The aim of this mixed treatment comparison (MTC) meta-analysis was to determine glucagon like peptide-1 (GLP-1) receptor agonists’ effects on cardiovascular (CV) outcomes in patients with type 2 diabetes (T2DM).

Methods
A comprehensive, systematic review was conducted using EMBASE and Medline databases. All included trials were large CV outcome trials of GLP-1 agonists versus placebo in T2DM. The primary outcomes of this MTC meta-analysis were death from CV causes, non-fatal MI, and non-fatal stroke. Hospitalisation for heart failure (HF) was evaluated as a secondary endpoint.

Results
A total of four trials, including 33,457 patients, met eligibility criteria and were retained for the meta-analysis. Our pairwise meta-analysis results showed a 13% reduction in death from cardiovascular causes in patients who received GLP-1 agonists versus placebo (RR 0.87, 95% CI: 0.78–0.96). However, no statistically significant reduction was observed with GLP-1 agonists in terms of reducing non-fatal MI (RR 0.95, 95% CI: 0.86–1.04), non-fatal stroke events (RR 0.89, 95% CI: 0.76–1.03), and rates of HF hospitalisation (RR 0.94, 95% CI: 0.84–1.04). The network meta-analysis (NMA) showed no significant differences among all the interventions.

Conclusion
Glucagon like peptide-1 therapy was associated with a significant reduction in cardiovascular (CV) death. However, GLP-1 agonists seem to have a safety profile comparable to placebo in terms of reducing non-fatal myocardial infarction (MI), non-fatal stroke events, and rates of HF hospitalisation.

Keywords
Glucagon like peptide-1 receptor • Cardiovascular disease • Diabetes mellitus • Type 2 • Meta-analysis • Network Meta-analysis • Myocardial infarction
Introduction

According to the World Health Organization (WHO), approximately 422 million people worldwide had diabetes in 2014 [1]. From 1980 to 2014, the global prevalence of diabetes among adults, ages 18 years of age and older, has increased from 4.7% to 8.4%. In 2012, 1.5 million diabetes-related deaths occurred globally. Elevated blood glucose levels contributed to an additional 2.2 million deaths due to increased cardiovascular (CV) risk and other diseases. Moreover, adults with diabetes historically have a two or three times higher rate of CV disease than adults without diabetes [1].

Landmark clinical trials established that intensive glycemic management in patients with type 2 diabetes (T2DM) resulted in a significant reduction in microvascular complications [2]; however, its effects are less certain with macrovascular complications. In fact, very intensive glycemic control might be associated with increased CV mortality [3]. Moreover, the CV safety of some medications is at question, as in the case of rosiglitazone [4]. Thus, the US Food and Drug Administration (FDA) mandated that CV risk must be assessed in every new antidiabetic medication for the treatment of T2DM [4].

Several clinical trials have addressed the effect of antidiabetic medication use and CV outcomes. The reduction in CV events was observed with two sodium glucose cotransporter 2 (SGLT-2) inhibitors, namely, canagliflozin and dapagliflozin [5,6]. Similarly, a reduction in CV events was seen with glucagon like peptide-1 (GLP-1) agonists liraglutide and semaglutide but not with lixisenatide [7–9]. Another incretin-based drug class failed to show cardiovascular disease (CVD) benefits as in the case with saxagliptin, alogliptin, and sitagliptin [10–12].

The Exenatide Study of Cardiovascular Event Lowering (EXCEL) was recently published [13]. The trial assessed the CV safety and efficacy of a once-weekly, extended-release formulation of exenatide. To our knowledge, this is the first mixed treatment comparison (MTC) meta-analysis that included the results of the EXCEL. Thus, we here present a systematic review and an MTC meta-analysis of major randomised clinical trials to determine GLP-1 receptor agonists’ effects on CV outcomes in patients with T2DM.

Methods

This MTC meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-NMA) [14].

