Network meta-analysis of nine large cardiovascular outcome trials of new antidiabetic drugs

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\textbf{Abstract}

The aim of this network meta-analysis (NMA) was to indirectly compare the cardiovascular (CV) safety of new antidiabetic medications in patients with type 2 diabetes mellitus (T2DM). Data synthesis: A search of the Embase and MEDLINE databases was conducted systematically to identify cardiovascular outcome trials (CVOTs) of new antidiabetic medications (DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors) in patients with T2DM. The primary outcomes were the composite endpoint of CV death, nonfatal MI, and nonfatal stroke (MACE), death from CV causes, nonfatal MI, nonfatal stroke and death from any cause. Hospitalization for HF and unstable angina were evaluated as secondary endpoints. A total of 9 trials, including 87,162 patients, met the eligibility criteria and were retained for the analysis.

The NMA results showed no significant differences among the DPP-4 inhibitors (sitagliptin, alogliptin, and saxagliptin) in any of the CV endpoints. Similarly, no significant changes were seen in the NMA among the GLP-1 receptor agonists nor the SGLT-2 inhibitors. The pairwise meta-analysis showed that DPP-4 inhibitors have a CV safety profile comparable to placebo. GLP-1 agonists on the other hand, showed significant reduction in MACE (RR 0.92; 95% CI 0.87–0.97), death from CV causes (RR = 0.88; 95% CI 0.80–0.97), and death from any cause (RR = 0.89; 95% CI 0.82–0.96). SGLT-2 inhibitors showed significant reduction in hospitalization for heart failure events (RR 0.72; 95% CI 0.6–0.86) compared to placebo.

\textbf{Keywords:}
Glucagon Like Peptide-1 Receptor agonist
Sodium glucose cotransporter 2 inhibitor
Dipeptidyl peptidase IV inhibitor
Cardiovascular disease
Diabetes mellitus
Type 2
Meta-analysis
Network meta-analysis
Myocardial infarction
Nonfatal stroke
Heart failure
Unstable angina

Conclusion: This meta-analysis has shown that new antidiabetic medications do not impose any additional CV risk. The indirect comparison among the medications of each class resulted in no significant changes regarding CV endpoints and death from any cause.

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1. Introduction

There is a strong correlation between cardiovascular (CV) disease and diabetes. According to the National Diabetes Statistics Report of 2017, most diabetes-related hospital discharges were due to major CV events ischemic heart disease, and stroke [1]. Moreover, the risk of CV mortality is much higher in adults with diabetes than in those without diabetes [2,3].

In 2007, a meta-analysis was published suggesting that rosiglitazone, an anti-hyperglycemic agent in the thiazolidinedione class, was associated with an increased risk of myocardial infarction (MI) and CV-related death [4]. Shortly after these data were published, the Food and Drug Administration (FDA) started to require investigators to test new anti-hyperglycemic agents for CV safety (defined as non-inferiority of the study drug compared with placebo for a composite CV outcome) before approval [5]. Since then, several large randomized controlled trials have assessed the CV safety for new anti-hyperglycemic classes. Much interest has been directed toward the randomized controlled trials of three anti-hyperglycemic classes: dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

The DPP-4 inhibitor trials, which include SAVOR-TIMI 53 (Saxagliptin), EXAMINE (Alogliptin) and TECOS (Sitagliptin), showed no change in major adverse cardiovascular events (MACE) compared to placebo [6-8]. However, saxagliptin in SAVOR-TIMI 53 trial was associated with increased heart failure (HF) admissions, though this has not yet been proven to be a class-wide effect [6]. On the other hand, the LEADER (Liraglutide) and SUSTAIN-6 (Semaglutide) trials of GLP-1 receptor agonists showed significant reductions in MACE [9,10]. However, there was no CV benefit observed in the ELIXA (Lixisenatide) and EXSCEL (Exenatide) trials [11,12]. The CV safety of SGLT2 inhibitors was assessed in the EMPA-REG OUTCOME (Empagliflozin) and CANVAS (Canagliflozin) trials, both of which showed a lower risk of CV events compared to placebo [13,14].

