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Role of sodium-glucose cotransporter 2 inhibitors in cardiovascular events in patients with heart failure

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Abstract
Heart failure is a major cause of morbidity and mortality globally, with a significant impact on both patients' quality of life and healthcare costs. Sodium-glucose cotransporter 2 inhibitors (SGLT2-I), initially developed for the treatment of type 2 diabetes mellitus, have attracted particular interest due to their therapeutic potential in patients with heart failure, regardless of the presence of diabetes. This study aims to evaluate the efficacy of antidiabetic drug therapy with SGLT2-I in the treatment of heart failure. Specifically, the question is whether SGLT2-I therapy is more effective than placebo in improving heart failure symptoms, regardless of the presence of type 2 diabetes. The search was conducted in the PubMed database, and the search strategy included "SGLT2-I and cardiac patients". A total of 2580 articles were found. Randomized trials and cohort studies enrolling diabetic and non-diabetic patients diagnosed with heart failure with preserved and reduced ejection fraction were included. 11 studies were included in the meta-analyses, and the total number was 41,472 patients, of which 22,110 were patients treated with SGLT2-I and 19,362 were patients treated with placebo. The duration of follow-up was 9 to 42 months (3.5 years). The results of this meta-analysis indicate that the use of SGLT2-I is associated with a significant improvement in cardiovascular and renal status in heart failure patients with reduced and preserved ejection fraction, with or without type 2 diabetes.

Introduction

Heart failure (HF) is a major cause of morbidity and mortality globally, with a significant impact on both patients' quality of life and healthcare costs. In recent years, health research has identified new classes of drugs that can potentially improve the management of this complex pathology. Among these, sodium-glucose cotransporter 2 inhibitors (SGLT2-I), initially developed for the treatment of type 2 diabetes mellitus (DM), have attracted particular interest in this field due to their therapeutic potential in patients with HF, regardless of the presence of diabetes.[1,2] The main objective of this work is to clarify whether SGLT2-I may represent a new frontier in the therapy of HF, independently of the glycaemic profile of the patients. DM is a metabolic disease caused by a decrease in insulin activity secondary to a decreased availability of this hormone, an impediment to its normal action, or a combination of these two factors. Long term DM causes complications such as macroangiopathy,[3] that is, an early and serious atherosclerosis of the large vessels which is not specific to diabetic disease, and microangiopathy, characterized by alterations of the microcirculation in particular anatomical areas such as the retina, kidney and nerves and which instead turns out to be specific to diabetic disease. HF, also called cardiac insufficiency, is a pathology that determine the symptoms, clinical signs and complications of HF such as peripheral hypoperfusion, secondary to a cardiac output inadequate to the metabolic needs of the organism and venous congestion, secondary to the attempt of the organism to maintain an adequate cardiac output, exploiting the preload reserve, thus increasing the filling of the ventricles in diastole.[4] Dyspnea is the cardinal symptom of HF. Dyspnea results from pulmonary congestion that, due to interstitial edema, reduces the distensibility of the lungs. Pulmonary edema occurs in the advanced stages of HF, when interstitial edema progresses to alveolar edema. In this case, symptoms such as cough with frothy and sometimes pink sputum, hypoxia, tachypnea, and severe hypercapnia up to periodic Cheyne-Stokes breathing are added. Patients with diabetes have a significantly increased risk of developing HF, and, conversely, HF can lead to the onset of new cases of diabetes, especially type 2 diabetes.[4]

The primary aim of this study is to investigate the efficacy and the safety of SGLT2-I in patients with HF, regardless of the presence of a diabetic disorder. This study seeks to determine if SGLT2-I therapy is more effective than placebo to improve HF outcomes, such as cardiovascular mortality, hospitalization rates, and renal function.

