLT2i. Although some AEs were more prevalent among older patients, the majority of them were generally mild.

Key words: Sodium-glucose co-transporter 2 inhibitors (SGLT2i), Old patients, Type 2 diabetes, Efficacy, Safety
as well as an osmotic diuresis and inducing urinary caloric loss [8-10]. Osmotic diuresis may have contributed to lower blood pressure (BP), and caloric loss is a factor in the process of body weight loss [11-13]. The action of SGLT2i is independent of β-cell function, resulting in a low intrinsic risk of hypoglycaemia [14]. These benefits together with the convenience of once daily administration recommend it may be a useful treatment in the management of older patients with T2DM.

In spite of the advantage of SGLT2i in elderly patients, incidences of osmotic diuresis-related adverse events (AEs), genital mycotic infections (GIs), and urinary tract infections (UTIs) of SGLT2i should not be ignored [15]. In consideration of the low functional status and high incidence risk of complications of elderly patients with T2DM, the efficacy and safety of SGLT2i on elderly patients should be appreciated.

Thus, this meta-analysis was undertaken to compare the influence of SGLT2i on the efficacy and safety of elderly patients with the young ones.

Methods

Search strategy

Our study was carried out based on the preset protocol registered with Open Science Framework (OSF) (10.17605(OSF.IO/UB3Z6). The databases PubMed, Medline, Web of Science, Embase, and the Cochrane Library were searched for literature published before August 2021 using the following keywords: “SGLT2 inhibitor”, “SGLT2”, “sodium-glucose co-transporter 2”, “individual names of SGLT2 inhibitor”, “old”, “elderly”, “T2DM”. There was no language restriction on our searches. Studies comparing the efficacy and safety of SGLT2i in elderly patients with T2DM to young patients were considered. The patients who were 65 and older than 65 years old were defined as the elderly group and we chose patients less than 65 years old as the young group. This study contained at least one of these outcomes: the change of fasting blood glucose (FBG), hemoglobin A1C (HbA1c), BP and body weight (BW); incidence of AEs, serious AEs, and AE leading to discontinuation, hypoglycemia, volume depletion (VD), GIs, UTIs, renal-related AEs such as the decline of estimated glomerular filtration rate (<90 mL/min/1.73 m²) and renal impairment, and fracture. Unavailable data, duplicate articles, testing of overlapping population, non-clinical publications, and non-comparative research were all excluded in the present meta-analysis.

Data extraction

For included studies, two investigators independently extracted the following information from each study: the author name, publication year and country, number of participants, mean age, participant baseline characteristics, SGLT2i types, the clinical outcomes including FBG, HbA1c, BP, BW, AEs and so on. If there were any disagreements between the two investigators, the decision will be made by a third investigator. Moreover, investigators could contact the corresponding author of studies to obtain more information if important data were unavailable or absent.

Statistical analysis

The meta-analysis was carried out based on the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements [16]. All statistical analyses were carried out with Stata 14.0 (Stata Corp, College Station, TX, USA). The standard mean difference (SMD) with 95% confidence intervals (CIs) were calculated for dichotomous variables, while odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous variables. The $I^2$ statistic were for assessing heterogeneity among the studies. It represented large, moderate, and small heterogeneity when the $I^2$ statistic was higher than 75%, 50%, and 25%, respectively. If $I^2 <50\%$, a fixed-effect model was adopted; otherwise, a random-effect model was used. And we used subgroup analyses and sensitivity analyses to find possible sources of the heterogeneity.

Risk of bias

The quality of the included studies was evaluated by two reviewers. To assess the quality of cohort studies, the Newcastle-Ottawa Quality Assessment Scale (NOS) was utilized [17]; studies of low, intermediate, and high quality were defined with NOS scores of 1–3, 4–6, and 7–9 in the meta-analysis, respectively. While the Revised Jadad rating scale was used to assess RCTs [18]; studies of low and high quality were defined 1–3 and 4–5. Disagreements were resolved by discussion. Publication bias was assessed by Begg’s and Egger’s tests. The $p < 0.05$ was regarded as statistically significant.

