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Effects of sodium-glucose cotransporter 2 inhibitors on cardiovascular and cerebrovascular diseases: a meta-analysis of controlled clinical trials

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Objective: Evaluate the effects of sodium-glucose cotransporter 2 inhibitor (SGLT2i) on cardiovascular and cerebrovascular diseases.

Methods: Articles of SGLT2i on cardiovascular and cerebrovascular diseases were searched. Two authors independently screened the literature, extracted the data, assessed the quality of the study and performed statistical analyses using Review Manager 5.4.

Results: Random-effect model was used to merge the OR values, and the pooled effect showed that SGLT2i had significant preventive effects on cardiovascular death (OR=0.76, 95%CI 0.64 to 0.89), myocardial infarction (OR=0.90, 95%CI 0.84 to 0.96), heart failure (OR=0.69, 95%CI 0.64 to 0.74) and all-cause mortality (OR=0.65, 95%CI 0.58 to 0.73). Empagliflozin, dapagliflozin and canagliflozin all reduced the incidence of heart failure (OR=0.72, 95%CI 0.64 to 0.82; OR=0.56, 95%CI 0.39 to 0.80; OR=0.62, 95%CI 0.53 to 0.73), but only dapagliflozin displayed a favorable effect on inhibiting stroke (OR=0.78, 95%CI 0.63 to 0.98). SGLT2i could prevent stroke (OR=0.86, 95%CI 0.75 to 0.99), heart failure (OR=0.63, 95%CI 0.56 to 0.70) and all-cause mortality (OR=0.64, 95%CI 0.57 to 0.72) compared to DPP-4i. Furthermore, SGLT2i could reduce the incidence of heart failure (OR=0.72, 95%CI 0.67 to 0.77) and cardiovascular death (OR=0.72, 95%CI 0.54 to 0.95) in patients with high-risk factors.

Conclusions: SGLT2i affects cardiovascular death, myocardial infarction, heart failure and all-cause mortality. Only dapagliflozin displayed a favorable effect on inhibiting stroke. SGLT2i could prevent stroke, heart failure and all-cause mortality compared to DPP-4i. In addition, SGLT2i significantly reduced the development of heart failure and cardiovascular death in patients with high-risk factors.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42024532783.

KEYWORDS

sodium-glucose cotransporter 2 inhibitors, stroke, cardiovascular death, myocardial infarction, heart failure, all-cause mortality

1 Introduction

Diabetes mellitus is a class of metabolic diseases characterized by hyperglycemia. Type 2 diabetes caused by relative insulin deficiency or insulin resistance is prevalent in clinical practice. With the rapid development of the socio-economic conditions, the prevalence of type 2 diabetes has shown an increasing trend with each passing year. According to the study, there will be more than 640 million people with type 2 diabetes in 2024 (1). Hyperglycemia is often associated with disorders of lipid and protein metabolism, which induces and exacerbates oxidative stress and increases the risk of atherosclerotic vascular disease. Patients are highly susceptible to adverse outcomes such as cardiovascular disease, stroke or chronic renal insufficiency if they do not receive effective treatment at an early age (2-5). Cardiopathy and stroke are second only to cancer in terms of death and disability; the hyperglycemic state of the body results in a poor prognosis for cardiovascular disease. Currently, there is a limited range of antihyperglycemic agents (AHAs) available in the clinic and multiple drug loads may have adverse effects on the liver or kidney. So, it is crucial to choose a safe and effective class of glucose-lowering drugs.

Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is a class of prescription drugs approved for the treatment of type 2 diabetes. SGLT2i reduces blood glucose without increasing the risk of hypoglycemia in patients with type 2 diabetes by blocking glucose and sodium reabsorption in renal proximal tubules (6). In addition, the mechanism of promoting urinary sodium excretion and diuresis by SGLT2i may allow it to decrease blood pressure and weight without increasing the heart rate, which has a preventive effect on the progression of atherosclerotic heart disease, heart failure or chronic kidney disease (6-9). Some findings suggested that SGLT2i could reduce the risk of stroke in Asian patients with type 2 diabetes (10); Zhou speculated that this favorable effect may be related to the reduction of atrial fibrillation/atrial flutter by SGLT2i (11). A metaanalysis found that although SGLT2i was more appropriate for type 2 diabetes patients who were at high risk of stroke compared to dipeptidyl peptidase 4 inhibitor (DPP-4i), the results of this study

showed that SGLT2i did not reduce the risk of stroke (12). Therefore, we need to confirm the cardiovascular and cerebrovascular effects of SGLT2i in further clinical studies as well as to verify whether the effect is related to diseases or race/ethnicity.

Up to now, several clinical studies have reported the therapeutic effects of SGLT2i on cardiovascular and cerebrovascular diseases (10, 13–60); but the evidence needs to deepen due to the differences in search strategies, interventions, inclusion populations, sample sizes and other factors. In this study, we conducted a meta-analysis of clinical controlled trials on cardiovascular and cerebrovascular diseases with SGLT2i by systematically searching literature at home and abroad.

2 Materials and methods

2.1 Searching progress

We searched of the following databases: PubMed, Cochrane library and Sinomed for clinical controlled trials of SGLT2i on the effects of cardiovascular and cerebrovascular diseases. Reference lists of all eligible articles and related previous review articles were also manually searched. The literature search for this meta-analysis was restricted to published results. Databases were searched from the earliest data to 3 January 2024 with the search terms: ((SGLT2 inhibitors) OR (Sodium-Glucose Transporter 2 Inhibitors) OR (Sodium-glucose cotransporter-2 inhibitors) OR (Dapagliflozin) OR (Canagliflozin) OR (Empagliflozin) OR (Ipragliflozin) OR (Luseogliflozin) OR (Tofogliflozin)) AND ((acute cerebral infarction) OR (acute cerebral stroke) OR (ischemia stroke) OR (cerebral infarction)) AND ((cardiac failure) OR (acute cardiac failure) OR (heart failure) OR (acute heart failure) OR (cardiac insufficiency) OR (congestive cardiac failure) OR (congestive heart failure)) AND ((myocardial infarction) OR (acute myocardial infarction) OR (ST-segment elevation myocardial infarction) OR (ST elevated acute myocardial infarction) OR (non-ST-elevation myocardial infarction) OR (heart attack)).

Eligible studies were screened and selected based on the following criteria: (1) published in English or Chinese language; (2) evaluated the effect of SGLT2i intervention in cardiovascular and cerebrovascular diseases; (3) clinical controlled trial; (4) reported at least one outcome.

2.2 Study selection and data extraction

Two reviewers independently checked all titles and abstracts for studies that could potentially meet the inclusion criteria. We retrieved full reports of these potentially eligible studies for detailed assessment by two reviewers, who then independently extracted information on study design, drug use, study location, characteristics of participants, sample size and relevant outcomes on to a preformatted spreadsheet (10, 13–60). Any uncertainties or discrepancies between the two reviewers were resolved through consensus after rechecking of the source data and consultation with the third reviewer. We also contacted authors if any areas of uncertainty needed clarification.

2.3 Risk of bias in results of included studies

Two reviewers independently assessed the risk of bias in included studies to avoid conflicts of interest of study investigators or funders. Randomized controlled trials (RCTs) were evaluated using the revised version of the Cochrane tool, known as RoB 2. While cohort studies were evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, which is recommended for assessing risk of bias in a nonrandomized study of interventions (NRSI) (61, 62). The articles were evaluated separately by two reviewers and disagreements were settled by discussion.

2.4 Statistical analysis

The primary outcomes were the incident rate of stroke, cardiovascular death, myocardial infarction, heart failure or all-cause mortality. The secondary outcomes were the incident rate of ischemic stroke, acute coronary syndrome (ACS) or revascularization. Subgroup analyses were carried out according to differences in interventions and population characteristics. The fixed-model was performed by odds ratio (OR) and 95% confidence intervals (CI) for dichotomous variables. The I² was calculated as an index of heterogeneity between studies. If a considerable heterogeneity exists, then the fixed-effects model is replaced by the random-effect model. The analyses were performed by Review Manager 5.4 (Cochrane Collaboration, United Kingdom, http://www.cochrane.org).

3 Results

3.1 Search results and characteristics of included studies

Our research yielded 368 articles in English or Chinese that were potentially relevant to this study. After screening the abstract, 121 articles were selected for full-text review. Of these, 49 articles were eligible and included in this meta-analysis (10, 13–60). Searching progress is shown in Figure 1. Nine of the included studies were RCT (14, 23, 40, 42–45, 48, 60), and the rest 40 trials were cohort studies. Nine trials were multi-center studies (14, 16, 23, 24, 31, 36, 40, 42, 43). Eight studies were published in Chinese (44–49, 59, 60), and the rest were published in English. There are 1270038 patients received SGLT2i treatment (dapagliflozin: 21145 patients (27, 36, 40, 41, 46, 47, 49, 60); empagliflozin: 110227 patients (20, 23, 27, 32, 39, 42, 43); canagliflozin:55950 patients



(33, 44, 45, 48, 59) and 1339802 assigned to the control group (glucagon-like peptide 1 (GLP-1RA): 427963 patients (15, 17, 20, 28, 30, 33–35, 37, 39, 53); DPP-4i: 469049 patients (10, 18, 20–22, 26, 27, 31–33, 36, 50, 53, 55–58). The sample size ranges from 30 to 133139 in the SGLT2i treatment group and the control group. Due to the large sample size and complex population characteristics of this meta-analysis, the exact dosage and frequency of treatment regimens were unclear. Only eleven trials reported the precise time of follow-up, and ranged from 1 month to 2 years (16, 20, 29, 37, 44, 45, 48–50, 56, 60). The detailed characteristics of the included studies are summarized in Supplementary Table 1.

3.2 Risk of bias

In this meta-analysis, only nine trials were RCTs (14, 23, 40, 42–45, 48, 60); one of which was found to be a high-risk trial after evaluating the quality of these studies with RoB 2 tool (45). The details are illustrated in Figure 2. The remaining cohort studies were evaluated in 7 dimensions for risk of bias using the ROBINS-I tool (10, 13, 15–22, 24–39, 41, 46, 47, 49–59). Figure 3 shows that 17 (42.5%) of the 40 papers had a low risk of bias (10, 15, 16, 19, 20, 24, 26, 32, 33, 36, 38, 39, 50, 51, 53, 57, 58), 16 (40%) had a medium risk of bias (13, 17, 18, 25, 27–31, 34, 35, 37, 52, 54–56) and 7 (17.5%) had a high risk of bias (21, 22, 41, 46, 47, 49, 59).

3.3 Main outcome

3.3.1 Incidence of stroke

Of these 49 included studies, 26 studies of SGLT2i with other AHAs reported the rate of incidence of stroke as an outcome (10, 14, 15, 18–24, 27, 30–33, 35–38, 41–43, 50, 56, 57, 59). A fixed-effect model was used for the pooled effect of these studies, which showed a significant heterogeneity (heterozygosity test, $\text{Chi}^2 = 76.74$, *P*<0.00001, $I^2 = 67\%$). Then, we used the random-effect model for comparison, which showed that SGLT2i did not reduce the incidence of stroke (OR=0.92, 95%CI 0.83 to 1.01, *P*=0.07) (Figure 4).