Literature Search

A comprehensive, systematic review was conducted using EMBASE and Medline databases (up to September 2017). Keywords were GLP-1 receptor agonist, liraglutide, exenatide, lixisenatide, albiglutide, dulaglutide, semaglutide, cardiovascular disease, cardiovascular outcome, cardiovascular death, randomized controlled trials, and type 2 diabetes. Key articles were cross-referenced for additional citations. Language was limited to the English language.

Inclusion Criteria

Studies were included in the MTC meta-analysis if they were (1) randomised clinical trials and (2) evaluated the effects of one of the GLP-1 agonists versus placebo on CV outcomes as their primary endpoint. Studies were excluded if they were non-randomised controlled trials, evaluated the effects of antidiabetic classes other than GLP-1 agonists or if they reported the effects of GLP-1 agonists on CV outcomes as secondary endpoints (Figure 1). Titles, abstracts, and full text reports were screened and reviewed by two authors (O.A. and O.A.) for inclusion. Disagreements were resolved by joint review and consensus with an escalation clause for a third author (M.A.) to mediate unresolved issues.

Data Extraction and Risk of Bias Assessment

All potentially relevant citations were reviewed by two independent reviewers (O.A. and R.A.). The data from the included studies were abstracted, and each reviewer cross-checked all the abstracted data for accuracy. The Cochrane risk of bias tool was used to assess the risk of bias for the included randomised controlled trials. Publication bias was not assessed due to the small number of included studies.

Outcome Measures

The primary outcomes of this MTC meta-analysis were death from CV causes, non-fatal myocardial infarction (MI), and non-fatal stroke. Hospitalisation for heart failure was evaluated as a secondary endpoint.

Data Synthesis and Analysis

For the pairwise meta-analysis, the Mantel–Haenszel (MH) random-effects model risk ratio (RR) and corresponding 95% CIs were calculated using the meta routine in Stata software (version 14.2, StataCorp LLC, College Station, TX, USA) to estimate the pooled treatment effects. Heterogeneity was assessed by using I² statistic. I² values <25 were defined as low, I² values between 25 and 50 as moderate, and I² > 75% as high-level heterogeneity. For the network meta-analysis (NMA), the Aggregate Data Drug Information System (ADDIS) software, v.1.16.6, was used to build Markov chain Monte Carlo simulation [15]. Consistency and inconsistency models were used to assess to which extent the results are consistent [16,17]. Random-effect variance and inconsistency variance were also evaluated to examine whether inconsistency is present among the included trials [16,17]. The consistency model was used to report the results of the outcomes of interest if there is no evidence of inconsistency across all the included trials. The models were based on 100,000 iterations for each four chains with a burn-in period of the first 20,000 iterations for each endpoint. The results of the NMA were reported as odds ratios (ORs) with 95% credible intervals (CrIs). GLP-1 agonists were also...
ranked for each endpoint on the basis of their probabilities reported by the ADDIS.

**Results**

A total of 202 publications were identified and reviewed, of which 198 were excluded based on study design, study population, duplication, and/or relevance to the research question (Figure 1). A total of four trials, including 33,457 patients, met the eligibility criteria and were retained for the MTC meta-analysis (Figure 2). The major summary of the included studies is given in Table 1. The baseline characteristics of enrolled patients are given in Table 2. The results of the risk bias assessment of the included trials are summarised in Supplementary Table 1.

**Summary of the Included Studies**

The EXSCEL study was a pragmatic trial, making it closer to real-world practice compared than the other studies [13]. It included a wide range of cardiovascular disease (CVD) patients with no age limit. The design was to allow 70% of the enrolled patients to have a previous CV event and 30% to have had no prior CVD. A total of 14,752 patients were enrolled, making it the largest trial to date that evaluated CV outcomes of one of the GLP-1 agonists. The median follow-up was 3.2 years, and the mean age was 62 years. At baseline, the median HbA1c was 8%, whereas the median duration of diabetes was 12 years, and 16.2% of patients had heart failure (HF). In this study, the use of another incretin therapy was allowed. At baseline, 14.9% of patients were receiving a dipeptidyl peptidase-4 (DPP-4) inhibitor [13].