Methods

Through a systematic review of the scientific literature and quantitative analysis of data from randomized clinical trials, we intend to provide a comprehensive and updated assessment of the impact of these drugs on the prognosis of patients with HF. This study aims to evaluate the efficacy of antidiabetic drug therapy with SGLT2-I in the treatment of HF. Specifically, the question is whether SGLT2-I therapy is more effective than placebo in improving the symptoms of HF, regardless of the presence of type 2 DM. Randomized trials and cohort studies enrolling diabetic patients diagnosed with HF with preserved ejection fraction and with reduced ejection fraction, as well as studies with non-diabetic patients with preserved and reduced ejection fraction, were included. We conducted a systematic review of the literature following the PRISMA Guidelines for systematic review and meta-analysis (Figure 1). The search was conducted in the PubMed database, and the search strategy included "SGLT2-I and cardiac patients". A total of 2580 articles were found, of which duplicates, studies without a control group, and all those that did not meet the inclusion criteria chosen for the study were excluded. Based on the inclusion and exclusion criteria, 11 studies were finally selected and chosen.

The criteria used for patient selection are the following. Inclusion criteria: i) age greater than 18 years; ii) HF under treatment; iii) presence or absence of type 2 DM; iv) presence of a placebo comparison cohort. Exclusion criteria: i) age under 18 years; ii) pregnancy and

breastfeeding; iii) patients with life expectancy less than 6 months; iv) symptoms of hypotension (systolic pressure <95mmHg); v) type 1 diabetes; vi) SGLT2-I intolerance; vii) estimated glomerular filtration rate (eGFR)<30

Statistical analysis

The data were analyzed using MedCalc version 23 (Ostend, Belgium). A meta-analysis of proportions was performed, listing the proportions (expressed as percentages) with their 95% confidence intervals (CI) found in each individual study included in the meta-analysis. The results of the individual studies, with their 95% CI, and the pooled proportions with 95% CI are shown in a forest plot. The size of each marker is relative to the weight of the study; p-values were as follows:

- p-value for cardiovascular mortality reduction: $p<0.001$, indicating a highly significant effect.
- p-value for hospitalization risk reduction: $p=0.002$, confirming a clinically relevant benefit.
- p-value for renal function protection: $p=0.005$, demonstrating a significant protective effect against renal function decline.

Study outcomes

1) Reduction in cardiovascular mortality: studies of this work show that SGLT2-I therapy was associated with a significant reduction in cardiovascular mortality.
2) Lower rates of HF hospitalization: individuals treated with SGLT2-I had lower hospital admission rates for HF exacerbations compared to placebo.
3) Improved renal outcomes: SGLT2-I improve the eGFR, delaying renal disease progression in HF patients.

Ethical committee

Ethics approval is not applicable to this paper. Systematic reviews of experimental clinical research on humans should also include information on the ethical standards of the trials. Therefore, all the studies taken into consideration in this meta-analysis have Ethics Committee approval as follows:

- Packer *et al*.: ethics approval was obtained at each study site, and all patients provided informed consent to participate in the study; the registration identifier at ClinicalTrials.gov is NCT03057977.
- Anker *et al*.: the ethics committee at each center approved the trial, and all patients provided written informed consent.
- Solomon *et al.*: the trial protocol was approved by a local or central institutional review board at each trial centre. All the patients provided written informed consent.
- Charaya *et al*.: this study involves human participants and was approved by the local ethics committee of the Sechenov First Moscow State Medical University of the Ministry of Health of Russia (Sechenov University), extract from Protocol No. 33- 20. Participants gave informed consent to participate in the study before taking part.
- Voors *et al*.: the ethics committee of each of the 118 sites in 15 countries approved the protocol, and all patients gave written informed consent.
- Bhatt *et al*.: the protocol was approved by the relevant health authority, institutional review board, or ethics committee at each participating site. An independent data and safety monitoring board oversaw the trial.
- Damman *et al*.: the trial was approved by the ethics committee at each study center, and the study was conducted following the Declaration of Helsinki and the International

Conference on Harmonisation Guidelines for Good Clinical Practice. All participating patients provided written informed consent.

- Petrie *et al*.: the trial was approved by the ethics committee at each study site, and all patients provided written informed consent. The trial was reviewed by an independent data monitoring committee.
- Peikert *et al*.: the protocol was approved by institutional review boards or ethics committees at each individual study site, and each patient provided written informed consent.
- Cannon *et al*.: the protocol (available with the full text of this article at NEJM.org) was approved by the relevant regulatory authorities and ethics committees responsible for each trial site.
- Mc Murray *et al*.: all participants provided written informed consent, and the trial was approved by an ethics committee at each site.