3.3.2 Incidence of cardiovascular death

Seventeen studies reported the effect of SGLT2i intervention on cardiovascular death (14, 17, 19, 21, 23, 25–28, 30, 31, 36, 40, 51, 56, 58, 59). Analyses using the fixed-effect model showed enormous heterogeneity (heterozygosity test, $\text{Chi}^2 = 95.37$, P < 0.00001, $I^2 = 83\%$). So, the studies were instead analyzed using random-effect model and the merged OR value of the effect value was 0.76 (95%CI 0.64 to 0.89, P = 0.0007) (Figure 5). Thus, the SGLT2i treatment group reduced the incidence of cardiovascular death compared to the non-SGLT2i control group.



| Marta Baviera 2021 Yaa-Hui Dong 2022 Ameenathul Mazaya Fawzy 2023 Edouard L Fu 2022 Gábor Sütő 2021 Antonio Gonzalez Perez 2023 Phyo T Htoo 2022 | | | • | | | | |
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| Iskandar Idris 2021 | | ŏ | ŏ | ŏ | ŏ | ŏ | - |
| Ja Young Jeon 2021 | | ă | ă | ŏ | | | |
| Mikhail Kosiborod 2018 | | | | | | | |
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| Bjorn Pasternak 2019 | | | | | | | |
| Elisabetta Patorno 2022 | | | | | | | |
| Elisabetta Patorno 2018 | | | | | | | |
| Elisabetta Patorno 2021a | | | | | | | |
| Elisabetta Patorno 2021b | | | | | | | |
| Frederik Persson 2018 | | | | | | | |
| Elmor D Pineda 2020 | | | | | | | |
| HoJin Shin 2022 | | | | | | | |
| Reimar W Thomsen 2021 | | | | | | | |
| Chun-Ting Yang 2022 | | | | | | | |
| Yi Zhu 2022 | | | | | | | |
| Yao-Hui Jiang 2021 | | | | | | | |
| Yao-Hui Jiang 2022 | | | | | | | |
| Yan-Ping Yin 2021 | | | | | | | |
| Elvira D'Andrea 2023 | | | | | | | |
| Wei-Syun Hu 2023 | | | | | | | |
| Hui-Jeong Hwang 2023 | Ŏ | Ŏ | Ŏ | ŏ | Ŏ | Ŏ | Ŏ |
| Alexander Kutz 2023 | | ŏ | ŏ | Ö | ŏ | ŏ | ŏ |
| Osung Kwon 2023 | | ŏ | ŏ | ŏ | ŏ | ŏ | ŏ |
| Hsin-Fu Lee 2023 | | ŏ | ŏ | ŏ | ŏ | ŏ | ŏ |
| Young Sang Lyu 2023 | | ă | - | - | | | |
| Natalie McCormick 2023 | | | | | | | |
| Tadarro I. Richardson Ir 2023 | | | | | | | |
| Ving Ving Lin 2023 | | | | | | | |
| Ying-Ying Liu 2023 | | | | - | | | |

| | SGLT2i Non-SGLT2i | | | Odds Ratio | Odds Ratio | | |
|--|-------------------|------------|----------|-------------------------|------------|---------------------|---------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Antonio Gonzalez Perez 2023 | 39 | 11811 | 207 | 39744 | 3.6% | 0.63 [0.45, 0.89] | |
| Bernard Zinman 2015 | 164 | 4687 | 69 | 2333 | 4.2% | 1.19 [0.89, 1.58] | - |
| Bernard Zinman 2017 | 164 | 4687 | 69 | 2333 | 4.2% | 1.19 [0.89, 1.58] | - |
| Björn Pasternak 2019 | 169 | 20983 | 238 | 20983 | 5.3% | 0.71 [0.58, 0.86] | - |
| Caroline H. Nørgaard 2022 | 145 | 5275 | 223 | 8913 | 5.1% | 1.10 (0.89, 1.36) | + |
| Christopher P Cannon 2020 | 185 | 5499 | 87 | 2747 | 4.5% | 1.06 [0.82, 1.38] | + |
| Chun-Ting Yang 2022 | 263 | 21329 | 437 | 21329 | 5.8% | 0.60 [0.51, 0.70] | + |
| Elisabetta Patorno 2018 | 126 | 55560 | 136 | 55560 | 4.7% | 0.93 [0.73, 1.18] | - |
| Elisabetta Patorno 2021b | 214 | 45047 | 187 | 45047 | 5.3% | 1.15 [0.94, 1.39] | - |
| Elisabetta Patorno 2022 | 80 | 39072 | 73 | 39072 | 3.8% | 1.10 [0.80, 1.51] | |
| Elmor D Pineda 2020 | 22 | 1762 | 23 | 1762 | 1.8% | 0.96 [0.53, 1.72] | |
| Elvira D'Andrea 2023 | 126 | 60523 | 140 | 84091 | 4.7% | 1.25 [0.98, 1.59] | + |
| Frederik Persson 2018 | 69 | 10227 | 270 | 30681 | 4.4% | 0.77 [0.59, 1.00] | + |
| Gábor Sütő 2021 | 99 | 18526 | 113 | 18495 | 4.4% | 0.87 [0.67, 1.15] | - |
| HoJin Shin 2022 | 39 | 8613 | 63 | 17226 | 3.0% | 1.24 [0.83, 1.85] | |
| Iskandar Idris 2021 | 198 | 28720 | 247 | 28720 | 5.4% | 0.80 [0.66, 0.97] | + |
| Ja Young Jeon 2021 | 397 | 41808 | 447 | 41808 | 6.0% | 0.89 [0.77, 1.02] | - |
| Jayoung Lim 2022 | 5 | 1842 | 4 | 1842 | 0.5% | 1.25 [0.34, 4.66] | |
| Kohei Kaku 2017 | 38 | 1006 | 20 | 511 | 2.0% | 0.96 [0.55, 1.67] | |
| Mikhail Kosiborod 2018 | 319 | 102580 | 409 | 102580 | 5.9% | 0.78 [0.67, 0.90] | + |
| Natalie McCormick 2023 | 99 | 4075 | 121 | 4075 | 4.4% | 0.81 [0.62, 1.07] | |
| Phyo T Htoo 2022 | 243 | 45706 | 250 | 45706 | 5.5% | 0.97 [0.81, 1.16] | + |
| Yaa-Hui Dong 2022 | 104 | 13016 | 119 | 13016 | 4.4% | 0.87 [0.67, 1.14] | + |
| Ying-Ying Liu 2023 | 2 | 112 | 3 | 112 | 0.3% | 0.66 [0.11, 4.03] | |
| Yi Zhu 2022 | 0 | 141 | 15 | 645 | 0.1% | 0.14 [0.01, 2.42] | |
| Young Sang Lyu 2023 | 4 | 186 | 8 | 593 | 0.5% | 1.61 [0.48, 5.40] | |
| Total (95% CI) | | 552793 | | 629924 | 100.0% | 0.92 [0.83, 1.01] | • |
| Total events | 3313 | | 3978 | | | | |
| Heterogeneity: Tau ² = 0.03; Chi ³ | = 76.74, | df = 25 (P | < 0.0000 | 1); I ² = 67 | % | | |
| Test for overall effect: Z = 1.84 (| P = 0.07) | | | | | | Favours [SGLT2i] Favours [Non-SGLT2i] |
| | | | | | | | |

Forest plot of the incidence of stroke.

| | SGL | T2i | Non-Se | GLT2i | | Odds Ratio | Odds Ratio |
|--|------------|-----------|-----------|-------------------------|----------|---------------------|---------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Antonio Gonzalez Perez 2023 | 127 | 11811 | 481 | 39744 | 8.0% | 0.89 [0.73, 1.08] | - |
| Björn Pasternak 2019 | 100 | 20983 | 163 | 20983 | 7.4% | 0.61 [0.48, 0.79] | |
| Caroline H. Nørgaard 2022 | 70 | 5275 | 150 | 8913 | 7.0% | 0.79 [0.59, 1.05] | |
| Chang Hee Kwon 2022 | 27 | 2958 | 130 | 10691 | 5.6% | 0.75 [0.49, 1.14] | |
| Christopher P Cannon 2020 | 341 | 5499 | 184 | 2747 | 8.1% | 0.92 [0.77, 1.11] | - |
| Donna Shu-Han Lin 2022 | 814 | 81152 | 187 | 20288 | 8.3% | 1.09 [0.93, 1.28] | + |
| Edouard L Fu 2022 | 31 | 5489 | 51 | 6886 | 5.3% | 0.76 [0.49, 1.19] | |
| Frederik Persson 2018 | 38 | 10227 | 160 | 30681 | 6.3% | 0.71 [0.50, 1.01] | |
| Hsin-Fu Lee 2020 | 69 | 11431 | 104 | 11431 | 6.8% | 0.66 [0.49, 0.90] | |
| Iskandar Idris 2021 | 213 | 28720 | 259 | 28720 | 8.1% | 0.82 [0.68, 0.98] | - |
| Jayoung Lim 2022 | 3 | 1842 | 5 | 1842 | 1.1% | 0.60 [0.14, 2.51] | |
| Kohei Kaku 2017 | 22 | 1006 | 25 | 511 | 4.1% | 0.43 [0.24, 0.78] | |
| Stephen D Wiviot 2019 | 245 | 8582 | 249 | 8578 | 8.1% | 0.98 [0.82, 1.18] | + |
| Tadarro L Richardson Jr 2023 | 48 | 21170 | 61 | 21170 | 6.0% | 0.79 [0.54, 1.15] | |
| Wei-Syun Hu 2023 | 646 | 17588 | 1189 | 17588 | 8.8% | 0.53 [0.48, 0.58] | - |
| Ying-Ying Liu 2023 | 1 | 112 | 2 | 112 | 0.4% | 0.50 [0.04, 5.54] | |
| Young Sang Lyu 2023 | 0 | 186 | 5 | 593 | 0.3% | 0.29 [0.02, 5.21] | |
| Total (95% CI) | | 234031 | | 231478 | 100.0% | 0.76 [0.64, 0.89] | • |
| Total events | 2795 | | 3405 | | | • | |
| Heterogeneity: Tau ² = 0.07: Chi ² : | = 95.37. d | f=16 (P · | < 0.00001 |); ² = 839 | % | | |
| Test for overall effect: Z = 3.39 (P | = 0.0007) | | | // | | | 0.02 0.1 1 10 50 |
| | , | | | | | | Favours [SGLT21] Favours [Non-SGLT21] |
| | | | | | | | |
| | | | | | | | |
| olot of the incidence of cardiov | ascular | death. | | | | | |

3.3.3 Incidence of myocardial infarction

A total of 33 studies reported the incidence of myocardial infarction with SGLT2i intervention (10, 14, 15, 17-26, 28, 30-33, 35-38, 40, 41, 43, 50-57). Heterogeneity was significant in the fixedeffect model analysis of these studies (heterozygosity test, Chi² = 95.61, P<0.00001, I^2 = 67%), after that, a random-effect model was used and pooled effect value was 0.90 (95%CI 0.84 to 0.96, *P*=0.002) (Figure 6). Thus, SGLT2i could reduce the incidence of myocardial infarction.

