

The cardiovascular effect of incretin-based therapies among type 2 diabetes: a systematic review and network meta-analysis

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Word count of the text: 200 for abstract and 3321 for main text

NO. of references: 40

NO. of tables: 1

NO. of figures: 2

NO. of supplement material: 16 Appendix files.

ABSTRACT

Objective: To evaluate the comparative cardiovascular safety of incretin-based therapies in patients with type 2 diabetes mellitus (T2DM).

Methods: Medline, Embase, the Cochrane Library and www.clinicaltrials.gov were searched for randomized controlled trials (RCTs) with duration ≥ 12 weeks. Network meta-analysis was performed, followed by subgroup analysis and meta-regression. The Grading of Recommendations Assessment, Development and Evaluation system was used to assess the quality of evidence. The outcome of interest was a composite of cardiovascular death, myocardial infarction, stroke and heart failure. Odds ratio (OR) with 95% confidence interval (CI) was calculated as the measure of effect size.

Results: 281 RCTs (76.9% double-blinded) with 180,000 patients were included, comparing incretin-based therapies with other six classes of anti-diabetic drugs or placebo. A statistically significant reduction in the risk of cardiovascular events was found in favour of GLP-1RAs when compared with placebo (OR 0.89, 95%CI: 0.80-0.99) and sulfonylurea (OR 0.76, 95%CI: 0.59-0.99), whereas DPP-4 inhibitors showed a neutral effect compared with placebo (OR 0.92, 95%CI: 0.83-1.01).

Conclusions: Incretin-based therapies show similar cardiovascular risk in comparison with metformin, insulin, thiazolidinediones, alpha-glucosidase inhibitor and sodium-glucose co-transporter 2. GLP-1RA could decrease the risk compared with sulfonylurea or placebo, while DPP-4I appears to have neutral effect on cardiovascular risk.

Key words: Incretin-based therapies, type 2 diabetes, network meta-analysis, cardiovascular effect

1. Introduction

Type 2 diabetes mellitus (T2DM) is a well-established risk factor for cardiovascular disease ¹. According to the results of the largest cohort study with 1.9 million subjects, T2DM was associated with a significantly increased risk of ischemic stroke (hazard ratio, HR=1.72), stable angina (HR=1.62), heart failure (HR=1.56) and non-fatal myocardial infarction (HR=1.54). Therefore, it is critical for anti-diabetic drugs not to increase the risk of cardiovascular events. The US Food and Drug Administration has required proof of cardiovascular safety to approve new glucose-lowering drugs since the increased risk of myocardial infarction associated with rosiglitazone in 2008².

Incretin-based therapies are a new class of anti-diabetic agents, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). DPP-4 inhibitors prevent the rapid degradation of GLP-1 through inhibition of DPP-4, thus enhancing pancreatic insulin secretion and suppress pancreatic glucagon secretion. GLP-1 RAs are analogues of GLP-1, which could stimulate insulin secretion, improve insulin resistance and slow down gastrointestinal motility³. Despite the increasing and widespread use of incretin-based therapies, substantial uncertainty about the cardiovascular safety still exists in these therapies.

So far there is lack of evidence comparing incretin-based therapies with other anti-diabetic treatments regarding cardiovascular safety in a trial network. The only one relevant network meta-analysis restricted incretin-based therapies to individual drugs of GLP-1 RAs⁴. While relevant pairwise meta-analyses have been available, they have not well demonstrated the cardiovascular safety issues of incretin-based therapies due to following limitations. Firstly, pairwise comparisons performed in these meta-analyses were mostly between DPP-4 inhibitors or GLP-1RAs and all active comparators combined in one class⁵⁻¹⁸. This may potentially dilute the specific effect of incretin-based therapies and make the interpretation

of results difficult from a clinical point of view. Secondly, some meta-analyses ^{5-14, 16-18} only included a limited number of trials focusing on one of the DPP-4 inhibitors or GLP-1RAs with relatively short trial duration (median follow-up of 1.5-3 years), leading to less statistical power for sparse-events data. Thirdly, clinical heterogeneity such age, trial duration, HbA1c% level, and years of T2DM was not properly explored in most of the meta-analyses ⁴⁻¹¹. Additionally, a majority of these studies ⁴⁻¹⁷ did not assess the quality of evidence and neglected its importance in explaining the results. All of these gaps restrain the evidence from fully informing clinical practice, making urgent need for high quality network meta-analysis.

