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A potential for sodium-glucose cotransporter-2 inhibitors in the management of metabolic syndrome: A systematic review and meta-analysis

Olagunju A *et al*. Sodium-glucose cotransporter-2 inhibitors in syndrome-x

Abstract

BACKGROUND

Landmark trials have established the benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) in cardiovascular disease including heart failure with reduced and preserved ejection fraction and renal diseases regardless of the presence of diabetes mellitus. However, studies evaluating the role of SGLT2-Is in metabolic syndrome (MetS) are limited.

AIM

This study primarily aimed to evaluate the impact of SGLT2-Is on the components of MetS.

METHODS

Two independent reviewers and an experienced librarian searched Medline, Scopus and the Cochrane central from inception to December 9, 2021 to identify placebo controlled randomized controlled trials that evaluated the impact of SGLT2-Is on the components of MetS as an endpoint. Pre- and post-treatment data of each component were obtained. A meta-analysis was performed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

RESULTS

Treatment with SGLT2-Is resulted in a decrease in fasting plasma glucose (–18.07 mg/dL; 95%CI: -25.32 to –10.82), systolic blood pressure (–1.37 mmHg; 95%CI: -2.08 to –0.65), and waist circumference (–1.28 cm; 95%CI: -1.39 to –1.18) compared to placebo. The impact on high-density lipoprotein cholesterol was similar to placebo (0.01 mg/dL; 95%CI: -0.05 to 0.07).

CONCLUSION

SGLT2-Is have a promising role in the management of MetS.

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Core Tip: This meta-analysis of randomized, placebo-controlled trials aimed to evaluate the impact of dapagliglozin and empagliflozin on metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III. In doing so, it highlighted a statistically significant improvement in fasting plasma glucose, systolic blood pressure and waist circumference. The effect of dapagliflozin and empagliflozin on high-density lipoprotein cholesterol was similar to that of placebo. In addition to its primary aim, this study also highlighted an improvement in other cardiometabolic parameters including hemoglobin A1C, uric acid and body weight in patients that received dapagliflozin and empagliflozin.

INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) are a relatively novel and revolutionary class of medications that reduce the reabsorption of glucose from the proximal tubules in the kidneys[1-4]. Their glycosuric effect led to their initial use in the management of patients with type 2 diabetes mellitus (DM)[1-4]. However, recent large, randomized control trials (RCTs) have highlighted the extension of their benefits to cardiovascular diseases (CVD) including heart failure with reduced and preserved ejection fraction and renal diseases regardless of the presence of DM[5-15]. However, to date, studies on the impact of SGLT2-Is in the management of metabolic syndrome (MetS) and its components remain inadequate. Metabolic syndrome is an emerging pandemic[16-19]. Its prevalence has risen from approximately 25% to 38% between the early 1990s to

2010s in the United States[16-19]. The prevalence has increased by 29.1% in people aged 40-60 years[16-19]. It has been defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III as the presence of 3 of 5 entities: (1) Waist circumference (WC) ≥102 cm in men and ≥88 cm in females; (2) Serum triglycerides (TGL) ≥150 mg/dL or on drug treatment for hypertriglyceridemia; (3) Serum high-density lipoprotein (HDL) cholesterol < 40 mg/dL in males and < 50 mg/dL; (4) Blood pressure (BP) ≥130/85 mmHg or on drug treatment for hypertension (HTN); (5) Fasting plasma glucose (FPG) ≥100 mg/dL or on drug treatment for elevated blood glucose[20]. A growing body of evidence exists supporting the association of MetS with the development and progression of CVD[17-20]. In a meta-analysis by Mottillo *et al*[19] a 2-fold increase in the risk of CVD and CV mortality in patients with MetS was noted. DM is a component of the MetS and affords a 2-4-fold increase in CVD Risk[21]. Hence, there is an urgent need to improve the management of MetS, which currently ranges from lifestyle interventions such as physical activity and caloric restriction through dietary modification to pharmacological and surgical approaches that address components of the MetS[4]. The primary aim of this study is to evaluate the impact of the SGLT2-Is on the MetS parameters noted in NCEP ATP III criteria. The secondary aim is to highlight the effect of SGLT2-Is on other cardiometabolic parameters including hemoglobin A1C (HbA1c), body weight (BW) and uric acid (UA). This study is derived from placebo controlled RCTs that have evaluated the impact of these medications on CVD and its risk factors, as well as reported pre/post treatment values of MetS components.