3.3.4 Incidence of heart failure

36 studies reported the incidence of heart failure (10, 13-18, 20-23, 25-41, 43, 50, 52-55, 58, 59). Heterogeneity analysis of these studies showed substantial heterogeneity (heterozygosity test, Chi² = 186.58, P<0.00001, I^2 = 81%). Therefore, the analysis was performed using the random-effect model with a pooled effect value of 0.69 (95%CI 0.64 to 0.74, P<0.00001) (Figure 7). It can be indicated that SGLT2i significantly reduced the occurrence of heart failure compared with non-SGLT2i.

| Young Sang Lyu 2023 2 186 9 593 0.2% 0.71 [0.15, 3.29 Yi Zhu 2022 5 141 76 645 0.5% 0.28 [0.11, 0.69] Yi Zhu 2023 527 17588 543 17588 4.9% 0.97 [0.65, 1.16] Wei-Syun Hu 2023 527 17588 543 17588 4.9% 0.97 [0.66, 1.10] Phyo T Hoo 2022 305 45706 406 45706 4.5% 0.75 [0.65, 0.87] Hours 2023 40 938 65 1876 1.9% 0.94 [0.64, 1.38] Natalia McCormick 2023 108 4075 153 4075 3.2% 0.70 [0.54, 0.39] Mikhail Kosiborod 2018 469 102580 586 102580 4.8% 0.78 [0.69, 0.89] Mikhail Kosiborod 2018 469 102580 586 102580 4.8% 0.78 [0.69, 0.89] Mikhail Kosiborod 2018 469 102580 586 102580 4.8% 0.78 [0.69, 0.89] Hishadar Idriz 2021 121 41808 156 41808 3.3% 0.77 [0.61, 0.89] Hui-Jeong Hwang 2023 1 777 5 2337 0.1% 0.69 [0.07, 5.14] Hui-Jeong Hwang 2023 1 777 5 2337 0.1% 0.69 [0.07, 5.14] Hui-Jeong Hwang 2023 1 777 5 2337 0.1% 0.69 [0.07, 1.16] Hui-Jeong Hwang 2023 1 1779 5 2337 0.1% 0.69 [0.07, 1.16] Hui-Jeong Hwang 2023 1 29 4110 143 4110 3.3% 0.80 [0.07, 1.16] Hui-Jeong Hwang 2023 1 29 4110 143 4110 3.3% 0.80 [0.07, 1.16] Hoin Shin 2022 38 8613 126 17226 2.1% 0.68 [0.67, 1.09] Hoin Shin 2022 38 8613 126 17226 2.1% 0.68 [0.67, 1.09] Hoin Shin 2022 123 3072 121 4022 1.0% 1.38 [1.01, 1.60] Himor D Pineda 2020 22 1762 22 1762 2.1 1762 1.0% 1.05 [0.57, 1.91] Hoin Shurhac 2023 210 45047 277 46047 4.3% 1.09 [0.02, 1.29] Hisabetha Patomo 2021 123 31072 3.1% 0.68 [0.67, 1.09] Hisabetha Patomo 2021 123 31072 137 3072 3.1% 0.63 [0.67, 1.91] Hisabetha Patomo 2021 28 15489 119 6886 2.8% 0.85 [0.64, 1.13] Caroline H. Nergaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Hoin Tig Yang 2022 20 296 5275 193 8913 3.2% 0.84 [0.65, 1.07] Hoin Shurhan Lin 2022 43 81152 87 20288 3.4% 0.53 [0.68, 0.79] Hisabetha Patomo 2020 130 5499 119 6586 7.5% 0.93 [0.87, 0.99] Heterogeneity, Tau* = 0.02; Chi* = 9.5.1, dif = 32 (P < 0.0001; P = 67% Te 3.3% 0.88 [0.65, 1.07] Hoin Bordy Charlen 2023 6575 193 8913 3.2% 0.84 [0.65, 1.07] Hour Ing Yang 2022 172 21067 1849 21068 3.4% 0.53 [0.68, 0.79] Heterogeneity, Tau* = 0.02; Chi* = 9.5.61 701 | Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
|--|--|------------|------------|----------|----------------|--------|---------------------|---|
| Yi Zhu 2022 5 141 76 645 0.5% 0.28 [0.11, 0.68] Yia-Hui Dong 2022 41 13016 4.7% 0.95 [0.62, 1.46] Wei-Syun Hu 2023 527 17588 543 17588 4.9% 0.97 [0.86, 1.10] Stephen D Wiwid 2019 393 8582 441 8578 4.6% 0.76 [0.65, 0.87] | Young Sang Lyu 2023 | 2 | 186 | 9 | 593 | 0.2% | 0.71 [0.15, 3.29] | |
| Yaa-Hui Dong 2022 41 13016 1.7% 0.95 [0.62,1.46] Wei-Syun Hu 2023 527 17588 543 17588 4.9% 0.97 [0.86,1.10] Phyo T Hoo 2022 305 45706 4.6% 0.97 [0.86,1.10] | Yi Zhu 2022 | 5 | 141 | 76 | 645 | 0.5% | 0.28 [0.11, 0.69] | |
| Wei-Sym Hu 2023 527 17568 543 17568 4.9% 0.97 0.86, 11.01 Slephen DWivid 2019 333 8592 441 8578 4.6% 0.98 0.77, 1.02 Osung Kwon 2023 40 938 85 1876 1.9% 0.49 (10.64, 1.38) Mikhai Kosiborod 2018 40 102580 586 102580 4.8% 0.77 [0.81, 0.98] Ja Young Jeon 2021 121 4100 12580 4.8% 0.78 [0.69, 0.89] | Yaa-Hui Dong 2022 | 41 | 13016 | 43 | 13016 | 1.7% | 0.95 [0.62, 1.46] | |
| Stephen D Wivid 2019 393 8562 441 8578 4.6% 0.98 [0.77, 10.2] Phyo T Hloo 2022 305 45706 406 45706 4.5% 0.75 [0.65, 0.87] Osung Kwon 2023 400 398 85 1876 1.9% 0.44 [0.64, 1.38] Natalie McCormick 2023 108 4075 153 4075 3.2% 0.70 [0.54, 0.90] Khait Kosbrood 2018 460 102560 568 102560 44% 0.78 [0.69, 0.89] Kohei Kaku 2017 29 1006 23 511 1.1% 0.63 [0.36, 1.10] Ja Young Jeon 2021 121 41808 3.3% 0.77 [0.61, 0.98] Hui-Leong Hwang 2023 1 779 5 2337 0.1% 0.60 [0.71, 1.51] Hsin-Fu Lee 2020 50 11431 80 11431 2.0% 0.83 [0.57, 1.21] Holin Fu Lee 2020 50 11431 80 11431 2.0% 0.83 [0.57, 1.91] Holin Fu Lee 2020 20 1762 2.1% 0.60 [0.42, 0.87] | Wei-Syun Hu 2023 | 527 | 17588 | 543 | 17588 | 4.9% | 0.97 [0.86, 1.10] | + |
| Phyo THeo 2022 305 45706 406 45706 4.5% 0.75 (0.68, 0.87) Osung Kwon 2023 40 938 85 1876 1.9% 0.94 (0.64, 1.38) Mikhail Kosiborod 2018 460 102580 568 102580 4.8% 0.78 (0.68, 0.89) + | Stephen D Wiviot 2019 | 393 | 8582 | 441 | 8578 | 4.6% | 0.89 [0.77, 1.02] | - |
| Osung Kwon 2023 40 938 65 19% 0.94 (0.64, 1.36) Natalie McCormick 2023 108 4075 153 4075 3.2% 0.70 (0.54, 0.90) Khail Kaku 2017 29 1006 23 511 1.1% 0.63 (0.68, 1.10) Ja Young Jeon 2021 121 14108 166 41808 33% 0.77 (0.61, 0.98) Hain-Fu Lee 2023 12 779 5 2337 0.1% 0.60 (0.77, 1.16) Hsin-Fu Lee 2020 50 11431 20% 0.83 (0.67, 1.21) | Phyo T Htoo 2022 | 305 | 45706 | 406 | 45706 | 4.5% | 0.75 [0.65, 0.87] | - |
| Natale McCorrnick 2023 108 4075 153 4075 3.2% 0.70 [0.54, 0.90] Mikhail Kosiborod 2018 460 102580 586 102580 4.8% 0.78 [0.59, 0.89] Ja Young Jeon 2021 121 41808 156 41808 3.3% 0.77 [0.61, 0.98] Ja Young Jeon 2021 121 41808 156 41808 3.3% 0.77 [0.61, 0.98] Iskandar Idris 2021 757 28710 762 28710 0.60 [0.07, 5.14] Hsin-Fu Lee 2023 129 4110 143 20% 0.60 [0.42, 0.67] Hsin-Fu Lee 2020 10 11431 60 11431 0.50 [0.57, 1.21] Hojin Shin 2022 38 8613 126 17226 2.1% 0.60 [0.42, 0.67] Gábor Sutő 2021 135 18419 99 18385 3.0% 1.38 [1.10, 1.60] Elvira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 [1.10, 1.60] Elisabeta Patorno 2021 123 39072 213 39072 3.1% 1.02 [0.79, 1.31] Elisabeta Patorno 2021b | Osung Kwon 2023 | 40 | 938 | 85 | 1876 | 1.9% | 0.94 [0.64, 1.38] | |
| Mikhai Kosiborod 2018 460 102580 586 102580 4.8% 0.78 [0.69, 0.89] Kohei Kaku 2017 29 1006 23 511 1.1% 0.63 [0.36, 1.10] Ja Young Jeon 2021 757 28710 762 28710 5.1% 0.99 [0.90, 1.10] Hui-Jeong Hwang 2023 1 779 5 2337 0.1% 0.60 [0.75, 14] Hain-Fu Lee 2020 50 11431 60 11431 2.0% 0.83 [0.57, 1.21] HoJin Shin 2022 38 8613 126 17226 2.1% 0.60 [0.42, 0.87] Gábor Stuť 2021 135 18419 99 18385 3.0% 1.36 [1.05, 1.77] Frederik Person 2018 87 10227 304 30681 3.3% 0.68 [0.67, 1.09] Elwira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 [1.10, 1.60] Elwira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 [1.10, 1.60] Elmor D Pineda 2020 22 1762 21 1762 1.0% 1.05 [0.57, 1.91] Elisabetta Patomo 2021 30 45072 277 45047 4.3% 1.09 [0.92, 1.28] Elisabetta Patomo 2021 81 5499 119 6886 2.8% 0.68 [0.64, 1.13] Donna Shu-Han Lin 2022 41 5499 119 6886 2.8% 0.68 [0.64, 1.13] Donna Shu-Han Lin 2022 122 21329 133 21329 3.4% 0.63 [0.50, 1.78] Chur-Ting Yang 2022 122 21329 133 21329 3.4% 0.63 [0.50, 1.78] Chursopher P Cannon 2020 120 122 21329 133 2.77 4.5564 1.22 [0.97, 1.53] Chursopher P Cannon 2020 30 5499 158 2.774 3.8% 0.48 [0.66, 1.27] Chang Hee Kwon 2022 20 2988 99 10691 1.4% 0.73 [0.45, 1.18] Elisabetta Patomo 2020 31 5499 158 2.774 3.8% 0.48 [0.66, 1.27] Chang Hee Kwon 2022 122 4687 126 233 3.5% 0.88 [0.70, 1.10] Herogeneity. Tau [*] = 0.02; Chi [*] = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 91369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity. Tau [*] = 0.02; Chi [*] = 35.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 91369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity. Tau [*] = 0.02; Chi [*] = 35.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 91369 100.0% 0.90 [0.84, 0.96] Heterogeneity. Tau [*] = 0.02; Chi [*] = 56.61, df = 32 (P < 0.00001); P = 67% Total events 7415 (P = 0.002) | Natalie McCormick 2023 | 108 | 4075 | 153 | 4075 | 3.2% | 0.70 [0.54, 0.90] | |
| Kohei Kaku 2017 29 1006 23 511 1.1% 0.63 0.63 1.10 Ja Young Jeon 2021 121 41808 156 41808 3.3% 0.77 10.61 0.98 Iskandar Idris 2021 757 28710 51% 0.99 0.99 0.90 0.10 Hui-Jeong Hwang 2023 129 4110 143 4110 3.3% 0.99 0.90 0.71 1.15 Hsin-Fu Lee 2020 50 11431 60 11431 2.0% 0.83 0.57 1.21 Holinshin 2022 38 8613 126 17226 2.1% 0.06 0.62,0.87 Gábor Stitő 2021 135 18419 91 8385 3.0% 1.36 (1.05, 1.77) Frederik Person 2018 87 10227 304 3068 3.3% 0.26 (0.79, 1.31) Elivabeta Patorno 2021 127 45047 277 45047 4.3% 1.09 1.02 1.09 4.3% Elisabeta Patorno 20218 816 </td <td>Mikhail Kosiborod 2018</td> <td>460</td> <td>102580</td> <td>586</td> <td>102580</td> <td>4.8%</td> <td>0.78 [0.69, 0.89]</td> <td>-</td> | Mikhail Kosiborod 2018 | 460 | 102580 | 586 | 102580 | 4.8% | 0.78 [0.69, 0.89] | - |
| Ja Young Jeon 2021 121 41808 156 41808 3.3% 0.77 [061,0.89] Iskandar Idris 2021 757 28710 762 28710 5.1% 0.99 [0.90, 1.10] Hui-Jeong Hwang 2023 1 779 6 2337 0.1% 0.60 [0.07, 5.14] Hsin-Fu Lee 2023 129 4110 143 4110 3.3% 0.90 [0.71, 1.15] Hsin-Fu Lee 2020 50 11431 60 11431 2.0% 0.83 [0.57, 1.21] Hsin-Fu Lee 2021 135 18419 99 18385 3.0% 1.38 [1.05, 1.77] Frederik Person 2018 87 10227 304 30681 3.3% 0.68 [0.67, 1.09] Elvira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 [1.10, 1.60] Elvira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 [1.10, 1.60] Elisabeta Patomo 2021 123 39072 121 39072 3.1% 1.02 [0.79, 1.31] Elisabeta Patomo 2021 130 45047 277 45047 4.3% 1.09 [0.92, 1.28] Elisabeta Patomo 2021 8 182 55560 190 55560 3.7% 0.96 [0.68, 1.13] Elisabeta Patomo 2022 81 5498 119 6886 2.8% 0.85 [0.64, 1.13] Donna Shu-Han Lin 2022 423 81152 87 20288 3.4% 1.22 [0.97, 1.53] Chard Hee Kwon 2022 20 2988 99 10681 1.4% 0.73 [0.45, 1.18] Charding Hee Kwon 2022 96 5275 193 8913 3.2% 0.68 [0.65, 1.07] Chard Hee Kwon 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Elisabeta Patomo 2021 81 1181 2 47 39744 3.2% 1.13 [0.88, 1.45] Elisabeta Patoma 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Elisabeta Patoma 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Elisabeta Patoma 2021 122 21329 193 21329 3.4% 0.74 [0.63, 0.87] Elisabeta Patoma 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Hardine Kuragaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Elisabeta Patoma 2015 223 4687 126 2333 3.5% 0.88 [0.84, 0.56] Heterogeneity: Tau [*] = 0.02; Ch [*] = 956.1, df = 32 (P < 0.00001); P = 67% Erator everall effect Z = 3.15 (P = 0.002) | Kohei Kaku 2017 | 29 | 1006 | 23 | 511 | 1.1% | 0.63 [0.36, 1.10] | |