Therefore, we aimed to collect all RCTs comparing incretin-based therapies with placebo or other anti-diabetic drugs among patients with T2DM for at least 12 weeks and conduct a network meta-analysis to assess the comparative cardiovascular safety of individual classes of anti-diabetic agents.

2. Methods

This study is registered with PROSPERO, number CRD42015020395.

2.1 Data sources and Searches

Medline, Embase and the Cochrane Central Register of Controlled Trials were searched from inception to April 28th, 2016 (see Web Appendix 1 for full details about the search strategy). Clinical trial registries (such as www.clinicaltrials.gov) were searched for unpublished trials. In addition, we also checked the reference list of all relevant articles to identify additional studies.

2.2 Study selection

Only RCTs (either double-blind, single-blind or open-label) written in English and with available data on cardiovascular events in which incretin-based therapies (including DPP-4 inhibitors and GLP-1RAs) compared with other active drugs or placebo in patients with T2DM were included. The duration of trials was at least 12 weeks. For studies that were longer than 12 weeks, final endpoint data were used for the analysis. The outcome of interest was a composite of cardiovascular events, which consisted of cardiovascular death, myocardial infarction, stroke (the three major adverse cardiovascular events (MACEs) defined by the Food and Drug Administration ¹⁹), and heart failure. For studies reporting adverse events but without specifically reporting cardiovascular events (zero-event in both arms), we also included them as zero-event in the analysis. The constant continuity correction method was used with an addition of a correction factor of 0.5 to the number of events and non-events in both treatment groups ²⁰. The eligibility of studies for inclusion criteria was assessed independently by four reviewers (SSW, JY, TC and FS) in duplicate. Any discrepancies were resolved by consensus between the two independent reviewers or by a senior investigator (FS).

2.3 Data extraction and quality assessment

Data were extracted using ADDIS software with respect to trial information (author, publication year, sample size, trial duration, types of intervention and control), population characteristics (background therapy, diabetes duration, age, baseline level of HbA1c), reported outcomes (number of cardiovascular events in each treatment group) and information on methodology. Four investigators (SSW, JY, TC and XCQ) extracted data independently, in duplicate. Risk of bias of included studies was assessed according to Cochrane risk of bias tool ²¹. Additionally, the GRADE (The Grading of Recommendations Assessment, Development, and Evaluation) framework was used to assess the quality of evidence contributing to each network estimate, which characterizes the quality of a body of evidence on the basis of the study limitations, imprecision, inconsistency, indirectness and publication bias for the primary outcomes ²².

2.4 Data Synthesis and Analysis

2.4.1 Methods for direct treatment comparisons

Standard pairwise meta-analysis was performed using DerSimonian-Laird random effects model. Odds ratios (OR) for cardiovascular events with 95% confidence interval (CI) were calculated as effect measures. The I^2 -statistic was calculated for heterogeneity, as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity. Besides, sensitivity analysis of pairwise meta-analysis was conducted to validate the robustness of the results by including double-blind studies and using only MACE as the outcome.

2.4.2 Methods for indirect and mixed comparisons

A random-effects network meta-analysis within a frequentist framework ²³ was then performed. OR for cardiovascular events with 95%CI was summarized. We estimated the ranking probabilities for all treatments of being at each possible rank for each intervention. The treatment hierarchy was summarized