The preapproval trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (SUSTAIN-6) enrolled a total of 3297 patients [8]. The study design allowed randomisation to two doses of once-weekly semaglutide (0.5 mg or 1.0 mg) versus placebo. Eligible patients were 50 years or older with T2DM and established CVD, HF, and chronic kidney disease (CKD) or aged 60 or older with subclinical CVD. About 83% of the enrolled subjects had an existent CVD. At baseline, this study had the oldest population compared to other trials, with a mean age of 64.6 years, the longest duration of diabetes at baseline (mean = 13.9 years), and the highest usage of insulin (58%), and more patients with HF (23.6%).

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**Fig. 1** Trial identification and inclusion.

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The liraglutide effect and action in diabetes evaluation of cardiovascular outcome results (LEADER) trial enrolled 9340 patients at high risk for CV events [7]. Patients enrolled had to be ≥50 years old with HbA1c of ≥7% and prior CVD, with renal dysfunction or peripheral vascular disease (PVD) or CHF. Also included were patients aged 60 years without CVD and at least one CV risk factor. About 81% of the enrolled patients had a CVD. The median follow-up was 3.8 years. The mean age of enrolled patients and body mass index (BMI) were similar to the EXSCEL. Mean duration of diabetes was 12.9 years, and mean HbA1c was 8.7%. Moreover, the study included the highest usage of sulfonylureas (SUs) (50.8%) at baseline.

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial involved a total of 6068 subjects [9]. This study included patients 30 years or older with acute coronary artery event within 180 days prior to screening. ELIXA is the only study of the four in which all subjects had an existing CVD. Similar to LEADER, the study included a placebo run in the period prior to randomisation. The median follow-up was 2.1 years, and the mean age of subjects was 60.3 years. Compared to other studies, ELIXA included patients with the shortest duration of diabetes (mean = 9.3 years) and lower mean HbA1c 7.7%, lower mean BMI 30.2, and lower usage of insulin, SU, and metformin at baseline (39.1%, 33%, and 66.3%, respectively). As expected, given only secondary prevention, patients included in ELIXA had the highest usage of statins, angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARBs), and aspirin at baseline (92.7%, 84.9%, and 94.4%, respectively) [9].

Three components of MACE-3 (major adverse cardiac events), cardiovascular death, non-fatal MI, and non-fatal stroke, were the primary outcome of all the included studies. The ELIXA trial had a fourth component of hospitalisation for unstable angina (UA) [9]. The EXSCEL met its primary endpoint of non-inferiority for MACE (HR, 0.91; 95% CI: 0.83–1.00; p < 0.00) [13]. SUSTAIN-6 also showed that semaglutide is not inferior to placebo for MACE (HR 0.74; 95% CI: 0.68–0.80, p = 0.001) [8]. The LEADER trial, on the other hand, met its primary endpoint of non-inferiority for MACE and showed superiority (HR 0.87, 95% CI: 0.78–0.97, p < 0.01) [7]. Lastly, ELIXA met its primary endpoint of non-inferiority for MACE-4 but not superiority (HR1.02; 95% CI: 0.89–1.17, p < 0.001 for non-inferiority) [9].

Hospitalisation for HF was addressed as a secondary endpoint in all four trials. In the EXSCEL, the number of events was 219 in exenatide versus 231 in the placebo group (HR, 0.94; 95% CI: 0.78–1.13) [13]. No significant difference in the rate of hospitalisation for HF was observed in SUSTAIN-6 trial (HR 1.11; 95% CI: 0.77–1.61, p = 0.57) [8].