Results

Overall, 11 randomized controlled trials have been analyzed, encompassing a total of 41,472 patients. Among these, 22,110 patients received SGLT2-I while 19,362 patients were assigned to the placebo group (Table 1). The duration of follow-up ranged from 9 to 42 months, allowing for a comprehensive assessment of both short- and long-term effects of SGLT2-I therapy in HF patients. At first, this study confirms that SGLT2-I therapy is associated with many clinical benefits in cardiac patients, regardless of the presence of a diabetic disease. In particular, the results demonstrate a reduction in cardiovascular mortality, a decrease in HF-related hospitalizations, and improved renal function preservation.

Main findings

Reduction in heart failure hospitalizations

The incidence of hospitalizations due to worsening HF was also significantly lower in the SGLT2-I group ($p=0.002$) (Figure 2). This proves the potential role of these drugs in stabilizing HF patients and preventing acute decompensation episodes, and the mechanism is linked to the osmotic diuresis and natriuresis (without excessive electrolyte loss) that reduce preload and afterload. This improves hemodynamic status and decreases congestion.

Renal function preservation

SGLT2-I therapy was associated with a significant slowing of renal function decline, as indicated by a lower incidence of eGFR reduction and albuminuria progression ($p=0.005$) (Figure 2). This renal protective effect is particularly important in HF patients, who are often at high risk of developing cardiorenal syndrome, and it is due to the reduction of intraglomerular hypertension and the prevention of hyperfiltration.

Adverse events

The presence of no significant adverse events among the SGLT2-I group compared with placebo, reporting mild and rare adverse effects such as urinary infections, was observed (Figure 3).

Cardiovascular mortality reduction

SGLT2-I-treated patients showed a statistically significant reduction in cardiac mortality compared to placebo ($p<0.001$) (Figure 4). This result aligns with previous large-scale trials, as DAPA-HF and EMPEROR-Reduced, which demonstrated how dapagliflozin and empagliflozin improved the risk of cardiovascular death.[2,7] This benefit is shown independently

of diabetes status, suggesting that SGLT2-I exerts cardioprotective effects beyond glycemic control.[8]

Reduction in major cardiac events
A reduction in major cardiac events was observed in the SGLT2-I group compared with placebo (Figure 5).

Benefit across different heart failure phenotypes
A subgroup analysis revealed that patients with HF with reduced ejection fraction (HFrEF) experienced a more pronounced improvement compared to those with HF with preserved ejection fraction (HFpEF) (Figure 6). However, even in the HFpRF group, SGLT2-I therapy was associated with better clinical outcomes, proving the hypothesis that these drugs provide benefits not only the ejection fraction improvement, but also through mechanisms related to anti-inflammatory, antifibrotic, and metabolic adaptations.

Discussion
The results of our meta-analysis strongly reinforce the growing evidence supporting the use of SGLT2-I in HF patients, regardless of the presence of diabetic status.[5]
SGLT2-I have a different mechanism of action those other conventional diuretics, that is more physiological than loop diuretics, which promote rapid sodium and fluid loss, causing electrolyte imbalances and neurohormonal activation. SGLT2-I promote osmotic diuresis and natriuresis, resulting in preload and afterload reduction while preserving hemodynamic stability. Moreover, SGLT2-I improves myocardial metabolism, enhancing ketone utilization from cardiac myocytes, ameliorating myocardial function and efficiency.[5]
Recent trials, such as DAPA-HF and EMPEROR-Reduced, have demonstrated how dapagliflozin and empagliflozin significantly reduce cardiovascular mortality and hospitalization rates in patients with HFrEF.[6] Our study not only confirms these benefits, but also extends these findings, because we demonstrate how these drugs can be used successfully in patients with HF but without diabetes, suggesting a broader cardiovascular protective effect.[7]
These drugs, originally introduced for glycemic control in type 2 DM, have emerged as a fundamental therapeutic option in cardiovascular medicine because of their consistent benefit across a wide range of patients, including those with HFrEF and HFpEF with or without type 2 DM.[2,8,9]
This suggests a pathophysiological role that goes far beyond glucose modulation: unlike traditional diuretics, SGLT2-I allows to get hemodynamic benefits without excessive electrolyte loss.[10] Mechanisms of benefit are: i) metabolic effects – SGLT2-I promote ketone metabolism, which enhances myocardial health; ii) hemodynamic effects – SGLT2-I improve natriuresis,[11] reducing intravascular volume, which leads to reducing preload and afterload without triggering neurohormonal activation or significant electrolyte disturbances; iii) renal protection – SGLT2-I avoid hyperfiltration, which induces nephropathy.[12]
More intriguingly, these drugs offer metabolic and anti-inflammatory benefits that appear to directly impact myocardial health. SGLT2-I enhance ketone body utilization by cardiac cells, providing a more efficient energy substrate in failing hearts. They also reduce myocardial fibrosis and ventricular stiffness,[13] key drivers of diastolic dysfunction in HFpEF, highlighting their therapeutic value even in forms of HF traditionally resistant to conventional therapy.