The aforementioned trials only compared the anti-hyperglycemic agent with placebo and did not conduct a direct comparison between agents. Thus, here we conduct a network meta-analysis (NMA) to indirectly compare the CV safety of new antidiabetic medications in patients with type 2 diabetes mellitus (T2DM).

2. Methods

2.1. Literature search

A search of the Embase and MEDLINE databases was conducted systematically to identify cardiovascular outcome trials (CVOTs) of new antidiabetic medications in patients with T2DM. The search timeframe used was from 2008 to December 2017. The following keywords were used: glucagon like peptide-1 receptor agonist, (liraglutide, exe-
natide, lixisenatide, albiglutide, dulaglutide, semaglutide; sodium glucose cotransporter 2 inhibitor (empagliflozin, canagliflozin, dapagliflozin); dipeptidyl peptidase IV inhibitor, (sitagliptin, saxagliptin, linagliptin, and alogliptin); cardiovascular disease; randomized controlled trials; and type 2 diabetes. The search was limited to the English language.

2.2. Inclusion and exclusion criteria

Studies were included in the NMA if they were (1) large, double-blind, placebo-controlled CVOTs in patients with T2DM and (2) evaluated the effects of DPP-4 inhibitors, SGLT-2 inhibitors or GLP-1 agonists versus placebo on CV outcomes as their primary endpoint. Studies were excluded if they were non-randomized controlled trials or if they evaluated the effects of insulin or medications other than the mentioned classes. Titles, abstracts, and full text reports were screened and reviewed by two independent authors for inclusion (Supplementary Fig. S1).

2.3. Data extraction and risk of bias assessment

Data were abstracted from the included trials by two independent authors. Each author cross-checked all the extracted data for accuracy. Risk of bias for all included trials was assessed using the Cochrane Risk of Bias Tool. The NMA was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) [15].

2.4. Outcome measures

The primary outcomes of this NMA were the composite endpoint of MACE (CV death, nonfatal MI, and nonfatal stroke), death from CV causes, nonfatal MI, nonfatal stroke and death from any cause. Hospitalization for HF and unstable angina were evaluated as secondary endpoints.

2.5. Data synthesis and analysis

The NMA was conducted using the Aggregate Data Drug Information System (ADDIS) software, v.1.16.6. ADDIS was used to build Markov chain Monte Carlo simulations [16]. Both consistency and inconsistency models were evaluated to examine to which extent the results of the NMA were consistent. In addition, random-effect variance and inconsistency variance were evaluated to assess whether inconsistency was present among included studies [17,18]. We used the consistency model to report the results of the NMA if there was no apparent evidence of inconsistency across all the evaluated studies. The results of the NMA were reported as odds ratios (ORs) with 95% credible intervals (CrIs). All the anti-hyperglycemic agents were ranked for each endpoint based on their probabilities as reported by ADDIS. In addition to the NMA, we performed a pairwise meta-analysis for each antidiabetic class. For each class, the Mantel-Haenszel (MH) random-effects model risk ratio (RR) and corresponding 95% CrIs were calculated using the metan routine in Stata software (version 14.2, StataCorp LLC, College Station, Texas) to estimate the pooled treatment effects. The I² statistic was used to assess heterogeneity.

3. Results

3.1. Search results

A total of 652 publications were identified and reviewed, of which 643 were excluded based on study design, study population, duplication, and/or relevance to the research question (Supplementary Fig. S1). A total of 9 trials, including 87,162 patients, met the eligibility criteria and were retained for the analysis. The summary of the included studies is provided in Supplementary Table S1. The results of the risk bias assessment of the included trials are summarized in Supplementary Table S2.