Death From Cardiovascular Causes

The pairwise meta-analysis showed a 13% reduction in death from cardiovascular causes in patients who received GLP-1 agonists versus those who received placebo (RR 0.87, 95% CI: 0.78–0.96; I² = 0%, p = 0.59) (Figure 3). The NMA showed no differences among all the interventions, with liraglutide the preferred agent (53%) followed by semaglutide (18%). (Supplementary Table 2 and Figure 1)

Non-Fatal MI

The pairwise meta-analysis showed no significant reduction in non-fatal MI events between the two groups (RR 0.95, 95% CI: 0.86–1.04, I² = 19.5%, p = 0.29) (Figure 3). Similar to the pairwise meta-analysis, the NMA results showed no reduction in non-fatal MI events with semaglutide as the preferred agent (66%), followed by liraglutide (19%). (Supplementary Table 2 and Figure 2)

Non-Fatal Stroke

Similar to non-fatal MI, the pairwise meta-analysis was notable to detect differences across all the interventions (RR 0.89, 95% CI: 0.76–1.03, I² = 15.8%, p = 0.31) (Figure 3). The NMA also failed to detect any differences among all the GLP-1 agonists with semaglutide as the preferred agent (70%), followed by exenatide (13%). (Supplementary Table 2 and Figure 3)

Hospitalisation for Heart Failure

In the pairwise meta-analysis, none of the evaluated GLP-1 agonists showed a beneficial reduction in the rates of hospitalisation for heart failure (RR 0.94, 95% CI: 0.84–1.04, I² = 0%, p = 0.740; Figure 3). The NMA findings were also consistent with those reported by the pairwise meta-analysis with liraglutide as the preferred agent (46%) followed by lixisenatide (23%). (Supplementary Table 2 and Figure 4)

Discussion

The FDA mandates that CV safety must be assessed in any new medication used for the management of T2DM [4]. Few large, completed GLP-1 agonist trials showed different results. Some studies have shown comparable CV event reduction to placebo, whereas the LEADER trial, for example, demonstrated CV benefit [7–9]. The objective of our meta-analysis is to determine the CV safety of GLP-1 agonists in large, randomised clinical trials.

GLP-1 agonists as a class have shown positive effect on body weight, blood pressure (BP), and HbA1c [18–20]. Overall, it is
In addition to favourable effects, clinical trials have raised a concern about elevated heart rate (HR) associated with this class [19,20]. This was found to be consistent with all GLP-1 agonists (although the magnitude differed) and thus considered more of a class effect [19]. The exact mechanism of such increase is unknown; however, despite that increase in HR, safety did not find an increased risk of CV mortality when compared to placebo at least in the trial populations under controlled conditions. Whether such an increase would be evidence of a negative effect on a specific group of patients (such as CHF) is yet to be determined.

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**Table 1  Summary of the studies included in the meta-analysis.**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Settings</td>
<td>Pragmatic, randomised, double-blind, placebo-controlled, event-driven trial</td>
<td>Randomised, double-blind, placebo-controlled, parallel-group trial</td>
<td>Randomised, double-blind, placebo-controlled, trial</td>
<td>Randomised, double-blind, placebo-controlled, parallel-group event-driven trial</td>
</tr>
<tr>
<td>Intervention</td>
<td>Exenatide once weekly vs placebo</td>
<td>Semaglutide once weekly vs placebo</td>
<td>Liraglutide once daily vs placebo</td>
<td>Lixisenatide once daily vs placebo</td>
</tr>
<tr>
<td>Dose</td>
<td>Subcutaneous injection, 2 mg once weekly</td>
<td>Subcutaneous injection, 0.5 mg or 1.0 mg of once weekly</td>
<td>Subcutaneous injection, maximum dose of 1.8 mg once daily</td>
<td>Subcutaneous injection, maximum dose of 20 µg of lixisenatide once daily</td>
</tr>
<tr>
<td>No. of patients</td>
<td>14,752</td>
<td>3297</td>
<td>9340</td>
<td>829 centres in 49 countries</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>3.2 years</td>
<td>2.1 years</td>
<td>3.8 years</td>
<td>2.1 years</td>
</tr>
<tr>
<td>Major inclusion criteria</td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes</td>
<td>Type 2 diabetes and acute coronary event within 30 years or older</td>
</tr>
<tr>
<td>No of primary MACE events</td>
<td>1744 (11.8%)</td>
<td>254 (7.7%)</td>
<td>1302 (13.9%)</td>
<td>805 (13.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c, glycated haemoglobin; CVD, cardiovascular disease; CHF, chronic heart failure; NYHA II or III, New York Heart Association class 2 or 3; CKD, chronic kidney disease; CV, cardiovascular; MACE, major adverse cardiovascular events; SUSTAIN, LEADER, ESXCEL, ELIXA.