Renal protection and hemodynamic benefits
Another important finding of this meta-analysis is the significant renal protective effect of SGLT2-I. We demonstrate how these drugs slow down the progression of chronic kidney disease in cardiopathic patients by reducing hyperfiltration, intraglomerular hypertension, and

albuminuria. This is a very important achievement for cardiac patients to avoid cardiorenal syndrome.[14]

Clinical implications

The fact that these drugs are beneficial for both patients (diabetic and non-diabetic cardiopathic individuals) suggests the importance of extending the guidelines recommendations, including the use of these drugs in all eligible cardiopathic patients. Based on our results, future studies should focus on optimal treatment combinations and the interaction of SGLT2-I with other HF pharmacotherapies, as angiotensin receptor-neprilysin inhibitors (ARNIs), β-blockers, and mineralocorticoid receptor antagonists (MRAs). Most randomized controlled trials focused on short-to-medium term outcomes, the heterogeneity in follow-up duration, patients' characteristics, and endpoints suggests the need to determine the long-term benefits and potential risks linked to prolonged SGLT2-I use. Future research should aim to identify biomarkers able to predict individual patient responses to SGLT2-I to create personalized treatment strategies.

Conclusions

This meta-analysis supports the use of SGLT2-I in the therapy of HF, despite the presence of a diabetic disorder. The evidence shows how SGLT2-I ameliorate cardiovascular and renal health in a safe and well-tolerated way, and this is why SGLT2-I should be included in the guidelines' recommendations for all eligible patient populations. Moreover, while short- and medium-term benefits are well established, further research is needed to confirm the durability of these outcomes over longer periods and to determine optimal treatment combinations with other HF medications such as ARNIs, MRAs, and β-blockers. Future studies should also focus on identifying biomarkers of therapeutic response, allowing for more personalized treatment strategies.

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Table 1. Main characteristics of the studies included in the meta-analyses.

Study	Year	Authors	N of patients
Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction	2021	Milton *et al.*	3730
Empagliflozin in heart failure with a preserved ejection fraction	2021	Anker *et al.*	5988
Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction	2022	Solomon *et al.*	6263
Impact of dapagliflozin treatment on renal function and diuretics use in acute heart failure: a pilot study	2022	Charaya *et al.*	102
The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial	2022	Adriaan *et al.*	530
Sotagliflozin in patients with diabetes and recent worsening heart failure	2020	Bhatt *et al.*	1222
Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure	2019	Dammam *et al.*	80
Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes	2020	Petrie *et al.*	4744
Efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to age: the DELIVER trial	2020	Peikert *et al.*	6263
Cardiovascular outcomes with ertugliflozin in type 2 diabetes	2020	Cannon *et al.*	8246
Effects of dapagliflozin in patients with kidney disease, with and without heart failure	2021	McMurray *et al.*	4304