and reported as surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA is a percentage interpreted as the probability of a treatment is the most effective without uncertainty on the outcome, which is equal to 1 when the treatment is certain to be the best and 0 when it is certain to be the worst. To check the assumption of consistency in the entire analytical network, a design-by-treatment approach was used ²⁴. A loop-specific approach was used to evaluate the presence of inconsistency locally in each closed loop. The node splitting method was used to assess the inconsistency of the model with separating evidence on a particular comparison into direct and indirect evidence. A global heterogeneity was assessed with I^2 -statistic and predictive interval plot ²⁵ that incorporate the extent of heterogeneity was used to evaluate the extent of uncertainty in the estimated effect size locally. Uncertainty affected by heterogeneity was defined as disagreement between the confidence intervals of relative treatment effects and their predictive intervals. Contribution plot was used to assess the contribution of each direct comparison to the estimation of each network meta-analytic summary effect, since it was helpful to evaluate the overall quality of evidence from network meta-analysis ²⁵. Additionally, a comparison-adjusted funnel plot was used to detect the potential publication bias in the results between small and large studies. To assess whether the results were impacted by study characteristics (effect modifiers), subgroup analysis was conducted according to age group, trial duration, HbA1c% level, years of T2DM, sample size, quality of study and sponsorship. Univariate and multivariate meta-regression was further conducted to control the confounding factors. Besides, sensitivity analysis of network meta-analysis was conducted to validate the robustness of the results by using only MACE as the outcome of interest and omitting open-label trials. All analyses were conducted using STATA 13.0 (pairwise meta-analysis, network meta-analysis, estimation of inconsistency and heterogeneity, funnel plot and SUCRA graphs) and R 3.3.0 (transforming data).

3. Results

3.1 Study characteristics

Overall, 281 trials met the inclusion criteria (see Web appendix 2 for full reference list). Flow chart of trials selection was shown in **Error! Reference source not found.** Eight treatments were analyzed, including incretin-based therapies (11 different DPP-4 inhibitors and 6 different GLP-1RAs), six other active anti-diabetic drugs [metformin, insulin, sulfonylurea, thiazolidinediones, alpha-glucosidase inhibitor (AGI) and sodium-glucose co-transporter 2(SGLT-2)] and placebo. 94.7% (266/281) of trials were two-arm studies and only 15 were multiple-arm studies (Appendix 3). Overall, 180,000 patients contributed to the analysis of cardiovascular events (see Web appendix 4 for evidence network). Appendix 3 summarized the characteristics of the included trials. Publication year varied from 2004 to 2016. Trial duration ranged from 12 to 312 weeks with a median follow-up of 24 weeks [interquartile range (IQR): 18-48 weeks]. The mean age of included patients was 57.0 years [standard deviation (SD) 4.6], the median duration of diabetes at baseline was 6.7 years (IQR: 4.7-8.8) and the mean baseline HbA1c level was 8.1% (SD 0.6%). Of the 281 trials included, DPP-4 inhibitors and GLP-1RAs were studies in 195 and 98 trials, respectively, and 12 trials involved both DPP-4 inhibitors and GLP-1RAs simultaneously. Among 195 trials including DPP-4 inhibitors, sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin were the most commonly studied drugs, with 75, 45, 23, 23 and 19 trials, respectively. Out of the 98 RCTs on GLP-1RAs, exenatide, liraglutide, lixisenatide, albiglutide, taspoglutide, dulaglutide and semaglutide were studied in 35, 31, 12, 8, 7, 5 and 1 trial, respectively.

3.2 Methodological quality and risk of bias results

In terms of quality of included studies, allocation concealment and blinding of outcome assessment were not clearly reported in 15.0% and 67.5% of the cases, respectively. By contrast, the methods for

randomization, blinding of participants and personnel and incomplete outcome data were appropriately described in the large majority of studies (95.5%, 78.0% and 100%, respectively). 21.7% (61/281) of trials were open label and 87.5% did not have selective reporting (the remaining 12.5% (35/281) was unclear due to no related protocol). Additionally, 89.3% (251/281) of trials were funded by company and only 2.1% (6/281) did not report the funding sources (see Web appendix 5 for risk of bias assessment). Overall, the risk of bias across studies was relatively low.