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Q7

not certain whether these effects explain the CV risk neutrality or benefit associated with this class in large, randomised clinical trials. Moreover, it was proposed that the CV benefit might be related to a direct effect on endothelin function, myocardium or vasculature instead of a reduction in body weight and BP [20,21].

In addition to favourable effects, clinical trials have raised a concern about elevated heart rate (HR) associated with this class [19,20]. This was found to be consistent with all GLP-1 agonists (although the magnitude differed) and thus considered more of a class effect [19]. The exact mechanism of such increase is unknown; however, despite that increase in HR, safety did not find an increased risk of CV mortality when compared to placebo at least in the trial populations under controlled conditions. Whether such an increase would be evidence of a negative effect on a specific group of patients (such as CHF) is yet to be determined.
Previous meta-analyses have proposed that the use of GLP-1 agonists in low CV risk patients is at least as safe as placebo and does not impose additional CV risk. Ding et al. conducted a meta-analysis that included a total of 13 trials (n = 11,943 patients) of GLP-1 agonist, placebo or conventional therapy [22]. The meta-analysis included studies of short duration that varied in terms of sample size and reported CV outcomes. Overall, the results suggest that the use of GLP-1 agonists have no significant effect on MACE [23].

Monami et al. published a meta-analysis to determine the effect of GLP-1 agonists on CV risk [23]. The meta-analysis included a total of 37 trials, of which the included trials were at least of 6 months’ duration. The meta-analysis results showed no significant difference in MACE when the GLP-1 agonists were compared to other agents (MH-OR 0.78, 95% CI: 0.54–1.13, p = 0.18). However, a significant reduction of GLP-1 agonists was observed when compared to placebo. It is important to note that most of the trials included patients with low CV risk and were designed to determine the effect of GLP-1 agonists on glycaemic control but not on CV outcomes [23].

Mahmoud et al. conducted a meta-analysis that included a total of six large clinical trials (55,248 patients) [24]. All included trials were designed to assess CV safety of incretin therapy versus placebo in patients with existing CVD or in high-risk patients. Three of them compared a GLP-1 agonist to placebo, and the other three addressed the safety of three DPP-4 inhibitors. The results showed that incretin-based therapy has a safety profile similar to placebo regarding cardiovascular mortality (OR 0.95, 95% CI: 0.87–1.03, p = 0.21, I² = 46%), MI (OR 0.95, 95% CI: 0.88–1.03, p = 0.18) [23].

Table 2 Baseline characteristics of studies included in the meta-analysis.