Results

Screening and patients characteristics

A total of 2,475 studies were identified in our initial screening, of which 44 underwent full-text review (Fig. 1). Finally, 13 articles [7, 15, 19-29] were included in our meta-analysis (Fig. 1). Supplementary Table 1 contains detailed information on the remaining 31 excluded studies. Table 1 shows the baseline demographics of the included studies, while Table 2 shows the clinical results. A total of 86,433 patients received SGLT2i, among them
14,431 were old patients, while 72,002 were young ones. Results of the quality assessment of included studies were recorded in Supplementary Tables 2, 3, the highest score was 9 points, and the lowest score was 6 points.

Efficacy

Glycemic efficacy

There were four articles [7, 10, 27, 29] that reported the improvement of FBG in patients who had received SGLT2i within the two age patient groups. The random-effect model was used since the \( p \)-value of heterogeneity between these studies was significant indicating that there was no significant statistical difference between old patients and the young ones in FBG (SMD = -0.02, 95% CI = -0.16 to 0.13; \( p = 0.836 \); \( I^2 = 61.8\% \), \( p = 0.049 \)) (Fig. 2A). Neither the Begg’s (\( p = 0.100 \)) tests nor the Egger’s (\( p = 0.481 \)) tests showed publication bias. In addition, seven studies [8, 22, 25, 26, 28-30] provided data regarding HbA1c. A fixed-effect model showed that older patients had smaller reductions in HbA1c compared to younger ones (SMD = -0.07, 95% CI = -0.14 to -0.00; \( p = 0.517 \); \( F = 0 \%), \( p = 0.063 \) (Fig. 2B). No bias of publication was found with Begg’s (\( p = 0.746 \)) and Egger’s (\( p = 0.595 \)) tests.

Blood pressure

Seven studies of six publications [21, 22, 24, 25, 27, 29] were included in our systolic BP (SBP) analysis. A random random-effect model revealed that there was no significant difference in SBP decrease between the young and elderly groups (SMD 0.11, 95% CI –0.05 to 0.26, \( p = 0.175 \); \( F = 80.7\% \), \( p = 0.000 \)). But the sensitivity analysis was performed because of a significant \( p \) value of heterogeneity, which showed that a study by Johnson JF [24] influenced the results obviously (Supplementary Fig. 1). After removing this study, the pooled results were SMD 0.02 (95% CI –0.04 to 0.09, \( p = 0.488 \); \( F = 0 \%), \( p = 0.837 \)) (Fig. 2C). Neither Begg’s (\( p = 0.260 \)) test nor Egger’s (\( p = 0.193 \)) test showed publication bias. And five studies [22, 24, 25, 29] of four publications were included in diastolic BP (DBP) analysis, there was no significant difference between two age groups in reduction of DBP (SMD = 0.03, 95% CI –0.09 to 0.15, \( p = 0.654 \); \( F = 55.2\% \), \( p = 0.063 \) (Fig. 2D). Neither Begg’s (\( p = 0.462 \)) test nor Egger’s (\( p = 0.259 \)) test showed publication bias.

Body weight

There were seven studies [7, 21, 24, 25, 27-29] regarding the reduction in total BW. There was no significant
statistical difference between two age groups (SMD –0.01, 95% CI –0.08–0.06; \( p = 0.749; I^2 = 0.0\%\) (Fig. 2E). No publication bias was noted with Begg’s \( p = 0.548 \) or Egger’s \( p = 0.410 \) tests.

**Safety**

**Adverse events (AEs)**

There were six studies [7, 15, 19, 23, 25, 27, 29] regarding the incidence of totally AEs, the random-effect model was used indicating that there was no significant difference between old patients and young ones (OR 1.32, 95% CI 0.87–1.99, \( p = 0.192; I^2 = 87.6\%\), \( p = 0.000 \) (Fig. 3A). Sensitivity and subgroup analysis (type of SGLT2i, countries) had not discovered the sources of the significant heterogeneity (data not shown). Besides, three studies [7, 15, 29] discussed the rate of SAEs. The pooled data also revealed that older patients had a greater incidence of serious AEs than the younger patients (OR 1.78, 95% CI 1.25–2.55, \( p = 0.001; I^2 = 10.5\%\), \( p = 0.327 \) (Fig. 3B). There were three studies [7, 27, 29] that reported AEs leading to discontinuation, and results indicated that the old age group had a higher incidence than the young age group (OR 2.34, 95% CI 1.53–3.59, \( p = 0.000; I^2 = 0\%\), \( p = 0.468 \) (Fig. 3C). No publication biases were noted in these outcomes.