MATERIALS AND METHODS

Data sources and searches

Two authors independently searched the electronic library database in Medline, Scopus and the Cochrane central from inception to December 9, 2021, using the following keywords: SGLT2-I, metabolic, cardiometabolic, TGL, FPG, BP, HDL, waist, abdominal, circumference, lipids, waist-to-height ratio, hypertriglyceridemia, HTN, MetS, RCT, random allocation, randomly allocated, random, and allocated randomly. Additionally,

different combinations of these keywords were applied in each database search. The search was extended to ClinicalTrials.gov. An independent search was also conducted by a qualified librarian using similar search terms.

Study selection

The eligible studies were RCTs, allocated patients to an SGLT2-I group (that received either Dapagliflozin or Empagliflozin) or a placebo group, reported baseline and post-treatment values ≥ 1 component of MetS, had a treatment duration 6 mo and were published in the English language. Studies not meeting these criteria were excluded. Disagreements on study selection were either resolved by consensus or by Farouk Mookadam. The study adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guideline[22] (PRISMA checklist).

Data extraction

Extracted data included duration of follow-up, sample size and dose of dapagliflozin and empagliflozin studied. Demographic and biomarker characteristics extracted at baseline and follow up included mean age, gender, race, DM, mean WC, FPG, TGL, HDL, systolic BP (SBP), diastolic BP (DBP), HbA1C, BW and UA.

Quality Assessment

The methodologic quality of the RCTs was assessed using the Jadad score. Points were allocated for randomization, blinding and accountability of the study participants, with a total score range from 0 to 5[23] (Table 1).

Outcomes

The primary outcomes of this study are post-treatment changes in WC, FPG, TGL, HDL, and BP. The secondary outcomes are post-treatment changes in BW, HbA1C and UA.

Data Analysis

All outcome data were reported as mean with standard deviation and were converted to conventional units. Data analysis was performed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration). The forest plots of the above outcomes were visually represented after pooling the mean differences using the random-effects model. Heterogeneity was assessed with the I^2 test. Post-hoc subgroup analyses including doses and/or SGLT2-I type were performed if there was significant heterogeneity.

RESULTS

Search results and study inclusion

The initial literature search identified a total of 2636 potentially relevant studies, 14 of which were gathered from ClinicalTrials.gov. After excluding 1042 duplicates, a total of 1594 studies were screened. Of these, 235 studies were selected for abstract and/or full text review. An additional 217 studies were excluded either because they did not meet the above inclusion criteria, precursors of long-term studies, had a cross-over design or had no published results. A total of 18 studies[5,15,24-39] were eligible for meta-analysis (Figure 1). Of these, 3 studies reported WC[30,33,36], 9 reported FPG[24-27,29,30,34-36,39], 4 reported TGL[5,30,35,38], 3 reported HDL[34,37,38], 7 reported SBP[12,15,28,29,33,35,36] and 6 reported DBP[24,26,28,33,35,39] (Table 2).

Participant characteristics

A total of 26427 patients were included in the analysis. The SGLT2-I group comprised a total of 15914 patients. Of these, 7355 patients received dapagliflozin and 8559 received empagliflozin. The placebo group comprised a total of 10513 patients (Table 2). 59.4% were men. Among studies with reported data, 75% were White, 19.9% were Asian and 4.8% were Black. The mean treatment duration was 79 wk. The mean age in the SGLT2-I group was 53.4 years, and 54.8 years in the placebo group. The vast majority (78.6%) were DM patients. The baseline and post-treatment values of MetS components and the cardiometabolic variables are presented in Tables 2B and 3.

SGLT2-Is and FPG: Nine RCTs in which a total of 1474 patients received SGLT2-Is were analyzed. The random effect model demonstrated a mean reduction in FPG of –18.07 mg/dL (95%CI: -25.32 to –10.82; I^2=99%) (Figure 2A). The significant heterogeneity persisted after a subgroup analysis based on dose of SGLT2-Is (2.5 mg *vs* 10 mg). 463 participants received the 2.5 mg dose which had a similar impact as placebo on FPG: -1.45 mg/dL (95%CI: -8.73 to 5.82; I^2 = 71%) (Figure 2B). The 10 mg dose resulted in a higher reduction in mean FPG of –30.02 mg/dL (95%CI: -38.97 to –21.08; I^2 = 87%) (Figure 2B).