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<tbody>
<tr>
<td></td>
<td>n = 14,752</td>
<td>n = 3297</td>
<td>n = 9340</td>
<td>n = 6068</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>62.0 ± 6</td>
<td>64.6 ± 7.4</td>
<td>64.3 ± 7.2</td>
<td>60.3 ± 9.7</td>
</tr>
<tr>
<td>Duration of diabetes, years, mean ± SD</td>
<td>12.0 ± 5</td>
<td>13.9 ± 8.1</td>
<td>12.9 ± 8.1</td>
<td>9.3 ± 8.3</td>
</tr>
<tr>
<td>HbA1c, %, mean ± SD</td>
<td>8.0 ± 0.9</td>
<td>8.7 ± 1.5</td>
<td>8.7 ± 1.6</td>
<td>7.7 ± 1.3</td>
</tr>
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<td>BMI kg/m², mean ± SD</td>
<td>31.5 ± 4.0</td>
<td>32.8 ± 6.20</td>
<td>32.5 ± 6.3</td>
<td>30.2 ± 5.7</td>
</tr>
<tr>
<td>CAD, %</td>
<td>52.9</td>
<td>MI 32.5</td>
<td>56.8</td>
<td>MI 22.1</td>
</tr>
<tr>
<td>Ischaemic heart disease 60.5</td>
<td>MI 30.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, %</td>
<td>Total 17</td>
<td>Total 14.9 Stroke 11.6 Hem stroke 3.3</td>
<td>Stroke or TIA 16.1</td>
<td>Stroke 5.2</td>
</tr>
<tr>
<td>CHF, %</td>
<td>16.2</td>
<td>23.6</td>
<td>17.8</td>
<td>22.3</td>
</tr>
<tr>
<td>HTN</td>
<td>NA</td>
<td>92.8</td>
<td>5.3 (HTN and left ventricular hypertrophy)</td>
<td>76.4</td>
</tr>
<tr>
<td>SBP mm Hg, mean ± SD</td>
<td>135 ± 10</td>
<td>135.6 ± 17.15</td>
<td>135.9 ± 17.8</td>
<td>129.5 ± 17</td>
</tr>
<tr>
<td>DBP mm Hg, mean ± SD</td>
<td>80 ± 5</td>
<td>77 ± 10.02</td>
<td>77.1 ± 10.2</td>
<td>NA</td>
</tr>
<tr>
<td>HR (beats/min), mean ± SD</td>
<td>72 ± 8</td>
<td>72.0 ± 10.91</td>
<td>NA</td>
<td>70.2 ± 10</td>
</tr>
<tr>
<td>GFR (mL/min per 1.73 m²), mean ± SD</td>
<td>76.3 ± 16</td>
<td>NA</td>
<td>NA</td>
<td>76.0 ± 21.3</td>
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<tr>
<td>Insulin use, %</td>
<td>46.4</td>
<td>58</td>
<td>44.6</td>
<td>39.1</td>
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<tr>
<td>SU, %</td>
<td>36.7</td>
<td>42.8</td>
<td>50.7</td>
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<tr>
<td>Metformin, %</td>
<td>76.6</td>
<td>73.2</td>
<td>76.5</td>
<td>66.3</td>
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<tr>
<td>DPP4, %</td>
<td>14.9</td>
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<td>Not allowed</td>
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<tr>
<td>Statin use, %</td>
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<td>72.8</td>
<td>72.2</td>
<td>92.7</td>
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<tr>
<td>ACE/ARB, %</td>
<td>48.7</td>
<td>49.8</td>
<td>51</td>
<td>84.9</td>
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<tr>
<td>Aspirin, %</td>
<td>63.6</td>
<td>63.9</td>
<td>62.9</td>
<td>94.4*</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c, glycated haemoglobin; BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; TIA, transient ischaemic attack; CHF, congestive heart failure; HTN, hypertension; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GFR, glomerular filtration rate; SU, sulfonylurea; DPP4, dipeptidyl peptidase-4 inhibitors; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; EXSCEL, LEADER, EXEL, ELIXA.

*Antiplatelet in general including aspirin.
p = 0.18, I² = 15%), stroke (OR 0.94, 95% CI: 0.84–1.05, p = 0.30, I² = 30%), and HF hospitalisation (OR 1.04, 95% CI: 0.95–1.13, p = 0.44, I² = 44%). When focusing on GLP-1 agonist trials only, a subgroup analysis showed a reduction in all-cause mortality (OR 0.89, 95% CI: 0.80–0.99, p = 0.03) compared to placebo. However, no such reduction was observed with DPP-4 inhibitors [24].

Similar to the results of the subgroup analysis by Mahmoud et al., we found a significant reduction in death from CV causes in patients who received GLP-1 agonists versus those who received placebo (RR 0.87, 95% CI: 0.78–0.96). The reduction magnitude was about 13%. Moreover, our pairwise meta-analysis showed that GLP-1 agonists have a safety profile similar to placebo regarding reduction in non-fatal MI, non-fatal stroke, and rates of hospitalisation for HF. The NMA showed no significant differences among all four agents. However, liraglutide was the preferred agent in reducing the risk of CV death events and rate of HF hospitalisation, although semaglutide was the preferred agent in reducing non-fatal MI and non-fatal stroke events.

