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Network meta-analysis of cardiovascular outcomes in randomized controlled trials of new antidiabetic drugs

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ABSTRACT

Background: Randomized controlled trials (RCTs) directly comparing cardiovascular outcomes of new antidiabetic drugs are lacking. We used network meta-analysis to compare new antidiabetic drug classes with respect to major adverse cardiovascular events (MACE) and mortality.
Methods: We searched MEDLINE, EMBASE, the Cochrane database, and ClinicalTrials.gov up to 30 December 2016 for RCTs involving SGLT-2 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors in diabetic patients that reported MACE and deaths. Outcomes were compared with frequentist and Bayesian methods using R statistics.
Results: Seven RCTs with altogether 62,268 patients were included in the network meta-analysis. The SGLT-2 inhibitor and GLP-1 RAs reduced MACE (OR 0.85, 95%CI 0.73–0.99 and 0.89, 0.82–0.97, respectively) and all-cause mortality (0.67, 0.55–0.81 and 0.89, 0.80–0.99, respectively) compared to placebo. Furthermore, the SGLT-2 inhibitor reduced all-cause mortality compared to GLP-1 RAs (0.76, 0.61–0.94). In contrast, DPP-4 inhibitors did not reduce MACE or mortality compared to placebo and were associated with higher all-cause mortality compared to the SGLT-2 inhibitor (1.53, 1.24–1.89) and GLP-1 RAs (1.16, 1.01–1.33).
Conclusions: All-cause mortality and MACE were reduced by the SGLT-2 inhibitor and GLP-1 RAs, but not DPP-4 inhibitors. The SGLT-2 inhibitor had the most beneficial impact on all-cause mortality. DPP-4 inhibitors showed no cardiovascular benefit and were inferior to the other two drug classes in preventing deaths.

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM)[2] is increasing, affecting about 400 million people worldwide [1]. Cardiovascular disease (CVD) is the major cause of comorbidity and mortality in T2DM patients, who are prone to myocardial infarction (MI) and stroke. The risk of CVD is 2–4 times higher in diabetic patients than in non-diabetic populations [2]. Therefore, preventing CVD is essential in these patients besides glucose control [3]. Lowering blood pressure and cholesterol have been shown to reduce cardiovascular events in people with diabetes [4,5]. However, control of cardiovascular risk factors in patients with diabetes is suboptimal even in the United States [6].

The American Diabetes Association and European Association for the Study of Diabetes recommend lifestyle intervention followed by metformin as the first-line therapy in T2DM [7]. Other classes of antihyperglycemic agents can be added to metformin. So far, there is no clear second line therapy after metformin; current guidelines endorse the use of sulphonylureas, thiazoladinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors [8]. Antidiabetic drugs may have cardiovascular effects independent of their glucose-lowering effects. Improved glycemic control has been shown to reduce diabetes-related microvascular complications [9], but whether it reduces macrovascular complications is more controversial [4,10]. Intensive glucose lowering and specific glucose-lowering drugs have been suspected to increase the risk of cardiovascular events [11,12]. In particular, rosiglitazone was reported to be associated with an increased risk of MI and death [13,14]. In response, the US Food and Drug Administration and the European Medicines Agency started to require all new antidiabetic therapies to demonstrate an acceptable

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] T2DM, type 2 diabetes mellitus. CVD, cardiovascular disease. MI, myocardial infarction. DPP-4, dipeptidyl peptidase-4. GLP-1 RAs, glucagon-like peptide-1 receptor agonists. SGLT-2, sodium-glucose co-transporter 2. MACE, major adverse cardiovascular events. ACS, acute coronary syndrome. RCT, randomized controlled trials. NMA, network meta-analysis.

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cardiovascular risk profile [15,16]. The composite endpoint, major adverse cardiovascular events (MACE), which includes cardiovascular death, nonfatal MI and nonfatal stroke, and other events such as myocardial ischemia and hospitalization for acute coronary syndrome (ACS), coronary revascularization or worsening heart failure, is therefore evaluated in cardiovascular outcome trials [16,17].

