Effects of sodium-glucose cotransporter 2 inhibitors on cardiovascular outcomes in elderly patients with comorbid coronary heart disease and diabetes mellitus

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ABSTRACT

OBJECTIVE To investigate the effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on cardiovascular outcomes in elderly Chinese patients with comorbid coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM).

METHODS A retrospective cohort study was conducted on 501 elderly inpatients (≥ 60 years) with comorbid CHD/T2DM in Department of Cardiovascular Medicine and Endocrinology, Chinese PLA General Hospital from January 2018 to December 2019. These patients were divided into two groups according to the administration of SGLT2i. All the demographic characteristics and clinical data were collected. Cardiovascular outcomes, including all-cause mortality, major adverse cardiovascular events (MACE), and hospitalization for heart failure (HHF), were followed up.

RESULTS In the cohort, there were 167 patients in the SGLT2i group and 334 patients in the control group. In the efficacy analyses, the incidence of MACE was lower in the SGLT2i group than in the control group: 3.6% vs. 9.3% (P = 0.022). A lower risk of MACE was observed in the SGLT2i group [hazard ratio (HR) = 0.40, 95% CI: 0.17–0.95]. There was no significant difference in the incidence of all-cause mortality or HHF between the two groups. No significant difference of HR was observed for all-cause mortality (HR = 0.41, 95% CI: 0.12–1.41) or HHF (HR = 0.58, 95% CI: 0.12–2.81).

CONCLUSIONS SGLT2i treatment exhibited benefits for elderly patients with comorbid CHD/T2DM with a lower risk for MACE.

It is estimated that more than 415 million adults have diabetes mellitus worldwide and there will be more than 640 million diabetic patients by 2040.[1] There are 114 million diabetic patients in China, which is more than any other country in the world.[2] In China, 47.0% of adults suffer from diabetes mellitus or prediabetes, which significantly increases the risk of coronary heart disease (CHD) and stroke.[3] Cardiovascular disease, renal disease, and infection are the main causes of mortality in patients with type 2 diabetes mellitus (T2DM).[4] With population ageing, chronic diseases and comorbidities are commonly seen in the elderly, and the incidence of comorbid CHD/T2DM is still on the rise.[5] Therefore, innovative therapeutic strategies should focus on the cardiovascular benefits in elderly diabetic patients.

As a novel hypoglycaemic agent, sodium-glucose cotransporter 2 inhibitor (SGLT2i) plays a glucose-lowering role by blocking glucose reabsorption in the proximal renal tubule, thus promoting the excretion of glucose by urine. SGLT2i can reduce the risk of cardiovascular death and hospitalization for heart failure (HHF), which has shown favourable effects on the prevention and treatment of cardiovascular outcomes.[6–9]
However, most of the studies are randomized controlled trials in which elderly patients with comorbid CHD/T2DM were excluded. Several real-world studies have finished but have not fully covered the Chinese population in Asia. The purpose of the present study was to investigate the effects of SGLT2i on cardiovascular outcomes in elderly Chinese patients with comorbid CHD/T2DM.

METHODS

Study Population

A retrospective cohort study was conducted on elderly patients (≥ 60 years) with comorbid CHD/T2DM, who were hospitalized in Department of Cardiovascular Medicine and Endocrinology, Chinese PLA General Hospital from January 2018 to December 2019. Patients who met the following criteria are eligible for the study: (1) inpatients aged 60 years or older with comorbid CHD/T2DM according to corresponding diagnostic criteria; and (2) inpatients had a complete clinical data record. Patients who met any of the following criteria will not be eligible for this study: (1) cardiogenic shock; (2) severe valvular heart disease; (3) malignant tumor; (4) acute cerebrovascular disease; (5) end-stage renal disease [estimated glomerular filtration rate (eGFR) < 15 mL/min per 1.73 m²]; (6) prolonged bedridden status; (7) mental illness; (8) severe anemia; (9) myocarditis; and (10) active infection.

A total of 501 elderly inpatients were finally included in the retrospective cohort study, including 167 patients treated with SGLT2i in the SGLT2i group (76 patients treated with dapagliflozin, and 91 patients treated with empagliflozin) and 334 patients who did not receive SGLT2i in the control group. The control group was treated with other glucose-lowering drugs, while SGLT2i, dapagliflozin or empagliflozin was added to the experimental group at a dose of 10 mg/day.