We have learned from the CV outcome trials that GLP-1 agonists differ in terms of reducing CV events. Differences among the studies in terms of design, study population and background medication use might have led to differences in CV outcomes. The GLP-1 agonists differ in terms of structure, pharmacodynamic and pharmacokinetics properties [25,26]. In the LEADER and ELIXA studies, both liraglutide and lixisenatide were administered once daily. However, only lixisenatide is considered a short acting agent [7,9]. Moreover, lixisenatide was the least potent in reducing HbA1c and other parameters such as body weight and SBP. It is likely that the short acting nature of lixisenatide and its reduced effect on HbA1c, body weight and SBP contribute to the neutral effect on CV outcomes [25–30]. On the other hand, EXSCEL and
SUSTAIN-6 trials included a once weekly formulation of exenatide and semaglutide respectively [8,13]. Such differences in frequency of drug administration might explain the differences in adherence among the trials.

The trials included differed in terms of glycaemic control at baseline. The LEADER and SUSTAIN-6 trials included patients with higher HbA1c (mean HbA1c 8.7%) [7,8]. However, the mean HbA1c in EXSCEL and ELIXA was 8% and 7.7%, respectively [9,13]. Interestingly, studies with higher HbA1c at baseline have shown an increased likelihood in the reduction of CV events. However, this reduction in CV events cannot only be attributed to the glycaemic control at baseline. A greater overall reduction in HbA1c from baseline was observed with GLP-1 agonists compared to placebo in all trials. In SUSTAIN-6, at week 104, the mean HbA1c level decreased from 8.7% at baseline to 7.6% in 0.5 mg semaglutide group and to 7.3% in 1.0 mg semaglutide group. Overall, HbA1c was 0.7% lower in the group receiving 0.5 mg semaglutide and 1% lower in the 1 mg group compared to the placebo group [8]. In EXSCEL, LEADER and ELIXA, the overall mean differences between the GLP-1 agonist group and the placebo group were –0.53%; –0.40% and –0.27%, respectively [7,9,13]. However, given the design of the trials, it is not possible to test the effect of the changes in glycaemic control on CV outcomes.

Our MTC meta-analysis has some important strengths. We have included all large GLP-1 CV outcome trials regarding T2DM. We have performed both pairwise meta-analysis and an NMA to determine the CV safety of GLP-1 agonists and to determine whether there is any difference among the treatment agents. All the included trials met their primary endpoint of non-inferiority for MACE and the expected number of events. To our knowledge, this is the first MTC meta-analysis to include the results of the EXSCEL and the largest to address GLP-1 agonist safety in the high-risk CV population.

**Limitations**

This MTC meta-analysis was focussed on the safety of GLP-1 agonists; thus, we have not included other incretin therapy (DPP-4) trials; we have focussed our analysis only on the individual components of primary outcomes of the trials (MACE-3) in addition to rates of HF hospitalisation. Moreover, the nature of the pooled data prevented us from performing more detailed analysis. Given the design of the included trials, it was not possible to test the effect of the changes in glycaemic control on CV outcomes. Publication bias of included trials could not be ruled out.

**Conclusion**

Glucagon like peptide-1 therapy was associated with a significant reduction in CV death. However, GLP-1 agonists seem to have a safety profile comparable to placebo in terms of reducing non-fatal MI, non-fatal stroke events, and rates of HF hospitalisation. The NMA showed no statistically significant differences among all the interventions. However, liraglutide was the preferred agent in reducing the risk of CV death events and rate of HF hospitalisation; and semaglutide was the preferred agent in reducing non-fatal MI and non-fatal stroke events. Real-world evidence studies are required to confirm the safety of GLP-1 agonists in patients with T2DM.

**Conflict of Interest**

The authors declare no conflicts of interest.

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**Author contributions**

MA: Statistical analysis, data interpretation and critical. Made supplementary material tables and figures. Wrote sections of the manuscript (methods and results). Edited the manuscript.

OA: Data extraction, literature search, analysed and interpreted the data. Made and reviewed tables and figures. Edited the manuscript. All authors read and approved the final manuscript.

**References**


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