SGLT2-Is and BP: The analysis for SBP included a total of 6662 participants from seven RCTs. There was a modest mean reduction in SBP of –1.37 mmHg (95%CI: -2.08 to –0.65, I^2 = 85%) (Figure 3A). A subsequent post-hoc analysis based on SGLT2-I type demonstrated the empagliflozin RCTs were responsible for the high heterogeneity. The mean reduction noted with empagliflozin was not statistically significant: -0.70 mmHg (95%CI: 1.72 to 0.32; I^2 = 97%). Dapagliflozin use was associated with a higher mean SBP reduction of -2.03 mmHg (95%CI: -2.83 to –1.24; I^2 = 8%) (Figure 3B). The analysis of 6 RCTs that comprised 1018 total patients demonstrated no reduction in DBP with SGLT2-I use compared to placebo: -0.50 mmHg (-1.76 to 0.75; I^2 = 97%) (Figure 4).

SGLT2-Is and WC: A total of 378 patients from 3 RCTs received an SGLT2-I. The random effect model highlighted a mean reduction in WC of –1.28 cm (95%CI: -1.39 to –1.18; I^2 = 0%) (Figure 5).

SGLT2-Is and HDL: A total of 1080 patients from 3 RCTs were analyzed for the impact of SGLT2-Is on HDL. There was no significant difference in post-treatment HDL between the SGLT-2I and placebo groups: 0.01 mg/dL (95%CI: -0.05 to 0.07; I^2 = 100%) (Figure 6).

SGLT2-Is and TGL: TGL levels pre or post treatment were not reported in all the trials. Hence this component of the MetS could not be analyzed in this meta-analysis.

SGLT2-Is and other cardiometabolic parameters: HbA1C, BW and UA.

SGLT2-Is resulted in a modest mean reduction in HbA1C: -0.68% (95%CI: -0.88 to –0.48; I^2 = 89%) (Figure 7A). A subgroup analysis based on doses (2.5 mg and 10 mg) demonstrated no change in heterogeneity and statistical significance. Both the 2.5 mg and 10 mg doses of SGLT-2I resulted in a statistically significant improvement in A1C (Figure 7B). There was a reduction in mean BW of –1.79 kg (95%CI: -2.07 to -1.51; I^2 = 97%) with SGLT2-I use (Figure 8A). This improvement in BW was noted regardless of SGLT2-I dose. The subgroup analysis based on dose and SGLT2-I type could not highlight the potential cause of the significant heterogeneity (Figures 8B and C). UA decreased with the use of SGLT2-I: -1.03 mg/dL (95%CI: -1.14 to –0.93; I^2 = 98%) (Figure 9A). This reduction was greater within the dapagliflozin subgroup: -4.52 mg/dL (95%CI: -8.96 to –0.08; I^2 = 100%) *vs* –0.20 mg/dL (95%CI: -0.51 to 0.12; I^2 = 88%) the empagliflozin subgroup. The impact on UA also appears to be dose-dependent: -1.05 mg/dL (95%CI: -1.98 to –0.12; I^2 = 99%) with 10 mg and –0.18 mg/dL (95%CI: -1.4 to 1.05; I^2 = 0%) (Figures 9B and C). Table 3 provides a summary of the placebo adjusted treatment effect of SGLT2-Is on metabolic parameters: HbA1C, BW and UA.

DISCUSSION

This meta-analysis of 18 placebo controlled RCTs was designed to primarily evaluate the impact of SGLT2-Is on the components of the MetS as defined by the NCEP ATP III criteria. In addition, it evaluated their impact on other cardiometabolic parameters including HbA1c, BW and UA. The major findings include: (1) An improvement in MetS components (FPG, WC and BP) in the SGLT2-I group compared to the placebo group, and (2) an improvement in HbA1c, BW and UA in the SGLT2-I group compared to the placebo group.