Demographic characteristics, lifestyle information, comorbidities and drug use of the subjects were collected by consulting medical records. Follow-up information of the subjects’ outcomes in the two groups was obtained by review of telephone interviews by trained reviewers. The cardiovascular outcomes investigated were all-cause mortality (death from any cause), major adverse cardiovascular events (MACE; defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality) and HHF. This study was approved by the Ethics Committee of Chinese PLA General Hospital (No.S2018-269-02) and was conducted according to the guidelines of the declaration of Helsinki Declaration. Written consent was obtained from each subject.

Variates and Term Definitions

Smoking was defined as cigarette smoked more than one pack/day for more than one year. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or taking antihypertensive medication. The diagnostic criteria of diabetes mellitus were fasting blood glucose ≥ 7.0 mmol/L, glycated hemoglobin (HbA1c) ≥ 6.5%, non-fasting blood glucose ≥ 11.1 mmol/L, or taking antihyperglycemic medication. The body mass index (BMI) was the weight in kilograms divided by the square of the height in meters. The eGFR (mL/min per 1.73 m²) = 175 × plasma creatinine − 1.234 × age − 0.179 × 0.79 (if female).

Statistical Analysis

Statistical analysis was performed with SPSS 24.0 (SPSS Inc., IBM, Armonk, NY, USA) and R software (version 4.0.2 for Windows, http://www.r-project.org/). Continuous variables were presented as mean ± SD or median (interquartile range) and categorical variables are presented as percentage. The Mann-Whitney U test and the χ² test were used to test the difference of baseline characteristics between the SGLT2i group and the control group. The association of the hypoglycemic agents with survival was assessed using Cox regression analysis. The primary model used only drug as a covariate (the SGLT2i group versus the control group), whereas the subgroup analyses were done with further adjustment of HbA1c. Pooled Kaplan-Meier survival plots were constructed to assess the cardiovascular events in the study population. All statistical tests were two-sided, with P-value < 0.05 considered statistically significant.

RESULTS

Baseline Clinical Characteristics

After screening according to criteria, a total of 501
elderly inpatients were finally included in the retrospective cohort study, including 167 patients who received SGLT2i and 334 patients who were treated with other glucose-lowering drugs. Except for HbA1c, the baseline clinical characteristics of the two groups were balanced (Table 1): the median age was 67 years (interquartile range: 63–71), 39% of patients were women, and the median duration of T2DM was ten years. A total of 78.8% of patients had hypertension, 11.2% of patients had heart failure, 7% of patients had atrial fibrillation, 52% of patients were treated with insulin, 92% of patients were treated with antiplatelet drugs and 96% of patients were treated with statins. The mean follow-up

| Characteristic                          | SGLT2i group (n = 167) | Control group (n = 334) | P-value |
|----------------------------------------|------------------------|-------------------------|---------|
| Age, yrs                               | 67.0 (63.0–71.0)       | 67.0 (63.0–71.0)        | 0.967   |
| Female                                 | 70 (41.9%)             | 127 (38.0%)             | 0.400   |
| Body mass index, kg/m²                 | 26.5 (24.2–29.3)       | 25.9 (24.5–27.8)        | 0.096   |
| Smoking                                | 64 (38.3%)             | 146 (43.7%)             | 0.249   |
| Coronary heart disease                 |                        |                         | 0.755   |
| Stable angina                          | 28 (16.8%)             | 48 (14.4%)              |         |
| Unstable angina                        | 126 (75.4%)            | 257 (76.9%)             |         |
| Myocardial infarction                  | 13 (7.8%)              | 29 (8.7%)               |         |
| Hypertension                           | 133 (79.6%)            | 262 (78.4%)             | 0.757   |
| Hyperlipidemia                         | 95 (56.9%)             | 161 (48.2%)             | 0.067   |
| History of atrial fibrillation         | 12 (7.2%)              | 25 (7.5%)               |         |
| History of heart failure               | 19 (11.4%)             | 37 (11.1%)              |         |
| History of cerebrovascular disease     | 51 (30.5%)             | 86 (25.7%)              | 0.257   |
| History of peripheral artery disease   | 6 (3.6%)               | 9 (2.7%)                | 0.578   |
| Total cholesterol, mmol/L              | 3.5 (2.8–4.3)          | 3.6 (3.1–4.4)           | 0.088   |
| Triglyceride, mmol/L                   | 1.4 (1.1–2.0)          | 1.4 (1.0–1.8)           | 0.174   |
| High-density lipoprotein cholesterol, mmol/L | 1.0 (0.8–1.2)       | 1.1 (0.9–1.2)           | 0.129   |
| Low-density lipoprotein cholesterol, mmol/L | 2.1 (1.6–2.8)       | 2.2 (1.7–2.8)           | 0.130   |
| N-terminal pro-B-type natriuretic peptide, pg/mL | 162.1 (60.7–555.5) | 164.1 (80.8–638.5)      | 0.457   |
| Estimated glomerular filtration rate, mL/min per 1.73 m² | 83.8 (67.6–102.0) | 86.1 (69.1–99.4)        | 0.897   |
| Duration of diabetes mellitus, yrs     | 14.0 (7.0–20.0)        | 10.0 (6.0–20.0)         | 0.100   |
| Glycated hemoglobin, %                 | 8.3 (7.5–9.2)          | 7.5 (6.7–8.1)           |         |