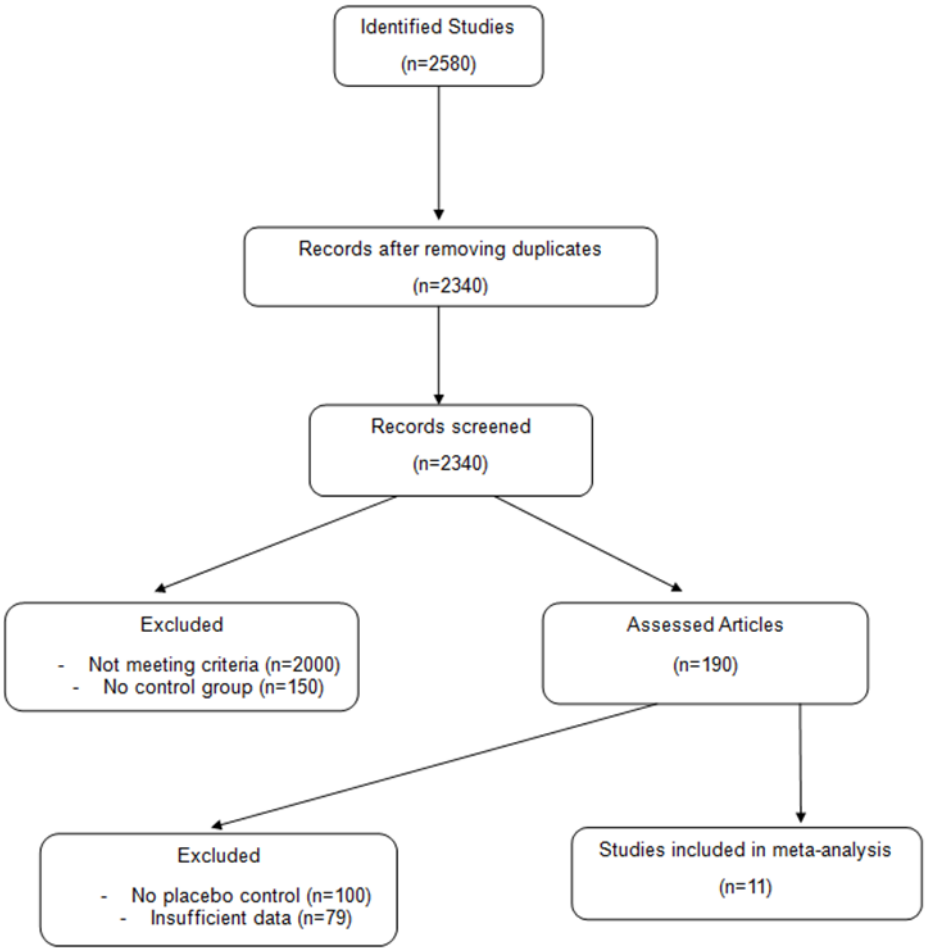

Figure 1. Flow-chart of the study selection in the meta-analyses.

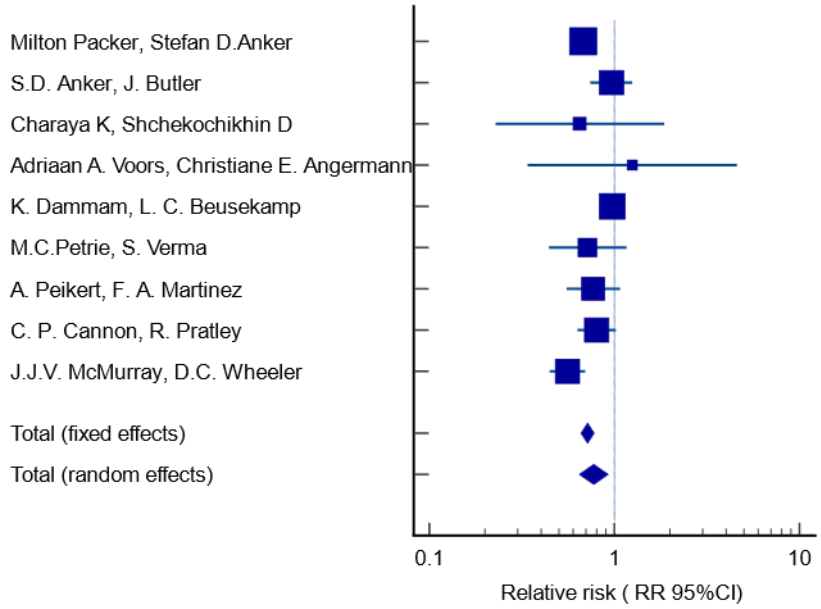

Figure 2. Relative risk of minor cardiovascular events from sodium-glucose cotransporter 2 inhibitor use *vs.* placebo (marker size relative to study weight). CI, confidence interval.