Previous meta-analyses[40-50] that evaluated the cardiometabolic effects of SGLT2-Is have only included at most four of the five components of MetS. Teo *et al*[40] evaluated WC, BP, FPG; Cho *et al*[49] analyzed WC, BP, HDL and Zaccardi *et al*[47] evaluated FPG, BP, HDL and TGL. In addition, the results of these studies have been inconsistent. While our study aimed to evaluate all components, we only had enough data for four components (FPG, BP, WC and HDL) owing to our inclusion criteria. In contrast to studies[42,43,50], our study did not highlight a significant improvement in HDL with the use of SGLT2-Is. The reason behind this might be an inadequate statistical power; this study analyzed only 3 RCTs owing to the inclusion criteria compared to 47, 5 & 15 RCTs by Sánchez-García *et al*[41], Chen *et al*[42], and Shi *et al*[50] respectively. This study also evaluated the effect of low-dose SGLT2-Is on HDL, however it is unlikely this played a role in the outcome as the analysis by Chen *et al*[45] demonstrated a dose-independent impact. While this study has a higher mean treatment duration of 79 wk compared to prior meta-analyses which have a mean duration of 29 wk[40-50], the magnitude of the improvement in FPG, WC and BP appear similar between this study and its counterparts. This might suggest that SGLT2-Is have a ceiling effect on the components of MetS.

A high heterogeneity is noticed across all outcomes except for WC. This could be related to the differences in baseline diabetic medications taken by the patients, different doses, inclusion of more than one type of SGLT-2I and differences in the severity of hyperglycemia among the patients. However, the subgroup analysis for FPG based on dose revealed a significantly elevated heterogeneity with all doses evaluated. This study could not adjust for the differences in baseline diabetic medications and severity of hyperglycemia because these were universally different across the included RCTs, and a patient level meta-analysis would be needed for this. The heterogeneity associated with SBP outcome in the empagliflozin subgroup may be due to the significant difference in sample size between the analyzed RCTs. A further sub analysis based on the sample size was not completed because there were only 2 studies in the empagliflozin subgroup for SBP. The difference in efficacy between both SGLT2-Is on SBP appears to be largely due to the significant difference in the number of RCTs that constitute both SGLT-2I subgroup

(2 RCTs in the empagliflozin subgroup *vs* 5 RCTs in the dapagliflozin subgroup). The small number of RCTs in the empagliflozin subgroup is due to this study's inclusion criteria. The differences between the patients' baseline antihypertensives could also be contributory to the high heterogeneity in the empagliflozin subgroup for SBP. The significant difference in treatment duration between the studies that evaluated DBP might explain the significant heterogeneity associated with 10 mg dose of dapagliflozin. Inadequate power might explain the lack of statistical significance in the reduction of DBP.

The mechanism by which SGLT2-Is lead to improvement in the components of MetS and other cardiometabolic parameters have been partially elucidated[1,51-55]. The glucosuria, osmotic diuresis and natriuresis induced by the inhibition of SGLT-2 and the sodium hydrogen exchanger appears to play an important role in the improvement of FPG, HTN and HbA1c[51,52]. Their impact on HTN also stems from their ability to reduce arterial stiffness and endothelial dysfunction[51-53]. Furthermore, the improvement in UA noted with SGLT2-Is has been associated with the upregulation of the glucose transporter 9, a major urate transporter that secretes UA in the proximal kidney[1,53]. Interestingly, SGLT2-Is' cardiometabolic benefits have been linked to modification of certain genes involved in homeostasis[51,55]. These include a potential upregulation of Angiotensin 1-7 which leads to improvement in HTN and arterial stiffness[51]. The upregulation of genes involved in lipid metabolism including peroxisome proliferator-activated receptor alpha, acetyl-CoA carboxylase, fibroblast growth factor 21 and adenosine monophosphate-activated protein kinase have been associated with the improvement in TGL, HDL and BW[50]. SGLT2-Is have also been associated with increased levels of glucagon-like peptide 1, which is known to slow gastric emptying and reduce weight gain[54].

Perhaps through the improvement in MetS components, the combination of the above mechanisms might explain the improvement in CV mortality and heart failure hospitalization associated with SGLT2-Is in landmark trials[1-4,6,7,9-13]. In addition to its role in CVD, MetS is an independent risk factor in the development of DM[55,56]. Patients with MetS are approximately three to five times more likely to develop type 2 DM[55,56].