Data are presented as median (interquartile range) or n (%).
time was 13.2 months (the SGLT2i group: 12.7 months and the control group: 13.5 months).

**Correlation between SGLT2i Administration and MACE**

The incidence of MACE was lower in the SGLT2i group than in the control group: 3.6% vs. 9.3%, \( P = 0.022 \) (Table 2). There was no significant difference in the incidence of nonfatal myocardial infarction, nonfatal stroke or cardiovascular mortality between the two groups.

We found that the SGLT2i administration was associated with a lower risk of MACE [hazard ratio (HR) = 0.40, 95% CI: 0.17–0.95] (Figure 1). There was no significant reduction in the risk of nonfatal myocardial infarction (HR = 0.51, 95% CI: 0.11–2.38), nonfatal stroke (HR = 0.44, 95% CI: 0.10–2.00) or cardiovascular mortality (HR = 0.32, 95% CI: 0.07–1.41) in the SGLT2i group.

**Incidence of All-cause Mortality and HHF**

There was no significant difference in the incidence of all-cause mortality and HHF between the two groups (Table 2). Although the values were lower, no significant difference of HR was observed for all-cause mortality (HR = 0.41, 95% CI: 0.12–1.41) and HHF (HR = 0.58, 95% CI: 0.12–2.81) (Figure 2).

**Subgroup Analyses**

Based on expert consensus on HbA1c targets for Chinese adults with T2DM, analyses were performed according to HbA1c (> 7.5% and ≤ 7.5%). We found that the benefits of SGLT2i tended to be similar in patients with HbA1c > 7.5%. The SGLT2i treatment was associated with a lower risk of MACE (HR = 0.24, 95% CI: 0.08–0.72) (Table 3). In patients with HbA1c ≤ 7.5%, there was no significant difference in the risk of cardiovascular outcomes between the two groups.

After adjusting HbA1c, subgroup analyses of MACE were performed according to age, sex, BMI (≥ 24 kg/m² and < 24 kg/m²), smoking status (yes or no), eGFR (< 60 mL/min per 1.73 m², 60 to 90 mL/min per 1.73 m², and ≥ 90 mL/min per 1.73 m²) and co-morbidities (Figure 3). In the male subgroup, the subgroup aged 60–70 years and the subgroup with hypertension and hyperlipidaemia, the SGLT2i administration was significantly associated with a reduced risk of MACE.

**DISCUSSION**

In the present study, we found a significant reduction in MACE in elderly patients in the SGLT2i group compared with the control group. The incidences of components of MACE, including nonfatal myocardial infarction, nonfatal stroke and cardiovascular mortality, were slightly decreased in the SGLT2i group, but there was no significant difference between the two groups.