**Hypoglycemia**

Two studies [15, 27] reported the incidence of hypoglycemia, no significant statistical difference between the two age groups was recorded (OR 0.90, 95% CI 0.38–2.09, \( p = 0.802; I^2 = 70.9\%\), \( p = 0.064 \) (Fig. 4A). Neither the Begg’s \( p = 1.000 \) test showed publication bias.

**Volume depletion**

Five studies [7, 15, 26, 27, 29] reported on the incidence of VD. A random-effect model indicated that the incidence of VD was increased in elderly patients as compared to younger patients (OR 2.04 95% CI 1.08–3.83, \( p = 0.027; I^2 = 67.3\%\), \( p = 0.016 \). However, the sensitivity analysis revealed that the Maegawa H [15] study was the cause of heterogeneity (Supplementary Fig. 2). After omitting this study, the pooled results were OR 2.80 (95% CI 1.82–4.32, \( p = 0.000; I^2 = 8.1\%\), \( p = 0.353 \) (Fig. 4B). Neither Begg’s \( p = 0.734 \) test nor Egger’s \( p = 0.697 \) test showed publication bias.

**Urinary tract infections**

Five studies [7, 15, 20, 27, 29] were included in the rate of UTIs. The pooled results showed that elderly patients had a higher incidence of UTI than the young ones (OR 1.37, 95% CI 1.18–1.60, \( p = 0.000; I^2 = 23.2\%\), \( p = 0.267 \) (Fig. 4C). Neither Begg’s \( p = 0.806 \) test nor Egger’s \( p = 0.08 \) test showed publication bias.

**Genital infections**

Five studies [7, 15, 20, 27, 29] discussed the rate of GIs. A fixed-effect model indicated the patients <65 years had increase risk of GIs relative to those ≥65 years of age (OR 0.69, 95% CI 0.55–0.87, \( p = 0.002; I^2 = 0\%\), \( p = 0.595 \) (Fig. 4D). Neither Begg’s \( p = 0.734 \) test nor Egger’s \( p = 0.696 \) test showed publication bias.

### Table 1 Characteristics of the 13 included articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Sample size</th>
<th>Female</th>
<th>Age (y)</th>
<th>Treatments</th>
<th>HbA1c (%)</th>
<th>eGFR (mL/min/1.73 m²)</th>
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<tr>
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<td>2018</td>
<td>USA</td>
<td>3,091/27,048</td>
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<td>≥65/&lt;65</td>
<td>SGLT2i</td>
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<td>NR</td>
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<tr>
<td>Amos TB [20]</td>
<td>2016</td>
<td>USA</td>
<td>4,650/26,607</td>
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<td>≥65/&lt;65</td>
<td>Canaglifozin</td>
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<td>Empaglifozin</td>
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<td>NR</td>
</tr>
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<td>≥65/&lt;65</td>
<td>Empaglifozin</td>
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<td>NR</td>
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<td>2017</td>
<td>USA</td>
<td>722/4,174</td>
<td>NR</td>
<td>≥65/&lt;65</td>
<td>SGLT2i</td>
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<td>NR</td>
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<td>83/76</td>
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<td>Dapaglifozin</td>
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<td>7.22/7.20</td>
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Values are all given as old/young age group; y, years; HbA1c, haemoglobin A1c; SGLT2i, sodium-glucose co-transporter 2 inhibitor; eGFR, estimated glomerular filtration rate; NR, not reported; USA, the United States of America; UK, United Kingdom.
<table>
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<th>HbA1c (%)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>BW (kg)</th>
<th>AEs</th>
<th>SAEs</th>
<th>AEs leading to discontinuation</th>
<th>Hypoglycemia</th>
<th>VD</th>
<th>UTIs</th>
<th>GIs</th>
<th>Renal-related AEs</th>
<th>Fracture</th>
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<td>NR</td>
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<td>NR</td>
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<td>NR</td>
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<td>3/2</td>
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</table>