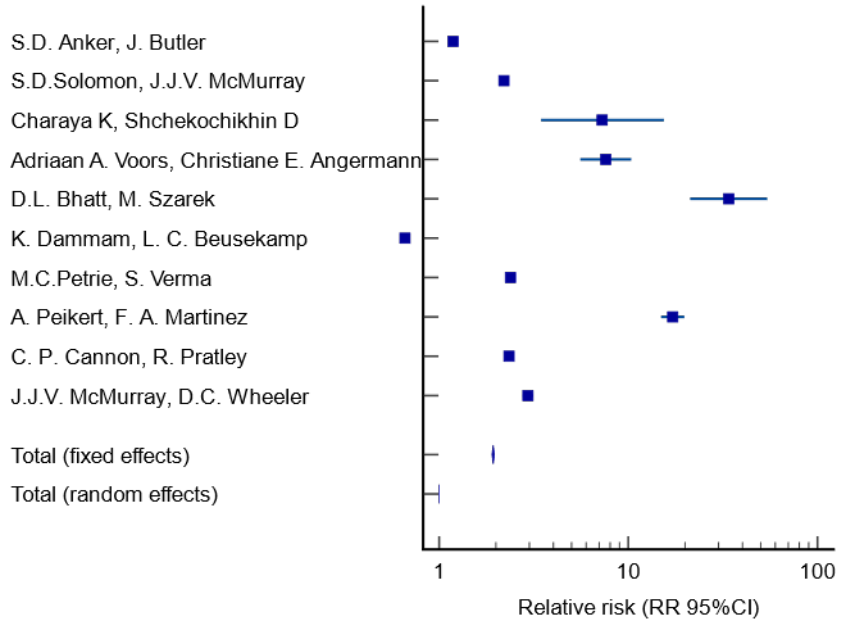

Figure 3. Forest plot. Relative risk of adverse events from placebo *vs.* sodium-glucose cotransporter 2 inhibitor use. CI, confidence interval.

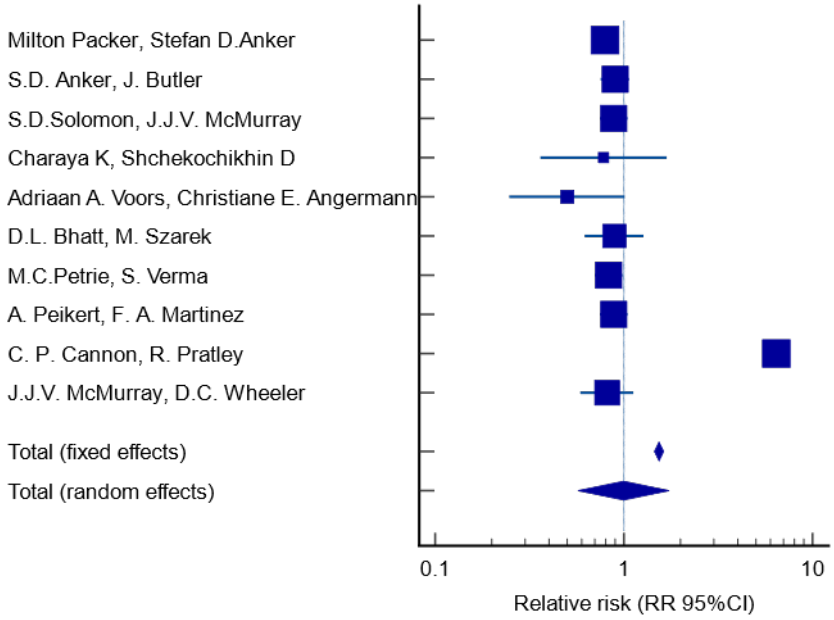

Figure 4. Forest plot. Relative risk of death from sodium-glucose cotransporter 2 inhibitor use *vs.* placebo (marker size relative to study weight). CI, confidence interval.