| Iskandar Idris 2021 757 28710 762 28710 51% 0.99 (0.90,1.10) Hui-Jeong Hwang 2023 1 779 5 2337 0.1% 0.60 (0.07,5.14) Hsin-Fu Lee 2020 50 11431 60 11431 2.0% 0.83 (0.57, 1.21) HoJin Shin 2022 38 8613 126 17226 2.1% 0.60 (0.42, 0.67) Gábor Sutő 2021 135 18419 99 18385 3.0% 1.38 (1.04, 2, 0.67) Frederik Persson 2018 87 10227 304 30681 3.3% 0.68 (0.67, 1.09) Elwira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 (1.10, 1.60) Elmor D Pineda 2020 22 1762 21 1762 1.0% 1.05 (0.57, 1.91] Elisabetta Patomo 2021 23 39072 121 39072 3.1% 1.02 (0.79, 1.31] Elisabetta Patomo 2021 81 55560 109 55560 3.7% 0.96 (0.78, 1.17] Elisabetta Patomo 2018 182 55560 13.7% 0.96 (0.78, 1.17] Elisabetta Patomo 2021 81 5499 119 6886 2.8% 0.68 (0.64, 1.13] Donna Shu-Han Lin 2022 122 21329 133 21329 3.4% 0.63 (0.50, 0.78] Christopher P Cannon 2020 120 122 21329 133 21329 3.4% 0.63 (0.50, 0.78] Christopher P Cannon 2020 220 2298 99 10691 1.4% 0.73 (0.45, 1.18] Chang Hee Kwon 2022 00 2958 99 10691 1.4% 0.73 (0.45, 1.18] Elisabetta Patomo 2020 330 5499 158 2.747 3.8% 1.05 (0.56, 1.27] Chang Hee Kwon 2022 122 21329 133 3.2% 0.84 (0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 (0.63, 0.87] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total (95% CI) 889129 | Ja Young Jeon 2021 | 121 | 41808 | 156 | 41808 | 3.3% | 0.77 [0.61, 0.98] | |
| Hui-Jeong Hwang 2023 1 779 5 2337 0.1% 0.60 [0.07, 5.14] Hain-Fu Lee 2023 129 4110 143 4110 3.3% 0.90 [0.07, 5.14] Hain-Fu Lee 2020 50 111431 60 11431 2.0% 0.83 [0.57, 1.21] HoJin Shin 2022 38 8613 126 17226 2.1% 0.60 [0.42, 0.87] Gábor Stúð 2021 135 18419 99 18365 3.0% 1.36 [1.05, 1.77] Frederik Persson 2018 87 10227 304 30681 3.3% 0.88 [0.67, 1.09] Elwira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 [1.10, 1.60] Elmor D'Ineda 2020 22 1762 21 1762 1.0% 1.05 [0.57, 1.91] Elisabetta Patorno 2021 13 3072 11 30072 3.1% 1.02 [0.79, 1.31] Elisabetta Patorno 2021 13 3072 11 30072 3.1% 1.02 [0.79, 1.31] Elisabetta Patorno 2021 81 55560 190 55560 3.7% 0.96 [0.78, 1.17] Edouard L Fu 2022 81 5489 119 6686 2.8% 0.85 [0.64, 1.13] Donna Shu-Han Lin 2022 423 81152 87 20288 3.4% 0.63 [0.50, 0.79] Chiristopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 122 20 2958 99 10691 1.4% 0.73 [0.45, 1.18] Eardine H Avrgaard 2022 96 5275 193 8913 3.2% 0.64 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zinman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 91369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 35.61, df = 32 (P < 0.00001); P = 67% Test for overall effect Z = 3.15 (P = 0.002) | Iskandar Idris 2021 | 757 | 28710 | 762 | 28710 | 5.1% | 0.99 [0.90, 1.10] | + |
| Hein-Fu Lee 2023 129 4110 143 4110 33% 0.00 [07.1.1.6] Hsin-Fu Lee 2020 50 11431 60 11431 2.0% 0.83 [0.57, 1.21] Hsin-Fu Lee 2020 30 11431 120 1722 2.1% 0.68 [0.67, 1.05] Gábor Suló 2021 135 18419 99 18385 3.0% 1.38 [1.05, 1.77] Frederik Persson 2018 87 10227 304 30681 3.3% 0.86 [0.67, 1.09] Eliva D'Andrea 2023 2.10 60523 2.20 84091 3.9% 1.33 [1.10, 1.60] Elimar D'Andrea 2020 2.2 1762 2.1 1762 1.0% 1.05 [0.57, 1.91] Elisabeta Patomo 2021 123 39072 121 39072 3.1% 1.02 [0.79, 1.31] Elisabeta Patomo 2021 130 45047 2.77 45047 4.3% 1.09 [0.92, 1.28] Elisabeta Patomo 2021 130 45047 2.77 45047 4.3% 1.09 [0.92, 1.28] Elisabeta Patomo 2021 81 5499 119 6886 2.8% 0.85 [0.64, 1.13] Donna Shu-Han Lin 2022 423 81152 87 20288 3.4% 1.22 [0.97, 1.53] Chun-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 30 5499 158 2.747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 96 5275 193 8913 2.2% 0.84 [0.65, 1.07] Elimara 2015 2.23 4687 126 2.233 3.5% 0.88 [0.61, 1.16] Error D'Astemak 2019 2.59 2098 3.49 20983 4.3% 0.74 [0.63, 0.67] Björn Pastemak 2019 2.59 2098 349 20983 4.3% 0.74 [0.63, 0.67] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total (95% CI) 580 CI 2.5 10 Eavource Sidd TOB Eavource Sidd TOB Eavource Sidd TOB E | Hui-Jeong Hwang 2023 | 1 | 779 | 5 | 2337 | 0.1% | 0.60 [0.07, 5.14] | |
| Hsin-Fu Lee 2020 50 11431 60 11431 2.0% $0.83[0.57, 1.21]$ HoJin Shin 2022 38 8613 126 17226 2.1% $0.001042, 0.87]$ Gábor Sul 2021 135 18419 99 18385 3.0% $1.36[1.05, 1.77]$ Frederik Persson 2018 87 10227 304 30681 3.3% $0.86[0.67, 1.09]$ Elwira D'Andrea 2023 210 60523 220 84091 3.9% $1.33[1.00, 1.60]$ Elmor D'Ineda 2020 22 1762 21 1762 1.0% $1.05[0.57, 1.91]$ Elisabeta Patomo 2021 33 39072 121 39072 3.1% $1.02[0.79, 1.31]$ Elisabeta Patomo 2021 8 185 25560 190 55560 3.7% $0.96[0.78, 1.17]$ Elisabeta Patomo 2018 182 55560 190 55560 3.7% $0.96[0.78, 1.17]$ Elisabeta Patomo 2018 182 55560 190 55560 3.7% $0.96[0.78, 1.17]$ Edouard LFu 2022 81 5499 119 6886 2.8% $0.86[0.64, 1.13]$ Donna Shu-Han Lin 2022 122 21329 193 21329 3.4% $0.53[0.50, 0.79]$ Chirstopher P Cannon 2020 330 5499 158 2.747 3.8% $1.02[0.97, 1.53]$ Chang Hee Kwon 2022 102 2132 9130 21329 3.4% $0.73[0.45, 1.18]$ Chang Hee Kwon 2022 90 2988 39 10691 1.4% $0.73[0.45, 1.18]$ Emand Zimman 2015 223 4687 126 2333 3.5% $0.84[0.70, 1.10]$ Heterogeneity. Tau [*] = 0.02; Chi [*] = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 91369 100.0% $0.90[0.84, 0.96]$ Total events 7415 8269 Heterogeneity. Tau [*] = 0.02; Chi [*] = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 91369 100.0% $0.90[0.84, 0.96]$ Total events 7415 8269 Heterogeneity. Tau [*] = 0.02; Chi [*] = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 91369 100.0% $0.90[0.84, 0.96]$ 0.1 0.2 0.5 1 2 5 10 Eavours Mon-SGU T20 Eavours Mon-SGU T20 Eavo | Hsin-Fu Lee 2023 | 129 | 4110 | 143 | 4110 | 3.3% | 0.90 [0.71, 1.15] | |
| HoJin Shin 2022 38 8613 126 17226 2.1% 0.60[0.42_0.87] Gábor Stilő 2021 135 18419 99 18385 3.0% 1.36 [1.05, 1.77] Frederik Person 2018 87 10227 304 30681 3.3% 0.88 [0.67, 1.09] Elwira D'Andrea 2023 210 60523 220 84091 3.9% 1.33 [1.10, 1.60] Elmor D'Ineda 2020 22 1762 21 1762 1.0% 1.05 [0.57, 1.91] Elisabetta Patorno 2021 123 30072 121 30072 3.1% 1.02 [0.79, 1.31] Elisabetta Patorno 2021b 301 45047 277 45047 4.3% 1.09 [0.78, 1.31] Elisabetta Patorno 2022 81 5459 119 6866 2.8% 0.96 [0.78, 1.17] Elisabetta Patorno 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Chun-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Elisabetta Zimma 2015 223 4687 126 2333 3.5% 0.84 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zimman 2015 223 4687 126 2333 3.5% 0.88 [0.87, 1.13] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% | Hsin-Fu Lee 2020 | 50 | 11431 | 60 | 11431 | 2.0% | 0.83 [0.57, 1.21] | |
| Gábor Sútő 2021 135 18419 99 18385 3.0% 1.36 [1.05, 1.77] Frederik Persson 2018 87 10227 304 30681 3.3% 0.86 [0.57, 1.09] Elivia D'Andrez 2023 210 60523 220 82091 3.9% 1.33 [1.10, 1.60] Eliva D'Andrez 2023 210 60523 221 1762 1.1% 1.05 [0.57, 1.91] Elisabeta Patorno 2021 13 39072 121 39072 3.1% 1.09 [0.92, 1.28] Elisabeta Patorno 2018 182 55560 190 55560 3.7% 0.96 [0.78, 1.17] Eduard L Fu 2022 81 5489 119 6886 2.8% 0.68 [0.64, 1.13] Donna Shu-Han Lin 2022 122 21329 132 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 30 5499 158 2747 3.8% 0.73 [0.45, 1.18] Caroline H. Nergaard 2022 20 298 20983 4.3% 0.74 [0.63, 0.87] + Björn Pasternak 2019 259 20983 3.97 2065, 5.5% 0.39 [0.87, 0.99] | HoJin Shin 2022 | 38 | 8613 | 126 | 17226 | 2.1% | 0.60 [0.42, 0.87] | |
| Frederik Person 2018 87 10227 304 30681 3.3% 0.86 [0.67, 1.09] Elwira D'Andrea 2023 210 60523 220 84091 3.3% 1.33 [1.10, 1.60] Elmor D Pineda 2020 22 1762 1.762 1.0% 1.05 [0.57, 1.91] Elisabetta Patorno 2021 133 39072 31% 1.02 [0.79, 1.31] Elisabetta Patorno 2018 182 55560 3.7% 0.96 [0.78, 1.17] Edisabetta Patorno 2018 182 55560 3.7% 0.96 [0.78, 1.17] Edisabetta Patorno 2021 21 320 8.4% 1.22 [0.97, 1.53] Donna Shu-Han Lin 2022 81 549 119 6886 2.8% 0.68 [0.50, 1.78] Chinstopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.56, 1.27] Chang Hee Kwon 2022 20 2986 99 10691 1.4% 0.73 [0.45, 1.18] Björn Pastemak 2019 259 20983 3.49 0.28 [0.70, 1.10] 4 4 Altonio Gonzalez Perez 2023 81 1811 247 3744 3.2% | Gábor Sütő 2021 | 135 | 18419 | 99 | 18385 | 3.0% | 1.36 [1.05, 1.77] | |
| Elvira D'Andrea 2023 210 60523 220 84091 3.9% 1.33[1.01.60] Elmor D'Ineda 2020 22 1762 21 1762 1.0% 1.05 [0.57, 1.91] Elisabetta Patorno 2021 123 39072 121 39072 3.1% 1.02 [0.79, 1.31] Elisabetta Patorno 2021b 301 45047 277 45047 4.3% 1.09 [0.78, 1.17] Elisabetta Patorno 2022 81 54560 190 55560 3.7% 0.96 [0.78, 1.17] Elisabetta Patorno 2018 182 55560 190 55560 3.7% 0.96 [0.78, 1.17] Elisabetta Patorno 2012 123 81152 87 20288 3.4% 1.22 [0.77, 1.53] Chun-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.86, 1.27] Charging Hee Kwon 2022 96 99 10691 1.4% 0.73 [0.45, 1.18] Earline Vargaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zinman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total (95% CI) 50.002) | Frederik Persson 2018 | 87 | 10227 | 304 | 30681 | 3.3% | 0.86 [0.67, 1.09] | |