No antidiabetic therapy has been clearly shown to reduce the risk of cardiovascular events in previous studies [4,10,17–19]. Recently, several large randomized controlled trials (RCTs) assessing the cardiovascular risk of new antidiabetic drugs have been published [20–24]. Their findings may influence the guidelines on treatment of diabetes as well as prevention of CVD encountered in T2DM patients. Due to the lack of head-to-head comparative trials, it is not known if a specific antidiabetic therapy is superior to others in reducing the risk of adverse cardiovascular events. Therefore, we performed a network meta-analysis (NMA) to compare the effects of new antidiabetic drugs on cardiovascular outcomes in patients with T2DM.

2. Methods

2.1. Search strategy and study selection

The NMA was designed according to the PRISMA Statement. We searched MEDLINE, EMBASE, the Cochrane database, ClinicalTrials.gov, and congress proceedings from recent cardiology conferences up to 30 December 2016 for RCTs on new antidiabetic drugs in T2DM patients. Search keywords were "dipeptidyl peptidase-4 inhibitor", "glucagon-like peptide-1 receptor agonist", "sodium-glucose co-transporter 2 inhibitor", "cardiovascular risk", "cardiovascular event", "death", and "MACE". No restriction of language and publication status was applied. Study inclusion criteria for this NMA were: (1) phase III/IV RCTs; (2) allocation of GLP-1 RAs, SGLT-2 or DPP-4 inhibitors; (3) cardiovascular outcome trials; (4) adult patients (≥18 years of age); (5) patients with established CVD or cardiovascular risk factors; and (6) report of the rate of both MACE and deaths.

2.2. Data extraction

Literature review and inclusion were carried out by two investigators (YF and MFT) independently. Discrepancies were resolved by consensus. For eligible studies, information about methods, year of publication, age, gender, sample size, body weight, intervention and control, duration of follow-up, glycated hemoglobin, cardiovascular risk factors, and duration of diabetes were extracted. Risk of bias was assessed using the Cochrane risk of bias assessment tool. The primary outcome was MACE, defined as the composite of cardiovascular mortality, nonfatal MI, and nonfatal stroke. Secondary outcomes included cardiovascular mortality, all-cause mortality, nonfatal MI, and nonfatal stroke. We followed the definitions of outcomes used in each trial.

2.3. Statistical analysis

We used both a frequentist approach [25] and a Bayesian framework [26] with non-informative priors to compare the effect of different antidiabetic drugs on outcomes at the trial level. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used as the summary statistics. A 95% CI not including 1.00 or a two tailed p-value <0.05 was considered statistically significant. Forest plots using fixed- and random-effects models to compare relative treatment effects were generated with a frequentist approach using the statistical package 'netmeta' (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.2.3). P-rank scores were generated to determine the probability of the antidiabetic drug having the largest effect size for each outcome. Sensitivity analysis was conducted by assessing the effect of removing individual trials. Heterogeneity and inconsistency across trials were assessed by Cochran's Q test and I^2 statistic; I^2 < 25%, within 25–50%, and >50% represented mild, moderate, and severe heterogeneity, respectively. Small study effects or potential publication bias were assessed using funnel plots, Begg's, Egger's, and trim-and-fill tests.

We evaluated the consistency of inferential estimates from hierarchical modelling using Markov chain Monte Carlo simulations, which were performed with 1000 tuning iterations and 5000 simulation iterations within a Bayesian framework using R statistical package 'gemtc' (version 0.8, https://cran.r-project.org/web/packages/gemtc/index.html) and 'rjags' (version 4–6, https://cran.r-project.org/web/packages/rjags/index.html). The protocol for this NMA was registered with the PROSPERO registry (number CRD42016050146).