Interestingly, while the risk is lower, it is independent of the presence of elevated FPG[55]. This highlights the complex yet incompletely understood connection between MetS, type 2 DM and CVD. Although the improvement in MetS components in this study appears to be modest, our findings anticipate a possible role for SGLT2-Is in the management of MetS. Hence, it highlights the need for RCTs to evaluate the impact of SGLT2-Is on MetS compared with current management modalities including lifestyle modification.

Limitations

The findings of this study should be interpreted cautiously bearing several limitations. First, the mean baseline HDL and DBP of included RCTs did not meet threshold values for MetS. This is likely because our primary objective was mostly a derivative of the secondary outcomes of the included RCTs. Second, owing to our inclusion criteria, only two of the included RCTs recruited patients without DM which limits the external validity of our study. Furthermore, we did not conduct a patient level analysis in those without DM. Third, this study limited its analysis to only dapagliflozin or empagliflozin and did not thoroughly compare the efficacy of both. Fourth, the improvement in MetS components noted by our analysis might be confounded by other medications taken by the RCTs' participants. Therefore, our analysis could not quantify the absolute effect of SGLT2-Is. This might imply the need for the evaluation of SGLT2-Is as a first line pharmacotherapy in treatment of MetS components. Additionally, MetS has multiple causes besides sedentary lifestyle, and unhealthy eating; it is usually heterogenous in its presentation due to the different possible combinations of its components; this study did not address these in its analysis. Lastly, not all included RCTs are open labelled and hence the risk of bias could not be reliably assessed by the Cochrane risk of bias tool.

CONCLUSION

SGLT2-Is were associated with an improvement in all components of MetS. There appears to be a role for their use in the management of patients with MetS regardless of the presence of DM and HF. Prospective studies are needed to further evaluate the role

of SGLT2-Is in patients with MetS either as first-line agents and/or add-on pharmacotherapy. This study, to the best of our knowledge, is the first to fully explore a possible role for SGLT2-Is in the management of MetS.

ARTICLE HIGHLIGHTS

Research background

According to the National Cholesterol Education Program Adult Treatment Panel III, metabolic syndrome is defined by the presence of three of five of the following: (1) Waist circumference (WC) $\geq$102 cm in men and $\geq$88 cm in females; (2) Serum triglycerides $\geq$150 mg/dL or on drug treatment for hypertriglyceridemia; (3) Serum high-density lipoprotein cholesterol < 40 mg/dL in males and < 50 mg/dL; (4) Blood pressure (BP) $\geq$130/85 mmHg or on drug treatment for hypertension; (5) Fasting plasma glucose (FPG) $\geq$100 mg/dL or on drug treatment for elevated blood glucose.

Research motivation

The growing prevalence of MetS, its association with the development of cardiovascular diseases (CVD) and the need to complement the therapeutic effect of lifestyle modification were the reasons behind conducting this study.

Research objectives

To evaluate the effect of SGLT2-Is on MetS using data derived from randomized, placebo-controlled trials.