There are three kinds of SGLT2i medications available in the clinic. It was reported in the EMPA-REG OUTCOME trial that empagliflozin reduced the risk of MACE and cardiovascular mortality compared to placebo by 14% and 38%, respectively.\(^6\) There were no significant differences in the rates of myocardial infarction or stroke.\(^6\) The DECLARE-TIMI 58 trial showed that dapagliflozin did not reduce the risk of MACE or cardiovascular mortality.\(^8\) In a real-world setting, the CVD-REAL Nordic trial showed that compared to other glucose-lowering drugs, the SGLT2i administration reduced the risk of cardiovascular mortality and MACE by 47% and

| Outcome                                | SGLT2i group (n = 167) | Control group (n = 334) | P-value |
|----------------------------------------|------------------------|-------------------------|---------|
| Major adverse cardiovascular events    | 6 (3.6%)               | 31 (9.3%)               | 0.022   |
| Cardiovascular mortality               | 2 (1.2%)               | 13 (3.9%)               | 0.095   |
| Nonfatal myocardial infarction         | 2 (1.2%)               | 8 (2.4%)                | 0.508   |
| Nonfatal stroke                        | 2 (1.2%)               | 10 (3.0%)               | 0.353   |
| Hospitalization for heart failure      | 2 (1.2%)               | 7 (2.1%)                | 0.724   |
| All-cause mortality                    | 3 (1.8%)               | 15 (4.5%)               | 0.127   |

Data are presented as \( n \)%.

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No significant difference was identified in the incidence of myocardial infarction and stroke. In the present study, the SGLT2i administration reduced the risk of MACE by 60% compared to other glucose-lowering drugs. There was no significant reduction in the risk of nonfatal myocardial infarction, nonfatal stroke or cardiovascular mortality in the SGLT2i group. Discrepant results among these studies could be related to the administration of different types of SGLT2i. Studies have shown that the selectivity of empagliflozin is twice as high as that of dapagliflozin and is ten times as high as that of canagliflozin. However, the use of empagliflozin was more common than that of dapagliflozin in the present study. In addition, the percentage of patients with cardiovascular disease in different clinical trials differed. The subjects in our study were all elderly patients with comorbid CHD/T2DM, while in the four large-scale clinical trials, the percentages of patients with cardiovascular disease at baseline were 99%, 65.6%, 40.6% and 100%, respectively.

Heart failure is a common and serious complication in patients with T2DM, leading to higher mortality. The EMPRISE study showed that the initiation of empagliflozin decreased the risk of HHF-specific (defined as the heart failure discharge diagnosis in the primary position) and HHF-broad
The probability of freedom from the outcome of hospitalization for heart failure (A) and all-cause mortality (B). The inset in each picture shows the same data on an enlarged y axis. HR: hazard ratio; SGLT2i: sodium-glucose cotransporter 2 inhibitors.

Table 3  Subgroup analyses of key efficacy outcome.

| Outcome                     | Hazard ratio | 95% CI  | P-value |
|-----------------------------|--------------|---------|---------|
| Glycated hemoglobin ≤ 7.5% |              |         |         |
| Major adverse cardiovascular events  | 0.75         | 0.17–3.34 | 0.709   |
| Hospitalization for heart failure  | –            | –       | –       |
| All-cause mortality           | 0.55         | 0.07–4.33 | 0.567   |
| Glycated hemoglobin > 7.5%   |              |         |         |
| Major adverse cardiovascular events  | 0.24         | 0.08–0.72 | 0.011   |
| Hospitalization for heart failure  | 0.75         | 0.13–4.50 | 0.752   |
| All-cause mortality           | 0.34         | 0.07–1.67 | 0.184   |

Refers to the number of patients of hospitalized for heart failure in the SGLT2i group was zero in this subgroup. SGLT2i: sodium-glucose cotransporter 2 inhibitors.
reduced the risk of MACE in patients with HbA1c ≥ 8.0%. In another instance, the administration of empagliflozin was associated with a reduced risk of MACE in the subgroup aged ≥ 65 years; while in our study, there was a significant reduction in patients aged 60 to 70 years. There was no significant difference in the subgroup aged over 70 years. In addition, SGLT2i treatment was associated with a lower risk of MACE in the subgroup with eGFR ≥ 90 mL/min per 1.73 m² in our study; while in the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of MACE in the subgroup with eGFR 60 to 90 mL/min per 1.73 m². Inconsistent subgroup analyses results were related to different baselines of subjects. In addition, some potential confounding factors may also lead to discrepancies. Nevertheless, subgroup analyses for MACE were mostly in favour of SGLT2i. The benefits of SGLT2i with respect to MACE tended to be similar across subgroups. There are several mechanisms involved in the cardioprotective effects of SGLT2i. A study found that SGLT2i could reduce the level of HbA1c by 0.5% to 1.0%. SGLT2i can also promote weight loss and reduce adipose tissue, including epicardial adipose tissue mass. SGLT2i-mediated natriuresis and osmotic diuresis help with the reduction of cardiac preload, contributing to lowering HHF. In addition, SGLT2i reduces the afterload by lowering blood pressure, and improving vascular function and aortic stiffness. Other mechanisms include the reduction of oxidative stress, the elimination of inflammation, the intervention of necrosis and cardiac fibrosis, and the improvement of cardiac metabolism and bioenergetics.