| Elmor D Pineda 2020 22 1762 21 1762 1.0% 1.05 [0.57, 1.91] Elisabetta Patorno 2021 123 39072 121 39072 3.1% 1.02 [0.79, 1.31] Elisabetta Patorno 2021b 301 45047 277 45047 4.3% 1.09 [0.92, 1.28] Elisabetta Patorno 2018 182 55560 190 55560 3.7% 0.96 [0.78, 1.17] Edouard L Fu 2022 81 5489 119 6886 2.8% 0.85 [0.64, 1.13] Donna Shu-Han Lin 2022 423 81152 87 20288 3.4% 1.22 [0.97, 1.53] Chur-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.65, 1.27] Christopher P Cannon 2020 330 5499 158 2747 3.8% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 1168 2.747 3.8% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 1168 2.747 3.8% 0.63 [0.50, 0.79] Christopher P Cannon 2020 340 5499 158 2.747 3.8% 0.68 [0.70, 1.10] Esmard Zimman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total events 7415 P = 56.61, df = 32 (P < 0.00001); P = 67% Total evental effect Z = 3.15 (P = 0.002) | Elvira D'Andrea 2023 | 210 | 60523 | 220 | 84091 | 3.9% | 1.33 [1.10, 1.60] | |
| Elisabetta Patorno 2022 123 39072 121 39072 3.1% 1.02 [0.79, 1.31] Elisabetta Patorno 2021b 301 45047 277 45047 4.3% 1.09 [0.92, 1.28] Elisabetta Patorno 2018 182 55560 190 55566 3.7% 0.96 [0.78, 1.17] Edouard L Fu 2022 81 5499 119 6886 2.8% 0.85 [0.64, 1.13] Donna Shu-Han Lin 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 158 2.747 3.8% 1.05 [0.56, 1.27] Chang Hee Kwon 2022 20 2986 99 10691 1.4% 0.73 [0.45, 1.18] Chang Hee Kwon 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zimman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Bernard Zimman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Attonio Gonzalez Perez 2023 83 11811 247 33744 3.2% 1.13 [0.88, 1.45] Attonio Gonzalez Perez 2023 83 11811 247 33744 3.2% 1.13 [0.88, 0.70, 1.99] Total (95% CI) 889129 91369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau" = 0.02; Chi" = 35.61, df = 32 (P < 0.00001); P = 67% Test for overall effect Z = 3.15 (P = 0.002) | Elmor D Pineda 2020 | 22 | 1762 | 21 | 1762 | 1.0% | 1.05 [0.57, 1.91] | |
| Elisabetta Patorno 2021b 301 45047 277 45047 4.3% 1.09 [0.92,1.28] Elisabetta Patorno 2018 182 55560 190 55560 3.7% 0.96 [0.78, 1.17] Elisabetta Patorno 2018 182 55560 190 55560 3.7% 0.96 [0.78, 1.17] Donna Shu-Han Lin 2022 81 5489 119 6886 2.8% 0.85 [0.64, 1.13] Donna Shu-Han Lin 2022 423 81152 87 20288 3.4% 1.22 [0.97, 1.53] Chuin-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 30 5499 158 2.747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 20 2958 99 10681 1.4% 0.73 [0.45, 1.18] Caroline H. Nørgaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zinman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Bernard Zinman 2015 223 4687 126 2333 3.5% 0.98 [0.70, 1.10] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total offer L Z = 3.15 (P = 0.002) | Elisabetta Patorno 2022 | 123 | 39072 | 121 | 39072 | 3.1% | 1.02 [0.79, 1.31] | |
| Elisabetta Patorno 2018 182 55560 190 55560 3.7% 0.96 [0.78, 1.17] Edouard L Fu 2022 81 5489 119 6886 2.8% 0.85 [0.64, 1.13] Donna Shu-Han Lin 2022 423 81152 87 20288 3.4% 1.22 [0.97, 1.53] Chur-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 20 2958 99 10691 1.4% 0.73 [0.45, 1.18] Caroline H. Nørgaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pasternak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Björn Pasternak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Björn Pasternak 2019 259 20983 349 210867 5.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 91369 100.0% 0.90 [0.84, 0.96] Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); P = 67% Total overall effect Z = 3.15 (P = 0.002) | Elisabetta Patorno 2021b | 301 | 45047 | 277 | 45047 | 4.3% | 1.09 [0.92, 1.28] | +- |
| Edouard L Fu 2022 81 5499 119 6886 2.9% 0.85 [0.64, 1.13] Dona Shu-Han Lin 2022 423 81152 87 20288 3.4% 1.22 [0.97, 1.53] Chni-Ting Yang 2022 122 21329 132 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 158 2.747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 20 2988 99 10691 1.4% 0.73 [0.45, 1.18] Craline H, Nørgaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zinman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 33744 3.2% 1.13 [0.88, 1.45] Atexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 35.61, df = 32 (P < 0.00001); P = 67% Test for overall effect Z = 3.15 (P = 0.002) | Elisabetta Patorno 2018 | 182 | 55560 | 190 | 55560 | 3.7% | 0.96 [0.78, 1.17] | + |
| Donna Shu-Han Lin 2022 423 81152 87 20288 3.4% 1.22 [0.97, 1.53] Chun-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 230 5499 1968 2747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 20 2958 99 10691 1.4% 0.73 [0.45, 1.18] Byörn Pasternak 2019 259 2098 349 20983 4.3% 0.74 [0.65, 1.07] Bernard Zimman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Bernard Zimman 2015 223 4687 126 2333 3.5% 0.98 [0.70, 1.10] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^s = 0.02; Chi ^p = 95.61, dfr = 32 (P < 0.00001); P = 67% Test for overall effect Z = 3.15 (P = 0.002) | Edouard L Fu 2022 | 81 | 5489 | 119 | 6886 | 2.8% | 0.85 [0.64, 1.13] | |
| Chun-Ting Yang 2022 122 21329 193 21329 3.4% 0.63 [0.50, 0.79] Christopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.56, 1.27] Christopher P Cannon 2020 2 20 2958 99 10681 1.4% 0.73 [0.45, 1.18] Caroline H. Nørgaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pasternak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Björn Pasternak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Björn Pasternak 2019 259 20983 349 20983 4.3% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Heterogeneity. Tau" = 0.0°; Chi ² = 95.61, df = 32 (P < 0.00001); P = 67% Test for overall effect Z = 3.15 (P = 0.002) | Donna Shu-Han Lin 2022 | 423 | 81152 | 87 | 20288 | 3.4% | 1.22 [0.97, 1.53] | |
| Christopher P Cannon 2020 330 5499 158 2747 3.8% 1.05 [0.86, 1.27] Chang Hee Kwon 2022 20 2958 99 10691 1.4% 0.73 [0.45, 1.18] Caroline H, Nørgaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zinman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Atexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.0; Chi ^p = 95.61, df = 32 (P < 0.00001); P = 67% Test for overall effect Z = 3.15 (P = 0.002) | Chun-Ting Yang 2022 | 122 | 21329 | 193 | 21329 | 3.4% | 0.63 [0.50, 0.79] | |
| Chang Hee Kwon 2022 20 2958 99 10691 1.4% 0.73 [0.45, 1.18] Caroline H. Nørgaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pastemak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Björn Pastemak 2019 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Test for overall effect: Z = 3.15 (P = 0.002) Test for overall effect: Z = 3.15 (P = 0.002) | Christopher P Cannon 2020 | 330 | 5499 | 158 | 2747 | 3.8% | 1.05 [0.86, 1.27] | + |
| Caroline H. Nørgaard 2022 96 5275 193 8913 3.2% 0.84 [0.65, 1.07] Björn Pasternak 2019 259 20983 349 20983 4.3% 0.74 [0.65, 0.87] Björn Pasternak 2019 259 20983 349 20983 4.3% 0.74 [0.65, 0.87] Bernard Zimman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau" = 0.02; Chi ² = 95.61, df = 32 (P < 0.00001); P = 67% Test for overall effect: Z = 3.15 (P = 0.002) | Chang Hee Kwon 2022 | 20 | 2958 | 99 | 10691 | 1.4% | 0.73 [0.45, 1.18] | |
| Björn Pasternak 2019 259 20983 349 20983 4.3% 0.74 [0.63, 0.87] Bernard Zinman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ^a = 0.02; Chi ^a = 95.61, df = 32 (P < 0.00001); i ^a = 67% Test for overall effect Z = 3.15 (P = 0.002) Est for overall effect Z = 3.15 (P = 0.002) | Caroline H. Nørgaard 2022 | 96 | 5275 | 193 | 8913 | 3.2% | 0.84 [0.65, 1.07] | |
| Bernard Zinman 2015 223 4687 126 2333 3.5% 0.88 [0.70, 1.10] Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.93 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Heterogeneity: Tau ² = 0.02; Chi ² = 95.61, df = 32 (P < 0.00001); I ² = 67% 0.90 [0.84, 0.96] Test for overall effect: Z = 3.15 (P = 0.002) 0.0001; I ² = 67% 0.1 0.2 0.5 1 2 5 10 Favours [Klopp-SGI T20] | Björn Pasternak 2019 | 259 | 20983 | 349 | 20983 | 4.3% | 0.74 [0.63, 0.87] | |
| Antonio Gonzalez Perez 2023 83 11811 247 39744 3.2% 1.13 [0.88, 1.45] Alexander Kutz 2023 1712 210067 1849 210067 5.5% 0.33 [0.87, 0.99] Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ² = 0.02; Chi ² = 95.61, df = 32 (P < 0.00001); I ² = 67% Test for overall effect: Z = 3.15 (P = 0.002) Favoure [Non-SGI 72] | Bernard Zinman 2015 | 223 | 4687 | 126 | 2333 | 3.5% | 0.88 [0.70, 1.10] | |
| Alexander Kutz 2023 1712 210067 1849 210067 5.5% $0.93[0.87, 0.99]$ Total (95% CI) 889129 919369 100.0% $0.90[0.84, 0.96]$ Total events 7415 8269 Heterogeneity: Tau ² = 0.02; Chi ² = 95.61, df = 32 ($P < 0.00001$); $P = 67\%$ Test for overall effect Z = 3.15 ($P = 0.002$) Easy our filter function of the second secon | Antonio Gonzalez Perez 2023 | 83 | 11811 | 247 | 39744 | 3.2% | 1.13 [0.88, 1.45] | + |
| Total (95% CI) 889129 919369 100.0% 0.90 [0.84, 0.96] Total events 7415 8269 Heterogeneity: Tau ² = 0.02; Chi ² = 95.61, df = 32 (P < 0.00001); i ² = 67% 0.1 0.2 0.5 2 10 Test for overall effect: Z = 3.15 (P = 0.002) Favours [Non-SGI T2i] Favours [Non-SGI T2i] Favours [Non-SGI T2i] | Alexander Kutz 2023 | 1712 | 210067 | 1849 | 210067 | 5.5% | 0.93 [0.87, 0.99] | + |
| Total events 7415 8269 Heterogeneity: Tau ² = 0.02; Chi ² = 95.61, df = 32 (P < 0.00001); I ² = 67% 0.1 0.2 0.5 1 2 5 10 Test for overall effect: Z = 3.15 (P = 0.002) Favours (Non-SGI T2i) | Total (95% CI) | | 889129 | | 919369 | 100.0% | 0.90 [0.84, 0.96] | • |
| Heterogeneity: Tau ² = 0.02; Chi ² = 95.61, df = 32 (P < 0.00001); I ² = 67% 0.1 0.2 0.5 1 5 10 Test for overall effect: Z = 3.15 (P = 0.002) 0.1 0.2 0.5 1 2 5 10 | Total events | 7415 | | 8269 | | | | |
| 0.1 0.2 0.5 1 2 5 10 Test for overall effect: Z = 3.15 (P = 0.002) Favours ISGI T2il Favours INon-SGI T2il | Heterogeneity: Tau ² = 0.02 ⁻ Chi ³ | *= 95.61 | df = 32 (P | < 0.0000 | 1): $ ^2 = 67$ | '% | | - <u>, , , , , , , , , , , , , , , , , , ,</u> |
| | Test for overall effect: Z = 3.15 (| P = 0.002) | | 0.0000 | .,, | | | 0.1 0.2 0.5 1 2 5 10 Favours [SGLT2i] Favours [Non-SGLT2i] |

| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% CI |
|--|------------|-------------|----------|--------------------|--------|---------------------|-------------------------------------|
| Alexander Kutz 2023 | 1371 | 210067 | 2381 | 210067 | 4.4% | 0.57 [0.54, 0.61] | • |
| Ameenathul Mazaya Fawzy 2023 | 5717 | 119621 | 7887 | 120413 | 4.6% | 0.72 [0.69, 0.74] | • |
| Bernard Zinman 2015 | 126 | 4687 | 95 | 2333 | 2.6% | 0.65 [0.50, 0.85] | |
| Björn Pasternak 2019 | 130 | 20983 | 265 | 20983 | 3.2% | 0.49 [0.39, 0.60] | |
| Caroline H. Nørgaard 2022 | 76 | 5275 | 164 | 8913 | 2.6% | 0.78 [0.59, 1.03] | |
| Chang Hee Kwon 2022 | 58 | 2958 | 404 | 10691 | 2.5% | 0.51 [0.39, 0.67] | |
| Christopher P Cannon 2020 | 139 | 5499 | 99 | 2747 | 2.7% | 0.69 [0.53, 0.90] | |
| Chun-Ting Yang 2022 | 349 | 21329 | 671 | 21329 | 3.9% | 0.51 [0.45, 0.58] | - |
| Donna Shu-Han Lin 2022 | 266 | 81152 | 56 | 20288 | 2.5% | 1.19 [0.89, 1.59] | + |
| Edouard L Fu 2022 | 74 | 5489 | 143 | 6886 | 2.5% | 0.64 [0.49, 0.86] | |
| Elisabetta Patorno 2018 | 262 | 55560 | 426 | 55560 | 3.7% | 0.61 [0.53, 0.72] | - |
| Elisabetta Patorno 2021a | 713 | 186040 | 938 | 186040 | 4.2% | 0.76 [0.69, 0.84] | + |
| Elisabetta Patorno 2021b | 234 | 45047 | 309 | 45047 | 3.5% | 0.76 [0.64, 0.90] | |
| Elisabetta Patorno 2022 | 268 | 39072 | 413 | 39072 | 3.7% | 0.65 (0.55, 0.75) | - |
| Elmor D Pineda 2020 | 77 | 1762 | 97 | 1762 | 2.3% | 0.78 [0.58, 1.07] | |
| Elvira D'Andrea 2023 | 108 | 60523 | 228 | 84091 | 3.0% | 0.66 [0.52, 0.83] | |
| Frederik Persson 2018 | 95 | 10227 | 467 | 30681 | 3.0% | 0.61 [0.49, 0.76] | |
| Gábor Sütő 2021 | 410 | 18003 | 470 | 17902 | 3.9% | 0.86 [0.76, 0.99] | - |
| HoJin Shin 2022 | 111 | 8613 | 326 | 17226 | 3.1% | 0.68 [0.54, 0.84] | |
| Hsin-Fu Lee 2020 | 73 | 11431 | 111 | 11431 | 2.4% | 0.66 [0.49, 0.88] | |
| Hsin-Fu Lee 2023 | 95 | 4110 | 154 | 4110 | 2.7% | 0.61 [0.47, 0.79] | |
| Hui-Jeong Hwang 2023 | 2 | 779 | 6 | 2337 | 0.2% | 1.00 [0.20, 4.96] | |
| Iskandar Idris 2021 | 425 | 28720 | 543 | 28720 | 3.9% | 0.78 [0.69, 0.89] | - |
| Ja Young Jeon 2021 | 289 | 41808 | 400 | 41808 | 3.7% | 0.72 [0.62, 0.84] | - |
| Jayoung Lim 2022 | 9 | 1842 | 40 | 1842 | 0.7% | 0.22 [0.11, 0.46] | |
| Kohei Kaku 2017 | 22 | 1006 | 16 | 511 | 0.8% | 0.69 [0.36, 1.33] | |
| Marta Baviera 2021 | 211 | 17729 | 417 | 17729 | 3.6% | 0.50 [0.42, 0.59] | - |
| Osung Kwon 2023 | 68 | 938 | 166 | 1876 | 2.4% | 0.81 [0.60, 1.08] | |
| Phyo T Htoo 2022 | 1189 | 45706 | 1602 | 45706 | 4.4% | 0.74 [0.68, 0.79] | - |
| Reimar W Thomsen 2021 | 186 | 14148 | 177 | 12628 | 3.2% | 0.94 [0.76, 1.15] | |
| Stephen D Wiviot 2019 | 212 | 8582 | 286 | 8578 | 3.4% | 0.73 [0.61, 0.88] | - |
| Tadarro L Richardson Jr 2023 | 56 | 21170 | 85 | 21170 | 2.1% | 0.66 [0.47, 0.92] | |
| Tien-Hsing Chen 2020 | 7 | 1100 | 503 | 39920 | 0.7% | 0.50 [0.24, 1.06] | |
| Yaa-Hui Dong 2022 | 196 | 13016 | 149 | 13016 | 3.1% | 1.32 [1.07, 1.64] | |
| Ying-Ying Liu 2023 | 6 | 112 | 9 | 112 | 0.4% | 0.65 [0.22, 1.88] | |
| Yi Zhu 2022 | 3 | 141 | 67 | 645 | 0.3% | 0.19 (0.06, 0.61) | |
| Total (95% CI) | | 1114245 | | 1154170 | 100.0% | 0.69 [0.64, 0.74] | • |
| Total events | 13633 | | 20570 | | | | - |
| Heterogeneity: Tau ² = 0.02: Chi ² = | 186.58, df | = 35 (P < 0 | .00001): | ² = 81% | | | |
| Test for overall effect: Z = 11.07 (P | < 0.000011 | | | | | | 0.1 0.2 0.5 1 2 5 10 |
| | | | | | | | Favours (SGL12) Favours (Non-SGL12) |
| | | | | | | | |
| | | | | | | | |