Research methods

A search of Medline, Scopus and the Cochrane central from inception to December 9, 2021 to identify randomized controlled trials (RCTs) that have evaluated the impact of SGLT2-Is on CVD and its risk factors, as well as reported pre/post treatment values of MetS components.
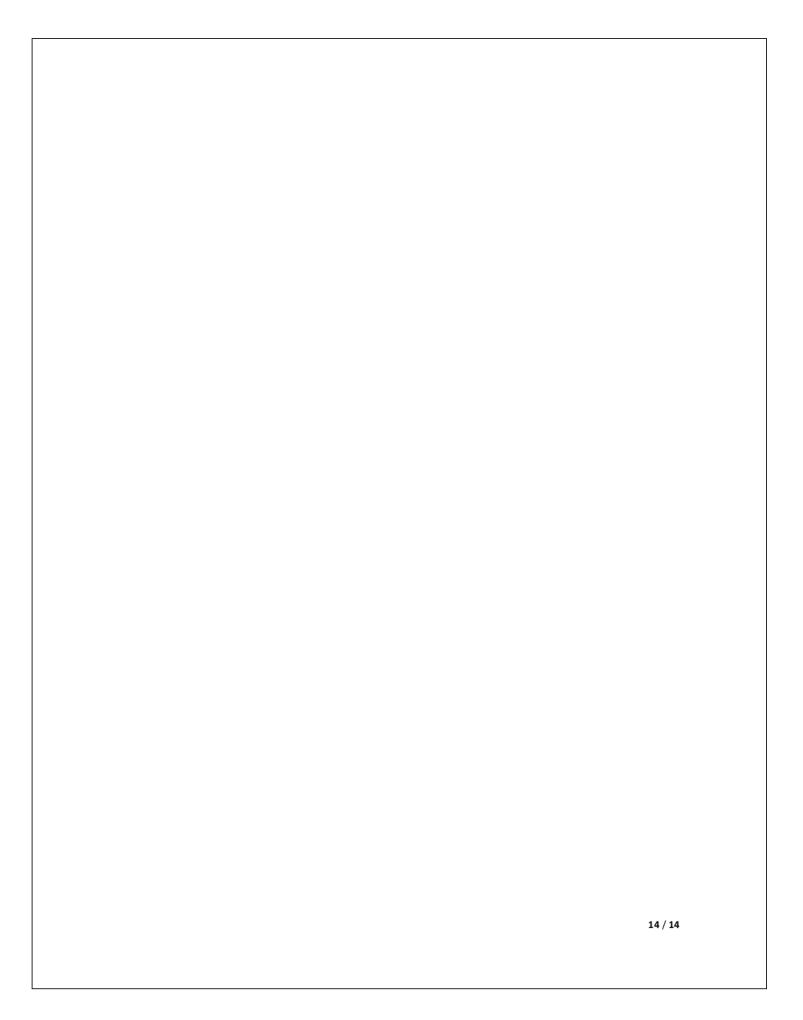
Research results

SGLT2-Is resulted in a decrease in FPG, systolic BP and WC.

Research conclusions

Further studies are needed to evaluate the use of SGLT2-Is as the first-line phamacotherapy in the management of MetS.

Research perspectives

This meta-analysis has highlighted the impact of SGLT2-Is on MetS using data from RCTs that have evaluated the impact of SGLT2-Is on CVD and its risk factors, as well as reported pre/post treatment values of MetS components. In an attempt to improve the management of MetS, we hope this study will be a precursor for future prospective studies that will establish the use of SGLT2-Is in the treatment of MetS.

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therapeutic approach to treatment of type 2 diabetes: Clinical data and mechanism of action", Journal of Diabetes Investigation, 2014.
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15 Aurélie Pahud de Mortanges, Dante Salvador Jr.,   17 words — < 1%
    Markus Laimer, Taulant Muka, Matthias Wilhelm,
    Arjola Bano. "The Role of SGLT2 Inhibitors in Atherosclerosis: A
    Narrative Mini-Review", Frontiers in Pharmacology, 2021
Crossref

16 Mukul Bhattarai, Mohsin Salih, Manjari Regmi,   14 words — < 1%
    Mohammad Al-Akchar et al. "Association of
    Sodium-Glucose Cotransporter 2 Inhibitors With Cardiovascular
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    Factors for Cardiovascular Disease", JAMA Network Open, 2022
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21 Mukul Bhattarai, Mohsin Salih, Manjari Regmi, Mohammad Al-akchar et al. "Comprehensive evaluation of cardiovascular efficacy and safety outcomes of SGLT2 inhibitors in high risk patients of cardiovascular disease: systematic review and meta-analysis", Cardiovascular Endocrinology & Metabolism, 2020
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Internet

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24 L.-H. Su. "Association of Androgenetic Alopecia with Metabolic Syndrome in Men: A Community-based Survey", British Journal of Dermatology, 04/2010
Crossref

8 words — < 1%

25 Ranjita Misra, Anoop Misra, N Kamalamma, Naval K. Vikram, Sunil Gupta, Sushum Sharma, Thakor Patel, Padmini Balagopal. "Difference in prevalence of diabetes, obesity, metabolic syndrome and associated cardiovascular risk factors in a rural area of Tamil Nadu and an urban area of Delhi", International Journal of Diabetes in Developing Countries, 2011
Crossref

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