Values are all given as old/young age group; FBG, fasting blood glucose; HbA1c, haemoglobin A1c; BW, body weight; BP, blood pressure; AEs, adverse events; SAEs, serious AEs; VD, volume depletion; UTIs, urinary tract infections; GIs, genital infections, NR, not report.
Renal-related AEs

There were three studies [15, 27, 29] reporting the rate of renal-related AEs, the meta-analysis results showed that aged 65 and older had a higher incidence of renal-related AEs than those who were younger than 65 (OR 2.61, 95% CI 1.78–3.81, \( p = 0.000; I^2 = 27.0\%\), \( p = 0.254\)) (Fig. 4E). Neither Begg’s (\( p = 1.000\)) test nor Egger’s (\( p = 0.353\)) test showed publication bias.

Fracture

There were two articles [15, 27] that documented the risk of fracture, and there was no statistically significant difference between two age groups (OR 0.54, 95% CI 0.15–1.95, \( p = 0.348; I^2 = 0\%\), \( p = 0.423\)) (Fig. 4F). Neither the Begg’s (\( p = 1.000\)) test showed publication bias.

Discussion

To our knowledge, this is the first meta-analysis comparing the efficacy and safety of SGLT2i between elderly diabetes patients and young ones. The efficacy of SGLT2i in senior T2DM patients was shown to be relatively satisfactory in the current studies. It was found that there were no notable differences in FBG changes between these two age groups in this analysis. But, the effect on HbA1c reduction in the elderly patients was not as good as that in the young patients. It might be due to the older group having a lower mean baseline HbA1c and estimated glomerular filtration rate (eGFR) compared with those in the younger group. The mechanism of action of SGLT2i is increasing UGE, the rate of which is affected by blood glucose and eGFR [30-32], therefore...
the efficacy of SGLT2i would be reduced in patients with lower HbA1c and eGFR. For instance, the blood-glucose-lowering effect of SGLT2i in patients with moderately impaired renal function is weaker than patients with normal or mild renal impairment [33, 34]. Moreover, it was found that BW and BP were not influenced by baseline age. Differently, Johnson JF and his colleagues reported an obvious reduction in SBP with SGLT2i treatment in older patients in comparison to younger ones [24]. Several factors might explain their findings. The first is an increased prevalence of volume depletion in older individuals using SGLT2i [35]. Secondly, slight BP reduction may be regulated by effects on small artery resistance in younger patients, but largely via effects on large artery stiffness in elderly ones [22]. The third one is that the elderly patients in their study had greater use of antihypertensive medications at baseline. This is in contrast to the findings of Weir M, who found that the use of anti-hypertensive medicines did not affect blood pressure reductions in patients receiving SGLT2i [36]. So, it can be concluded that increased awareness of BP monitor may help in the management of T2DM patients in the older group receiving a combination of anti-hypertensive and SGLT2i.

Regarding safety, while the incidence of overall AEs was similar among the two age groups, the incidence of SAEs and AEs leading to discontinuation were lower in young patients than in elderly patients. This could be explained by the frail body and immune dysfunction of elderly patients. Frailty is characterized by several disordered physiological systems, leading to enhanced vulnerability to a range of adverse outcomes (falls, change in functional level, admission to hospital, admission to a care home, premature death). Being bed-ride caused by falls or admission to hospital might lead to UTIs. Another reason is that older adults are prone to cognitive impairment, failing to properly identify the AEs and promptly treat or seek medical advice [4, 37]. The special mechanism of action of SGLT2i is insulin-independent, therefore, SGLT2i with a low risk of hypoglycemia is favorable for old patients [14]. Our findings revealed no differences in the incidences of hypoglycemia between old and young patients, indicating that the hypoglycemia risk of SGLT2i is unaltered by age. Further studies focusing on the hypoglycemia risk of old patients receiving SGLT2i are still needed.

Volume depletion would be serious if untreated and might result in cardiovascular, cerebrovascular, or renal events [38]. SGLT2i has a slight diuretic effect, and therefore volume-related events should be particularly concerned, especially in older patients [39]. In the present study, the results showed that the incidence of volume depletion was increased in elderly patients compared to younger patients, possibly due to changes in body composition with aging and delayed recognition of dehydration symptoms in old patients [30]. Therefore, when managing elderly patients being treated with SGLT2i, it is critical to evaluate potential volume depletion risk factors, such as dehydration, low blood pressure, or diuretics use, in regular medical checks and to

**Fig. 3**  Forest plot of safety of SLGT2i in two age groups. (A) AEs; (B) SAEs; (C) AEs leading to discontinuation.
encourage fluid consumption, as well as to strengthen monitoring and follow-up management [40, 41].