3.3.5 Incidence of all-cause mortality

Among the intervention studies of SGLT2i, 32 studies reported all-cause mortality (10, 13, 14, 16, 18–23, 25–29, 31–33, 35, 36, 38–41, 43, 50–56). As there was substantial heterogeneity (heterozygosity test, $\text{Chi}^2 = 635.84$, P < 0.00001, $I^2 = 95\%$), pooled analyses using the random-effect model was instead which resulted in a favorable pooled effect value of 0.65 (95%CI 0.58 to 0.73, P < 0.00001) for SGLT2i (Figure 8). In summary, SGLT2i could reduce all-cause mortality and improve survival.

3.4 Secondary outcome

3.4.1 Incidence of ischemic stroke

Fourteen studies reported the incidence of ischemic stroke between SGLT2i group and non-SGLT2i group (13, 15–17, 25, 26, 28, 29, 40, 51–55). Firstly, we pooled the OR value from these studies by fixed-effect model, as a result, a significant heterogeneity was found (heterozygosity test, Chi² = 47.65, P<0.00001, I^2 = 73%). Then the random-effect model was instead, and it was found that SGLT2i could not reduce ischemic stroke in patients (OR=0.95, 95%CI 0.87 to 1.05, P=0.32).

3.4.2 Incidence of revascularization

Only six studies reported the incidence of revascularization as an outcome (27, 33, 37, 43, 55, 56). A pooled analysis of outcome events from these studies using the fixed-effect model revealed tremendous heterogeneity of results (heterozygosity test, $\text{Chi}^2 = 23.96$, *P*=0.0002, *I*²

= 79%). When analyzed using the random-effect model, the merged OR value was 0.85 (95%CI 0.65 to 1.11, P=0.23). In conclusion, SGLT2i did not reduce the occurrence of revascularization.

3.4.3 Incidence of acute coronary syndrome

Events of ACS in patients with SGLT2i have been reported in four studies (13, 27, 29, 59). However, a significantly and huge heterogeneity was found by fixed-effect model (heterozygosity test, $\text{Chi}^2 = 19.53$, P=0.0002, $I^2 = 85\%$), then a random-effect model was used and pooled OR value was 0.98(95%CI 0.86 to 1.12, P=0.77). This means that SGLT2i is not beneficial in preventing the development of ACS. Detailed data for the above secondary endpoints are shown in Figure 9.

3.5 Subgroup analyses

3.5.1 Incidence of cardiovascular and cerebrovascular diseases under different interventions

Seven studies analyzed the effect of empagliflozin on cardiovascular and cerebrovascular diseases (20, 23, 27, 32, 39, 42, 43); eight studies analyzed the effect of dapagliflozin on it (27, 36, 40, 41, 46, 47, 49, 60); and only five studies analyzed the effect of canagliflozin on it (33, 44, 45, 48, 59). Appropriate effect models were selected based on the magnitude of heterogeneity. Pooling these studies about different types of SGLT2i revealed that dapagliflozin prevented stroke (OR=0.78, 95%CI 0.63 to 0.98, P=0.03), myocardial infarction

| Church and Carls are as an | SUL | Tetel | Non-S | ULIZI | Maint | Ulus Rallo | Mul Dandam 05% Cl |
|--|------------|-----------|---------|-------------------------|---------|---------------------|---------------------|
| Study of Subgroup | Events | 10001 | Events | 10101 | vveigni | M-H, Kandom, 95% CI | M-H, Random, 95% CI |
| Alexander Kutz 2023 | 2804 | 210067 | 3070 | 210067 | 3.9% | 0.76 [0.72, 0.80] | |
| Ameenathul wazaya Fawzy 2023 | 2/44 | 131188 | 4304 | 131188 | 3.9% | 0.62 [0.59, 0.65] | - |
| Antonio Gonzalez Perez 2023 | 307 | 12978 | 1796 | 44286 | 3.8% | 0.57 [0.51, 0.65] | |
| Bernard Zinman 2015 | 269 | 4687 | 194 | 2333 | 3.0% | 0.67 [0.55, 0.81] | |
| Bjorn Pasternak 2019 | 282 | 20983 | 494 | 20983 | 3.7% | 0.57 [0.49, 0.65] | |
| Chang Hee Kwon 2022 | 58 | 2958 | 471 | 10691 | 3.2% | 0.43 [0.33, 0.57] | |
| Christopher P Cannon 2020 | 473 | 5499 | 254 | 2747 | 3.7% | 0.92 [0.79, 1.08] | |
| Chun-Ting Yang 2022 | 248 | 21329 | 433 | 21329 | 3.7% | 0.57 [0.49, 0.66] | |
| Donna Shu-Han Lin 2022 | 1692 | 81152 | 386 | 20288 | 3.8% | 1.10 [0.98, 1.23] | Г |
| Elisabetta Patorno 2018 | 24 | 55560 | 27 | 55560 | 2.1% | 0.89 [0.51, 1.54] | |
| Elisabetta Patorno 2021b | 310 | 45047 | 293 | 45047 | 3.7% | 1.06 [0.90, 1.24] | Ť |
| Elisabetta Patorno 2022 | 58 | 39072 | 112 | 39072 | 3.1% | 0.52 [0.38, 0.71] | |
| Elvira D'Andrea 2023 | 190 | 60523 | 242 | 84091 | 3.6% | 1.09 [0.90, 1.32] | Ť |
| Frederik Persson 2018 | 120 | 10227 | 644 | 30681 | 3.5% | 0.55 [0.46, 0.67] | + |
| Gábor Sütő 2021 | 287 | 18583 | 333 | 18583 | 3.7% | 0.86 [0.73, 1.01] | - |
| HoJin Shin 2022 | 43 | 8613 | 114 | 17226 | 2.9% | 0.75 [0.53, 1.07] | |
| Hsin-Fu Lee 2020 | 243 | 11431 | 425 | 11431 | 3.7% | 0.56 [0.48, 0.66] | - |
| Hsin-Fu Lee 2023 | 161 | 4110 | 264 | 4110 | 3.5% | 0.59 [0.49, 0.73] | + |
| Hui-Jeong Hwang 2023 | 26 | 779 | 171 | 2337 | 2.6% | 0.44 [0.29, 0.67] | |
| Iskandar Idris 2021 | 367 | 28720 | 516 | 28710 | 3.7% | 0.71 [0.62, 0.81] | + |
| Ja Young Jeon 2021 | 174 | 41808 | 245 | 41808 | 3.5% | 0.71 [0.58, 0.86] | + |
| Jayoung Lim 2022 | 4 | 1842 | 60 | 1842 | 1.0% | 0.06 [0.02, 0.18] | |
| Kohei Kaku 2017 | 41 | 1006 | 32 | 511 | 2.4% | 0.64 [0.40, 1.02] | |
| Marta Baviera 2021 | 353 | 17729 | 829 | 17729 | 3.8% | 0.41 [0.36, 0.47] | - |
| Osung Kwon 2023 | 34 | 938 | 116 | 1876 | 2.7% | 0.57 [0.39, 0.84] | |
| Phyo T Htoo 2022 | 370 | 45706 | 461 | 45706 | 3.7% | 0.80 [0.70, 0.92] | + |
| Reimar W Thomsen 2021 | 234 | 14148 | 234 | 12628 | 3.6% | 0.89 [0.74, 1.07] | - |
| Stephen D Wiviot 2019 | 529 | 8582 | 570 | 8578 | 3.8% | 0.92 [0.82, 1.04] | + |
| Tien-Hsing Chen 2020 | 12 | 1100 | 778 | 39920 | 2.0% | 0.55 [0.31, 0.98] | |
| Wei-Syun Hu 2023 | 1727 | 17588 | 3811 | 17588 | 3.9% | 0.39 [0.37, 0.42] | • |
| Yi Zhu 2022 | 1 | 141 | 9 | 645 | 0.3% | 0.50 [0.06, 4.02] | |
| Young Sang Lyu 2023 | 0 | 186 | 11 | 593 | 0.2% | 0.14 [0.01, 2.32] | |
| Total (95% CI) | | 924280 | | 990184 | 100.0% | 0.65 [0.58, 0.73] | ♦ |
| Total events | 14185 | | 22365 | | | | |
| Heterogeneity: Tau ² = 0.09: Chi ² = | 635.84, df | = 31 (P < | 0.00001 |); I ² = 95% | | - | |
| Test for overall effect: Z = 7.10 (P < | 0.00001) | | | | | (| J.U1 U.1 1 10 100 |

Forest plot of the incidence of all-cause mortality.



(OR=0.83, 95%CI 0.74 to 0.93, P=0.002), heart failure (OR=0.56, 95% CI 0.39 to 0.80, P=0.002), and all-cause mortality (OR=0.50, 95%CI 0.30 to 0.82, P=0.006). At the same time, empagliflozin reduced the incidence of myocardial infarction (OR=0.82, 95%CI 0.73 to 0.91, P=0.0003), heart failure (OR=0.72, 95% CI 0.64 to 0.82, P<0.0001), and all-cause mortality (OR=0.68, 95%CI 0.55 to 0.84, P=0.0004); canagliflozin only had a positive effect on the occurrence of heart failure (OR=0.56, 95%CI 0.39 to 0.80, P=0.002).

Eleven studies reported the therapeutic effects of SGLT2i on cardiovascular and cerebrovascular diseases compared with GLP-1RA. These studies reported four diseases (including stroke, myocardial infarction, heart failure and all-cause mortality) and the details on the occurrence of each disease were provided (15, 17, 20, 28, 30, 33–35, 37, 39, 53). It was found that SGLT2i only had a significant preventive effect on heart failure (OR=0.83, 95%CI 0.74 to 0.93, P=0.002) compared to GLP-1RA.

Four diseases (including stroke, myocardial infarction, heart failure and all-cause mortality) were reported in seventeen studies (10, 18, 20–22, 26, 27, 31–33, 36, 50, 53, 55–58). What a pity, a considerable heterogeneity was found in all four subgroups by the fixed-effect model. Finally, a random-effect model was used and pooled OR value was 0.86 (95%CI 0.75 to 0.99, P=0.04) in the subset of stroke, 0.63 (95%CI 0.56 to 0.70, P<0.00001) in the subset of heart failure, and 0.64 (95%CI 0.57 to 0.72, P<0.00001) in the subset of all-cause mortality.

The details of the above are shown in Table 1. Summarily, in different types of SGLT2i, empagliflozin, dapagliflozin and canagliflozin all reduced the incident rate of heart failure, but only dapagliflozin could reduce the incident rate of stroke. Compared with DPP-4i, SGLT2i had a positive therapeutic effect on stroke, heart failure and all-cause mortality; however, compared with GLP-1RA, it only had a positive impact on heart failure.