A total of three large DPP-4 inhibitor trials to date have assessed CV safety (Supplementary Table S1). SAVOR-TIMI 53 (saxagliptin) included a total of 16,492 patients with a median follow-up of 2.1 years [6]. EXAMINE (Alogliptin) included a total of 5380 patients with T2DM [7]. Unlike the other studies, EXAMINE included patients with recent coronary artery syndrome only. The median follow-up was 1.5 years, and the mean age of participants was the lowest among the 3 trials (61 years). Though it included patients with established coronary artery disease, this study featured the lowest use of angiotensin converting enzyme inhibitor (ACE) or Angiotensin II receptor blockers (ARBs) (26%) at the beginning of the study [7]. TECOS (Sitagliptin) included a total of 14,671 patients 50 years or older with T2DM and CV disease [8]. The median follow-up was 3 years and the study included the lowest mean of HbA1c (7.2%) at baseline [8].

A total of 4 trials assessed the CV safety of GLP-1 receptor agonists. ELIXA (Lixisenatide) included a total of 6068 subjects with recent acute coronary artery events [11]. The median follow-up was 2.1 years, and the mean age of subjects was 60.3 years [11]. SUSTAIN-6 enrolled a total of 3297 patients randomized to two doses of once-weekly semaglutide (0.5 mg or 1.0 mg) versus matched placebo [10]. LEADER enrolled 9,340 patients with prior CVD or risk factors. Patients were assigned either to liraglutide once daily or to a matched placebo. The median follow-up was 3.8 years, and a total of 72% of patients had established CVD at baseline [9]. EXSCEL was the only trial to allow the use of another incretin therapy. At baseline, 14.9% of patients were receiving a DPP-4 inhibitor. A total of 14,752 patients with T2DM were enrolled. In this trial, there was a wide range of CV diseases among patients, no age limit, and a median follow-up of 3.2 years [12].

The CV safety of SGLT-2 inhibitors was assessed in two trials; EMPA-REG (Empagliflozin) and CANVAS (Canagliflozin). EMPA-REG included patients 18 years of age or older with established CVD. Participants were assigned to either empagliflozin 10 mg, 25 mg or matched placebo. The mean follow-up of the study was 3.1 years and the mean age of participants was 63 [13]. CANVAS integrated data from 2 trials (CANVAS and CANVAS-R). CANVAS assessed the CV safety of canagliflozin, while CANVAS-R focused on renal endpoints in patients with T2DM [14]. A total of 10,142 individuals with ele-
 Fig. 1 – Ranking results of DPP 4 inhibitors (sitagliptin, alogliptin and saxagliptin).
reducing MACE (69%), nonfatal MI (67%) and nonfatal stroke (69%) events (Fig. 2). Liraglutide on the other hand, was ranked first in reducing CV death (58%), death from any cause (44%) and HF hospitalizations (46%) events (Fig. 2).

3.4. SGLT-2 inhibitors

The pairwise metaanalysis showed that SGLT-2 inhibitors were associated with a significant 28% reduction in HF hospitalizations events compared to placebo (RR 0.72; 95% CI 0.6–0.86) (Supplementary Fig. S4). There was a signal of increased events of stroke with SGLT-2 inhibitors compared to placebo, however, such increase was not statistically significant (RR 1.11; 95% CI 0.92–1.33) (Supplementary Fig. S4).

Only two SGLT-2 inhibitors (empagliflozin and canagliflozin) were included in the NMA. The indirect comparison showed no significant differences between empagliflozin, canagliflozin, or placebo in regard to all endpoints (Supplementary Table S5). The ranking on the other hand showed that empagliflozin was ranked first in reducing MACE (86%), CV death (90%), nonfatal MI (73%), death from any cause (90%) and HF hospitalizations (68%). For stroke events, placebo was ranked first (48%) followed by canagliflozin (43%) (Fig. 3).

4. Discussion

Patients with T2DM are at higher risk for CV complications compared to the general population [1]. Unlike microvascular complications, reduction of CV complications with tight glycemic control showed less certain results as in the case of ACCORD and ADVANCE trials [19–21]. Away from glycemic control, it is important that antidiabetic medications not impose additional CV harm. Since 2008, several CVOtTs were conducted to ensure CV safety of all new antidiabetic medications, and many are still ongoing.