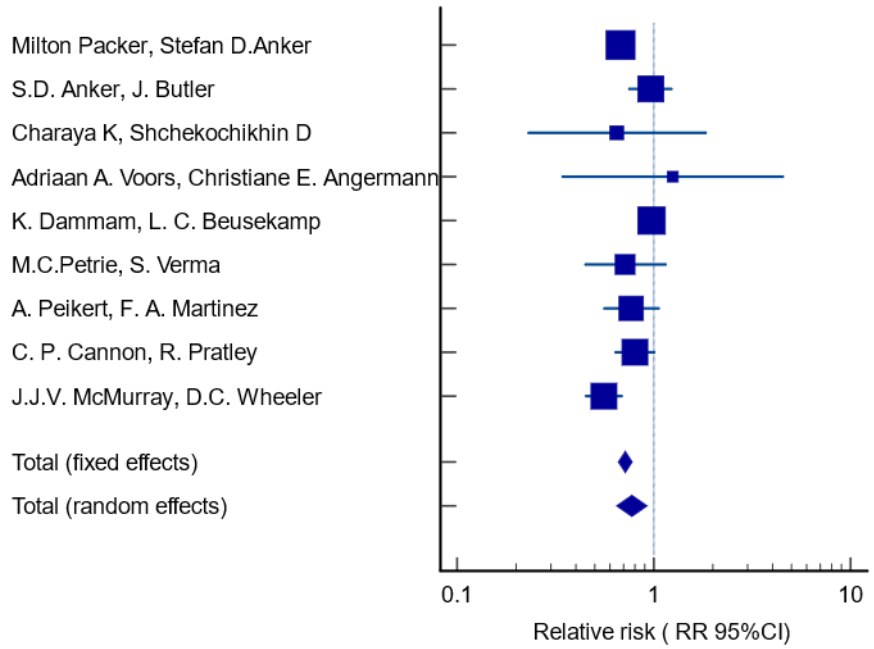

Figure 5. Forest plot. Relative risk of major cardiovascular events from sodium-glucose cotransporter 2 inhibitor use (marker size relative to study weight). CI, confidence interval.

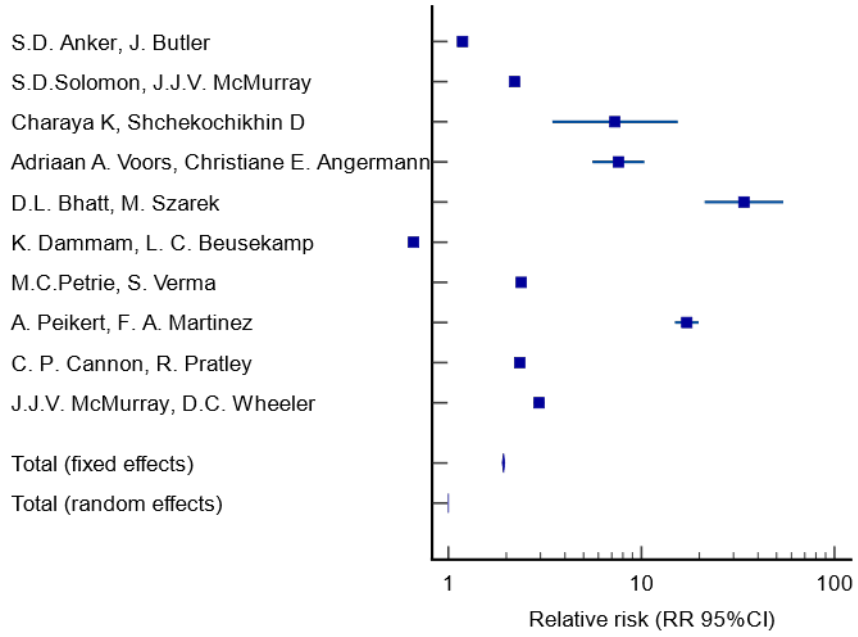

Figure 6. Forest plot. Relative risk of major cardiovascular events from sodium-glucose cotransporter 2 inhibitor use. CI, confidence interval.