3. Results

Of 8410 potentially relevant abstracts initially screened, seven two-armed trials with altogether 62,268 patients that were randomized to GLP-1 RAs (n = 9350), the SGLT-2 inhibitor (n = 4687), DPP-4 inhibitors (n = 18,238), and placebo (n = 29,845) were finally included in the NMA. The search process is shown in the PRISMA flowchart (Fig. S1). The main characteristics of included trials are shown in Table 1. They all had a low risk of bias assessed using the components recommended by the Cochrane Collaboration (Tables S1, S2). Baseline patient characteristics are summarized (Table S3). Three antidiabetic drugs and placebo resulted in 6 theoretical comparisons for each outcome of interest (Fig. S2).

NMA with a frequentist approach showing the change in outcomes with different antidiabetic drugs is summarized in Table 2 and Fig. 1. Compared with placebo, GLP-1 RAs and the SGLT-2 inhibitor significantly reduced the rate of MACE, cardiovascular mortality and all-cause mortality among patients with T2DM (Fig. 1A–C). The SGLT-2 inhibitor resulted in a lower cardiovascular and all-cause mortality than GLP-1 RAs and DPP-4 inhibitors. In contrast, DPP-4 inhibitor recipients had a risk of MACE or mortality similar to those receiving placebo, but higher all-cause mortality than those receiving GLP-1 RAs and the SGLT-2 inhibitor. No significant difference was found in the risk of nonfatal MI and nonfatal stroke (Table 2 and Fig. 1D, E). P-rank scores confirmed the ranking of these therapies. The SGLT-2 inhibitor was ranked the highest in reducing the risk of MACE, cardiovascular mortality, and all-cause mortality while GLP-1 RAs were ranked the second highest (Table S4). As the ELIXA and EXAMINE trials recruited T2DM patients with ACS within 180 days, which were different from the inclusion criteria in other trials, we further performed a NMA excluding these two trials. The results were essentially unchanged (Table S5).

Moderate heterogeneity was found for MACE (I^2 = 38.1%, p = 0.17); insignificant heterogeneity was found for nonfatal MI, cardiovascular mortality, all-cause mortality, and nonfatal stroke (I^2 = 1.3%, 16.5%, 16.9%, and 20.7%, respectively) across the whole network. Sensitivity analysis showed that the heterogeneity for MACE was due to the SUSTAIN-6 and ELIXA trials. After excluding them, I^2 could be reduced to 0% and 15%, respectively (Table S6, S7).

Using random-effects instead of fixed-effects model, or Bayesian instead of frequentist analysis, did not materially affect the results.

Table 1
Major characteristics of trials included in the network meta-analysis.

Studies	Year	ClinicalTrials.gov Identifier	Patients (antidiabetic drug/placebo)	Antidiabetic drug	Drug type	Primary endpoints
LEADER [22]	2016	NCT01179048	9340 (4668/4672)	Liraglutide vs. placebo	GLP-1 RA	Cardiac death, non-fatal MI, non-fatal stroke
SUSTAIN-6 [23]	2016	NCT01720446	3297 (1648/1649)	Semaglutide vs. placebo	GLP-1 RA	Cardiac death, non-fatal MI, non-fatal stroke
ELIXA [21]	2015	NCT01147250	6068 (3034/3034)	Lixisenatide vs. placebo	GLP-1 RA	Cardiac death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina
EMPA-REG OUTCOME [24]	2015	NCT01131676	7020 (4687/2333)	Empagliflozin vs. placebo	SGLT-2 inhibitor	Cardiac death, non-fatal MI, non-fatal stroke
SAVOR-TIMI 53 [18]	2013	NCT01107886	16,492 (8280/8212)	Saxagliptin vs. placebo	DPP-4 inhibitor	Cardiac death, non-fatal MI, non-fatal stroke
TECOS [20]	2015	NCT00790205	14,671 (7257/7266)	Sitagliptin vs. placebo	DPP-4 inhibitor	Cardiac death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.
EXAMINE [19]	2013	NCT00968708	5380 (2701/2679)	Alogliptin vs. placebo	DPP-4 inhibitor	Cardiac death, non-fatal MI, non-fatal stroke

Abbreviations used in Table 1: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; RA = receptor agonist; SGLT-2 = sodium-glucose co-transporter 2.