DPP-4 inhibitors are often used in the management of T2DM as second or third line options [22]. To date, a total of 3 CVOtTs of DPP-4 inhibitors have been completed (EXAMINE, TECOS, and SAVOR-TIMI 53) [6–8]. All three medications (sitagliptin, alogliptin, saxagliptin) have met the noninferiority criteria set by the FDA for MACE. However, none have shown superiority to placebo in reducing CV events [6–8].
previously published meta-analyses, DPP-4 inhibitors demonstrated CV safety comparable to placebo [23–25]. As a class, DPP-4 inhibitors were ranked last, behind GLP-1 agonists and SGLT-2 inhibitors in reducing MACE and other CV outcomes [24,25]. Similarly, in our meta-analysis results did not show a statistically significant reduction in MACE and other CV outcomes.

It is important to note that in SAVOR-TIMI 53, saxagliptin was associated with an increase in hospitalization due to HF for patients both with and without a history of HF [6]. In our meta-analysis, DPP-4 inhibitors showed a 13% increase in HF hospitalization compared to placebo (RR = 1.13; 95% CI 1.00–1.28). However, this increase was not statistically significant and largely driven by the SAVOR-TIMI 53 trial. Only 2 studies (SAVOR-TIMI 53 and TECOS) have reported hospitalization for HF events and were therefore included in the analysis.

After the publication of the EXAMINE data, a more extensive analyses showed that death rates following nonfatal CV events were similar between alogliptin and placebo. However, a significantly higher risk of CV death (four fold) was seen with those with heart failure events [26]. As a result, the FDA issued a safety alert suggesting the discontinuation of saxagliptin and alogliptin in patients with HF [27,28]. In our NMA, although no significant differences were observed among all DPP-4 inhibitors, alogliptin was ranked as the preferred agent in reducing MACE while sitagliptin was ranked second. Alogliptin was ranked as the preferred agent in reducing CV death, nonfatal stroke and death from any cause. Moreover, sitagliptin was the preferred agents in reducing HF hospitalization events.

A total of 4 trials addressed the CV safety of GLP-1 receptor agonists. The EXAMINE trial involved subjects with a recent acute coronary artery event [11]. The remaining 3 trials included patients with either established CV disease or patients with moderate to high CV risk factors. All four medications (ixiglumud, liraglutide, semaglutide and exenatide) have met noninferiority criteria set by the FDA and impose no extra CV risk. Liraglutide showed a significant reduction in MACE, all-cause mortality and CV mortality [9], and semaglutide showed a significant reduction in MACE as well as nonfatal stroke [10]. Moreover, once-weekly exenatide has shown a statistically significant reduction in all-cause mortality [12]. The
FDA recently approved the use of liraglutide in patients with T2DM and established CV disease for the purpose of reducing MACE [3].

In our meta-analysis, GLP-1 agonists showed a significant reduction in MACE, CV death and death from any cause. Our results are consistent with previously published meta-analyses [24,25,29–31]. Bethel and et al. have shown a significant 10% relative risk reduction (RRR) of MACE (HR 0.9, 95% CI 0.82–0.99; p = 0.033), and a significant 12% reduction in all-cause mortality (HR 0.88, 95% CI 0.81–0.95; p = 0.002) favoring GLP-1 agonists over placebo [29]. Moreover, a significant 13% reduction in CV mortality compared to placebo (HR 0.87, 0.79–0.96; p = 0.007) was observed. However, no significant differences were seen between GLP-1 agonists and placebo in MI, stroke, hospitalization of HF and unstable angina events [29]. On the other hand, a meta-analysis by Jia et al. showed a significant reduction in all-cause mortality and CV death with GLP-1 agonists. A subgroup analysis of long acting GLP-1 agonists showed a significant reduction in only MACE and nonfatal stroke [30].