It is a well-known fact that the risk of UTIs and GIs is generally increased in patients with diabetes due to the availability of glucose in the uroepithelium and changes in immune function [42]. This risk is increased in people on SGLT2 inhibitors due to increased glucosuria [43]. The pooled results of our study showed that old patients had a higher risk of UTIs than young patients; it could be explained by the immune dysfunction and a more frequent history of infections [20]. Another concern is the risk of GIs. The reason for the increasing risk of GIs with SGLT2i is that glucose may serve as a substrate or nutritional factor and UGE can promote fungal growth on genital tissues [44]. Some researchers discovered a higher incidence of GIs in elderly patients than in young individuals, which was attributed to the elderly patients’ worse immune function [45, 46]. However, in our meta-analysis, the incidence of GIs in elderly patients receiving SGLT2i was lower than in young ones. Our result was consistent with Nyirjesy et al. [47]. They have reported T2DM patients receiving SGLT2i with moderate renal impairment have a low incidence of GIs. We concluded that the GIs risk of elderly patients is determined by several factors, including a history of genital fungal infections, awareness of genital hygiene, and renal function. Thus, we suggest that elderly patients receiving SGLT2i with a history of infections of the genital and urinary tracts should take more time to attend the follow-up; increasing consciousness of genital hygiene should be listed in self-government; and a management plan, if UTIs and GIs occur, should be considered, be it to self-treat with oral anti-fungal therapy, or to seek medical advice.

Aging is associated with a progressive decline in eGFR and slower renal function recovery times [48], so close observation of elderly patients’ renal condition after treatment with SGLT2 is required. Our meta-analysis revealed that older patients were more likely than younger individuals to have renal-related AEs.
Unfortunately, there has been little data to assess the change of eGFR. But, some researchers reported that events of poor renal creatinine clearance occurred more often in older patients than younger patients, probably because of diuretic effect of SGLT2i and poor detection of dehydration symptoms in elderly patients. Although this drop did not completely return to baseline levels in older patients, the eGFR decreasing appeared to be transient status in nature rather than the process of renal pathology, and this initial small decline followed by long-term stability might be related to restoration of tubuloglomerular feedback or blood pressure reduction [49, 50]. Owing to their small magnitude, these changes were not thought to be clinically useful and would not discontinue SGLT2i treatment.

Bone fracture risk is mentioned as a side effect of several SGLT2i, since changes in the reabsorptions of glucose and sodium by SGLT2i may impact the control of renal calcium and phosphate reabsorption [51]. Older patients are at higher risk for fracture. So it was worth noting whether an increased risk of fracture in elderly patients receiving SGLT2i. However, our analysis results in no increased risk of bone fractures were found in elderly patients compared with young ones.

Our meta-analysis has few limitations. Firstly, all of the researches included were from wealthy nations such as the United States and Europe, which led to a lack of representation. Second, the risk of other AEs between elderly patients and young ones could not be assessed due to a lack of available data, such as skin complications, ketone body-related events. Third, most of the studies were observational design; so, the selection and confounding bias might exist. Given the selection bias, the elderly patients must differ from the young ones in terms of attention to their health consequences, the burden of life and work, and consciousness of genital hygiene.

**Conclusions**

In the present study, although the improvement of HbA1c in elderly patients receiving SGLT2i was not as good as that in young patients, relatively satisfying effectiveness was observed in the FBG, BW, BP in the elderly adults. Some AEs, such as, VD, UTIs, GIs, renal function impairment had a higher risk in old patients than young ones, but most of these events were generally mild, rarely led to treatment discontinuation, or recovered following appropriate treatments. Raising awareness of AEs and devoting more time to follow-up might aid in the care of elderly patients. Furthermore, little guidance establishes for the treatment of older diabetes adults, so a large sample size and long-term follow-up studies for old patients with SGLT2i are still needed to set appropriate guidance.

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**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