TABLE 1 The incidence of cardiovascular and cerebrovascular diseases in different intervention measures.

| Outcomes of | Samp | le size | OR | 95%CI | Р | Hetero | geneity | Model |
|--------------------------|--------------|---------|------|-----------|----------|--------|-----------|--------|
| different interventions | Intervention | Control | | | | I2 (%) | Р | |
| Empagliflozin vs Non-Emp | pagliflozin | | 1 | I | | | | |
| stroke | 96079 | 92718 | 1.06 | 0.94,1.20 | 0.33 | 0 | 0.79 | Fixed |
| Myocardial infarction | 90471 | 87622 | 0.82 | 0.73,0.91 | 0.0003 | 44 | 0.15 | Fixed |
| Heart failure | 105540 | 103013 | 0.72 | 0.64,0.82 | <0.00001 | 52 | 0.07 | Random |
| All-cause mortality | 105540 | 103013 | 0.68 | 0.55,0.84 | 0.0004 | 75 | 0.001 | Random |
| Dapagliflozin vs Non-Dap | agliflozin | | | | | | | |
| stroke | 12561 | 36529 | 0.78 | 0.63,0.98 | 0.03 | 0 | 0.77 | Fixed |
| Myocardial infarction | 20222 | 42344 | 0.83 | 0.74,0.93 | 0.002 | 35 | 0.16 | Fixed |
| Heart failure | 19920 | 42715 | 0.56 | 0.39,0.80 | 0.002 | 66 | 0.02 | Random |
| All-cause mortality | 20393 | 43719 | 0.50 | 0.30,0.82 | 0.006 | 88 | < 0.00001 | Random |
| Canagliflozin vs Non-Can | agliflozin | | | | | | | |
| stroke | 55750 | 55750 | 0.91 | 0.72,1.16 | 0.46 | 0 | 0.83 | Fixed |
| Myocardial infarction | 55756 | 55755 | 0.94 | 0.77,1.15 | 0.54 | 0 | 0.72 | Fixed |
| Heart failure | 55868 | 55867 | 0.62 | 0.53,0.73 | <0.00001 | 0 | 0.98 | Fixed |
| All-cause mortality | 55756 | 55755 | 0.40 | 0.13,1.28 | 0.12 | 67 | 0.05 | Random |
| SGLT2i vs GLP-1RA | | | | | | | | |
| stroke | 107718 | 111356 | 1.09 | 0.97,1.21 | 0.14 | 0 | 0.65 | Fixed |
| Myocardial infarction | 284224 | 228395 | 0.98 | 0.91,1.05 | 0.54 | 19 | 0.28 | Fixed |
| Heart failure | 484412 | 427063 | 0.83 | 0.74,0.93 | 0.002 | 79 | < 0.00001 | Random |
| All-cause mortality | 273645 | 211261 | 1.00 | 0.94,1.05 | 0.90 | 29 | 0.22 | Fixed |
| SGLT2i vs DPP-4i | | | | | | | | |
| stroke | 267650 | 312048 | 0.86 | 0.75,0.99 | 0.04 | 72 | <0.0001 | Random |
| Myocardial infarction | 401444 | 445839 | 0.89 | 0.80,1.00 | 0.04 | 76 | < 0.00001 | Random |
| Heart failure | 419779 | 463700 | 0.63 | 0.56,0.70 | <0.00001 | 84 | < 0.00001 | Random |
| All-cause mortality | 399375 | 443804 | 0.64 | 0.57,0,72 | <0.00001 | 83 | < 0.00001 | Random |

3.5.2 Incidence of cardiovascular and cerebrovascular diseases in different characteristics of patients

Furthermore, fifteen studies explicitly stated whether the subjects had cardiovascular and cerebrovascular diseases or were at other high risk (14, 15, 21, 23, 25, 27, 34, 40, 42, 43, 51, 54–56, 59). Firstly, four outcomes (including stroke, myocardial infarction, heart failure and cardiovascular death) in these studies were analyzed by using the fixed-effect model. However, some significantly and huge heterogeneity were found, then appropriate effect models were selected based on the magnitude of heterogeneity. It was found that SGLT2i demonstrated significant benefits in heart failure (OR=0.72, 95%CI 0.67 to 0.77, P=0.02) in high-risk patients (Table 2).

3.6 Publication bias

Funnel plot was done to show the publication bias and results were shown in Figures 10, 11. Because of the complexity of population characteristics included in the study and the large gaps in sample sizes, some of the graphs show asymmetry; that is, there is publication bias.

4 Discussion

SGLT2i is a new class of insulin-independent drug for type 2 diabetes, which acts highly selectively on renal proximal tubules to block glucose reabsorption and increase the elimination of excess glucose from the body (63). In order to clarify the intervention effect of SGLT2i on cardiovascular and cerebrovascular diseases, researchers have prepared and conducted several clinical trials. EMPA-REG OUTCOME was a multi-center prospective study in which investigators found that the empagliflozin group could significantly reduce the risk of major adverse cardiovascular events in type 2 diabetes patients who were at high risk compared to the placebo

group after following up for mean 3.1 years (23). This finding eventually caused SGLT2i was recommended by the American Diabetes Association and the European Association for the Study of Diabetes for the treatment of high-risk type 2 diabetes patients who suffer from arteriosclerotic cardiovascular disease (64). Current studies have found that SGLT2i does not reduce the incidence of stroke (42), and to some extent, it even increases the risk of ischemic stroke (65). The results of our study showed that SGLT2i does have great advantages in the prevention of cardiovascular and cerebrovascular diseases: SGLT2i could significantly reduce the incidence of myocardial infarction, heart failure, cardiovascular death and all-cause mortality; in subgroup analyses, the risk of heart failure was seen to be decreased by SGLT2i regardless of the type of SGLT2i; furthermore, in high-risk patients, SGLT2i exerted a positive effect in preventing the occurrence of heart failure and cardiovascular death. It was interesting to note that although SGLT2i reduced the risk of stroke compared to DPP-4i, but it had no preventative effect on the occurrence of stroke or ischemic stroke when comparing to non-SGLT2i.

At present, the mechanism of SGLT2i intervention in cardiovascular and cerebrovascular diseases is still being discovered and improved. Hemodynamic optimization and renal effect were thought to be the main two mechanisms (23, 66). Osmotic diuresis by SGLT2i reduces blood volume and cardiac load; in turn, sodium excretion decreases intraglomerular pressure by activating tubuloglomerular feedback (23, 67). On the other hand, SGLT2i has been shown to enhance endothelial cell function by reducing inflammation and oxidative stress (41, 68, 69), thereby improving coronary blood flow and myocardial energy metabolism (70). In contrast, SGLT2i is not as effective for stroke. Hypovolemia and elevated hematocrit from osmotic diuresis may be associated with an increased risk of stroke (42, 43), which seems to be a plausible explanation given that a meta-analysis has found that upright hypotension increases the risk of stroke (71).

GLP-1RA enhances insulin secretion by activating the GLP-1 receptor and inhibits glucagon secretion. It is able to delay gastric emptying and reduce the amount of food intake through central appetite suppression, ultimately achieving the effects of lowering

TABLE 2 The incidence of cardiovascular and cerebrovascular diseases in different characteristics of patients.

| | | | 1 | | | | | | | | | | | |
|---|--------------|---------|------|-----------|-----------|---------------|-----------|--------|--|--|--|--|--|--|
| Outcomes of different popula- | Sample | size | OR | 95% | Р | Heterogeneity | | Model | | | | | | |
| | Intervention | Control | | CI | | 12 (%) | Р | | | | | | | |
| with cardiovascular and cerebrovascular risk factors | | | | | | | | | | | | | | |
| stroke | 27358 | 19403 | 1.00 | 0.88,1.13 | 0.95 | 44 | 0.11 | Fixed | | | | | | |
| Myocardial infarction | 56921 | 60394 | 0.95 | 0.89,1.01 | 0.08 | 0 | 0.63 | Fixed | | | | | | |
| Heart failure | 92160 | 95226 | 0.72 | 0.67,0.77 | < 0.00001 | 17 | 0.29 | Fixed | | | | | | |
| Cardiovascular death | 47298 | 52187 | 0.72 | 0.54,0.95 | 0.02 | 88 | < 0.00001 | Random | | | | | | |
| without cardiovascular and cerebrovascular risk factors | | | | | | | | | | | | | | |
| stroke | 32211 | 32211 | 0.89 | 0.73,1.09 | 0.26 | 0 | 0.87 | Fixed | | | | | | |
| Myocardial infarction | 30369 | 30369 | 0.94 | 0.76,1.17 | 0.58 | 0 | 0.95 | Fixed | | | | | | |
| Heart failure | 165350 | 165350 | 0.73 | 0.47,1.13 | 0.15 | < 0.00001 | 90 | Random | | | | | | |
| Cardiovascular death | 19195 | 19195 | 0.85 | 0.61,1.19 | 0.35 | 0 | 0.62 | Fixed | | | | | | |



FIGURE 10

Funnel plot of publication bias on main and secondary outcomes. (A) Funnel plot of publication bias on stroke; (B) Funnel plot of publication bias on cardiovascular death; (C) Funnel plot of publication bias on myocardial Infarction; (D) Funnel plot of publication bias on heart failure; (E) Funnel plot of publication bias on all-cause mortality; (F) Funnel plot of publication bias on secondary outcomes.



FIGURE 11

Funnel plot of publication bias on subgroup analysis. (A) Funnel plot of publication bias on subgroup analysis of Empagliflozin; (B) Funnel plot of publication bias on subgroup analysis of Empagliflozin Dapagliflozin; (C) Funnel plot of publication bias on subgroup analysis of Canagliflozin; (D) Funnel plot of publication bias on subgroup analysis of SGLT2i VS GLP-1RA; (E) Funnel plot of publication bias on subgroup analysis of SGLT2i VS DPP-4i; (F) Funnel plot of publication bias on subgroup analysis who were at high risk; (G) Funnel plot of publication bias on subgroup analysis who were not at high risk.

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blood glucose and body weight (72). In recent years, with the indepth studies of the drug, researchers have found that in addition to its hypoglycemic and weight-loss effects, it can improve mitochondrial dysfunction, reduce inflammatory mediators and leukocyte-endothelial interactions, which can prevent the onset and progression of atherosclerosis (73). DPP-4i promotes insulin release from pancreatic beta cells by reducing the inactivation of glucagon-producing polypeptide (74). A large number of studies have been conducted on the comparative clinical efficacy of these three classes of drugs, but the conclusions are conflicting (13, 17, 22, 30, 34, 36, 75). In addition, studies have found that empagliflozin improves sympathetic nerve activity and is more favorable for glycemic control and management of cardiometabolic parameters (76, 77); while dapagliflozin shows more benefits in heart failure (78, 79). In previous studies, investigators have found some heterogeneity in outcome comparisons, which depending on the presence of chronic cardiac and renal diseases in patients before inclusion in the study. With the above in mind, this study conducted a number of subgroup analyses to further analyze the clinical effects of SGLT2i from multiple perspectives.

Although a large number of articles have been published on the topic of SGLT2i and cardiovascular diseases, there are some unique aspects of our work. In this study, we added the keyword "stroke" to focus more on the cerebrovascular diseases which are controversial. We included more studies and larger sample than others, and got more results, what is a supplement to the previous meta-analysis. Patients with type 2 diabetes often have multiple comorbidities, such as microvascular disease and renal disease, which has led to high-risk bias when combining statistics. Therefore, researchers should design and carry out trials with high selectivity, high accuracy, rigorous design and large sample size, and conduct in-depth mechanism exploration to provide a more reliable basis for the application of SGLT2i.

The major limitation of this meta-analysis is the complex and diverse population characteristics of the included studies which may induce a racial heterogeneity. Secondly, among the 49 studies, only nine RCTs and the rest trials were cohort studies, this may lead to a reduction in the methodological quality of clinical controlled studies. Furthermore, when analyzing some results, there was a significant heterogeneity and publication bias due to the small number of included studies and the complexity of population characteristics. Therefore, more prospective clinical studies with a larger sample size may strengthen the evidence.

5 Conclusions

In conclusion, our meta-analysis summarized the efficacy of SGLT2i in cardiovascular and cerebrovascular diseases. The incidence of cardiovascular death, myocardial infarction, heart failure and all-cause mortality was reduced with the use of SGLT2i, but no significant preventive effect was seen for the occurrence of stroke, ischemic stroke, acute coronary syndrome and revascularization. Subgroup analyses showed that the different types of SGLT2i reduced the incidence of heart failure, but only dapagliflozin reduced the incident rate of stroke. SGLT2i had a positive preventive effect on the incidence of stroke, heart failure and all-cause mortality compared

to DPP-4i. Furthermore, SGLT2i significantly reduced heart failure and cardiovascular mortality in patients who were at high risk. Further, more studies focusing on the mechanism still needs to be done.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

FW: Data curation, Formal analysis, Software, Visualization, Writing – original draft. CL: Data curation, Formal analysis, Writing – original draft. LC: Data curation, Investigation, Writing – original draft. SG: Data curation, Software, Writing – original draft. JZ: Funding acquisition, Project administration, Supervision, Writing – review & editing. HW: Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1436217/ full#supplementary-material

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