The strengths of the present study are related to the selection of the study population. As a new hypoglycaemic agent, SGLT2i has shown favourable effects on the prevention and treatment of cardi-

| Subgroup                     | Number of patients | Control | Hazard ratio (95% CI) | P-value |
|------------------------------|--------------------|---------|-----------------------|---------|
| **Total cohort**             |                    |         |                       |         |
| Sex                          |                    |         |                       |         |
| Female                       | 3/100              | 11/127  | 0.52 (0.14–1.92)      | 0.323   |
| Male                         | 3/97               | 20/207  | 0.24 (0.07–0.83)      | 0.025   |
| Age, yrs                     |                    |         |                       |         |
| 60–70                        | 2/112              | 20/209  | 0.15 (0.04–0.67)      | 0.013   |
| ≥ 70                         | 4/55               | 11/125  | 0.77 (0.23–2.60)      | 0.668   |
| Body mass index, kg/m²       |                    |         |                       |         |
| ≥ 24                         | 3/131              | 20/276  | 0.29 (0.09–1.02)      | 0.053   |
| < 24                         | 3/36               | 11/58   | 0.32 (0.09–1.21)      | 0.093   |
| Smoking                      |                    |         |                       |         |
| Yes                          | 3/64               | 14/146  | 0.40 (0.11–1.44)      | 0.160   |
| No                           | 3/103              | 17/188  | 0.30 (0.09–1.06)      | 0.061   |
| Hypertension                 |                    |         |                       |         |
| Yes                          | 4/133              | 22/262  | 0.32 (0.11–0.96)      | 0.042   |
| No                           | 2/34               | 9/72    | 0.40 (0.08–1.97)      | 0.261   |
| Hyperlipidemia               |                    |         |                       |         |
| Yes                          | 4/95               | 20/161  | 0.27 (0.09–0.80)      | 0.018   |
| No                           | 2/72               | 11/173  | 0.44 (0.09–2.13)      | 0.308   |
| eGFR, mL/min per 1.73 m²     |                    |         |                       |         |
| < 60                         | 3/26               | 6/54    | 1.22 (0.29–5.17)      | 0.786   |
| 60–90                        | 2/70               | 13/138  | 0.26 (0.06–1.18)      | 0.081   |
| ≥ 90                         | 1/71               | 12/142  | 0.12 (0.02–0.93)      | 0.042   |

Figure 3 Subgroup analyses of major adverse cardiovascular events. eGFR: estimated glomerular filtration rate; SGLT2i: sodium-glucose cotransporter 2 inhibitors.
vascular events. However, there was no special study targeting the elderly population in China. The present study investigated the effects of SGLT2i on cardiovascular outcomes in elderly Chinese patients with comorbid CHD/T2DM.

LIMITATIONS

There were some mentionable limitations of the study. Firstly, as this was a retrospective cohort study, some confounding factors may exist, which we have not considered. Secondly, the study was a single-centre study, and because of the specific study population, the results of this study cannot be extended to all patients with T2DM. Last but not least, as a new type of hypoglycaemic drug, SGLT2i has not been widely used, especially among the elderly population in China. More subjects used empagliflozin than dapagliflozin in the present study, thus, assessment of head-to-head differences was not possible between different SGLT2i administration. Therefore, it is necessary to conduct largescale clinical trials at multiple centres.

CONCLUSIONS

In summary, the study demonstrated that SGLT2i treatment exhibited benefits for elderly patients with comorbid CHD/T2DM with a lower risk for MACE.

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