Two recently published NMAAs have shown that GLP-1 agonists are likely to be ranked first in reducing stroke and more likely to be ranked second in reducing MACE, CV death and all-cause death behind SGLT-2 inhibitors [24,25]. In our study the ranking was based on individual medications instead of classes. Among GLP-1 agonists, semaglutide was ranked first in reducing MACE, nonfatal MI and nonfatal stroke events. Liraglutide was the preferred agent in reducing CV death, death from any cause and HF hospitalization events. Overall, it is not definitely established yet if the CV benefit seen with GLP-1 agonists is indeed a class effect or not [3].

Two CVOTs (EMPA-REG and CANVAS trials) have addressed the safety of SGLT-2 inhibitors [13,14]. Both studies have shown a significant reduction in MACE and hospitalization for HF. In the EMPA-REG trial the significant reduction in MACE was largely driven by reduction in CV death [13]. However, in the CANVAS program, the individual components of the primary endpoint did not reach significance [14]. In our meta-analysis, a statistically significant reduction in hospitalization for HF was seen with SGLT-2 inhibitors compared to placebo. In our NMA, empagliflozin was the preferred SGLT-2 inhibitor in reducing MACE, CV death, nonfatal MI, death from any cause and HF hospitalizations. Important to note that placebo was preferred over SGLT-2 inhibitors in regards to nonfatal stroke events followed by canagliflozin. In recently published meta-analyses, SGLT-2 inhibitors as a class were ranked first in reducing MACE, CV death and all-cause death compared to DPP-4 inhibitors and GLP-1 agonists classes [24,25].

A significant percentage of patients with T2DM might develop HF [3]. Unlike DPP-4 inhibitors and GLP-1 agonists, SGLT-2 inhibitors (empagliflozin and canagliflozin) have shown promising results in reducing hospitalization due to HF events. Although in both trials (EMPA-REG and CANVAS trials) most participants did not have a history of HF, the reduction in HF hospitalization was true for both individuals with and without HF. It is possible that the SGLT-2 inhibitors might have a role in reducing and possibly preventing HF [13,14]. Thus, several trials are currently testing the efficacy of SGLT-2 inhibitors in HF patients with or without diabetes [3].

Based on the results of the major CVOTs, the most recent American Diabetes Association (ADA) guidelines have updated the pharmacological approaches in treating T2DM [3,32]. Although metformin is still the preferred initial pharmacological option, a medication proven to reduce both MACE and CV death, such as empagliflozin and liraglutide, is recommended for patients with established CV disease who are already on metformin. Moreover, patients with established CV disease who are already on metformin may benefit from the addition of canagliflozin to reduce MACE [32]. These recommendations are consistent with the CVOTs since most of the enrolled patients in these trials were already treated with metformin and had a high risk of or established CV disease. Lastly, a patient-centered approach in treating T2DM is encouraged by the ADA, and the choice of medication should be based on several factors, such as efficacy, cost, weight effect, hypoglycemia risk, rather than on CV benefit alone.

5. Limitations

This NMA is focused only on CV outcomes. Thus, we did not investigate glycemic control or common adverse events associated with the three classes (GLP-1 agonists, SGLT-2 inhibitors and DPP-4 inhibitors). There are differences in terms of population and study design among the trials and to what extent those differences would have affected the results is unknown. However, the CVOTs used were all of high quality with low risk of bias as shown in the quality assessment table (Supplementary Table S2). All the studies have included 3-point MACE (CV death, nonfatal MI and nonfatal stroke) as their primary endpoint. However, the TECOS and ELIXA studies have included unstable angina in their composite endpoint (4-point MACE). To date, there is a small number of CVOTs completed and only two SGLT-2 inhibitors have been tested for CV safety.

6. Conclusion

In conclusion, the NMA failed to find a significant difference among the medications of each class in reducing MACE, other CV endpoints and death from any cause. The pairwise meta-analysis results showed that DPP-4 inhibitors had a CV safety comparable to placebo with a no statistically significant increase in hospitalizations for HF events. GLP-1 agonists showed CV and mortality benefit while SGLT-2 inhibitors showed a significant reduction in HF events.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.pcd.2019.01.003.

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