3.3 Results of pairwise meta-analysis

Figure 2 showed the effects of incretin-based therapies and other active anti-diabetic drugs on cardiovascular events from pairwise meta-analyses. A total of 1,496 and 2,560 cardiovascular events developed in 30,962 and 70,401 patients with GLP-1RAs and DPP-4 inhibitors while 3,935 cardiovascular events occurred among 51,204 patients with placebo. GLP-1RAs were associated with a significant reduction of cardiovascular events compared with placebo (OR=0.89, 95%CI: 0.82-0.69), while no significant difference was found when compared with other active comparators. DPP-4 inhibitors showed a neutral effect compared with placebo (OR=0.95, 95%CI: 0.89-1.01) and a decreased risk compared with sulfonylurea (OR=0.69, 95%CI: 0.53--0.89). No statistically significant difference was found in terms of cardiovascular events between sulfonylurea (OR=0.65, 95%CI: 0.22-1.94), thiazolidinediones (OR=0.84, 95%CI: 0.35 -2.01), SGLT-2 (OR=0.86, 95%CI: 0.28-2.68) and placebo (see Web appendix 6 for pairwise analysis). As shown in Web appendix 7, sensitivity analysis of pairwise meta-analysis by using only MACE as the outcome of interest and including only double-blind trials confirmed the beneficial cardiovascular effect of GLP-1RAs in comparison to placebo or sulfonylurea.

3.4 Results of network meta-analysis

Results of the network meta-analysis are reported in Figure 2. For risk of cardiovascular events, the

reduction was statistically significant for GLP-1RAs versus placebo (OR=0.89, 95%CI: 0.80-0.99) and sulfonylurea (OR=0.76, 95%CI: 0.59-0.99). The protective effect of GLP-1RAs was not observed in network meta-analysis compared with other active comparators [ranging between 0.72 (95% CI: 0.45-1.14) for thiazolidinediones to 1.12 (95% CI: 0.37-3.36) for AGI]. As for DPP-4 inhibitors, a neutral effect was detected when compared with placebo (OR=0.92, 95%CI: 0.83-1.01) and any active comparators. Besides, no significant association with cardiovascular events was found among any active comparators. According to the contribution plot of the network (see Web appendix 8), the comparison of placebo (treatment 1) versus GLP-1RAs (treatment 9) and DPP-4 inhibitors (treatment 2) had the largest contribution in the entire network (17.2% and 19.9%, respectively).

The test of global inconsistency did not detect any significant difference between the consistency and inconsistency models ($p=0.368$). Test for local inconsistency showed that most loops were consistent since their 95% CIs included 1 according to the inconsistency plots (see Web appendix 9 for assessment of inconsistency). The common heterogeneity through the multivariate meta-analysis was 0.06. The test of inconsistency from node-splitting model showed no significant difference in most comparisons, only three comparisons was with significant difference between direct and indirect comparisons (see Web appendix 9 for assessment of inconsistency). The global I^2 value was 0%. Predictive interval plot indicated that none of the comparisons were substantially affected by the estimated heterogeneity in the network (see Web appendix 10 for assessment of heterogeneity). At visual inspection, funnel plot for cardiovascular events (see Web appendix 11 for comparison-adjusted funnel plot) was quite symmetric and did not suggest any significant risk of publication bias in our sample of included studies.

Table 1 showed the mean values of SUCRA for providing the hierarchy of 9 treatments on cardiovascular events (Web appendix 12 showed the ranking probabilities of each treatment). According

to SUCRA, GLP-1RAs ranked first on decreasing cardiovascular risk among all 9 treatments with probability of 69.9%. According to GRADE, the quality of evidence ranged between very low and moderate, but was rated as low for most comparisons, moderate for GLP-1RAs versus placebo and low for DPP-4 inhibitors versus placebo (see Web appendix 13 for contribution summary of risk of bias assessment and Web appendix 14 for quality of evidence according to GRADE framework). Quality of evidence was low for overall ranking of treatment for cardiovascular events (see Web appendix 14 for quality of evidence according to GRADE framework).

In addition, sensitivity analysis of network meta-analysis by using only MACE as the outcome of interest and including double-blind trials confirmed the beneficial cardiovascular effect of GLP-1RAs versus placebo and sulfonylurea, plus the neutral effect of DPP-4 inhibitors versus placebo, which were in agreement with those previous produced (see Web appendix 7 for sensitivity analysis). Subgroup analyses demonstrated that the beneficial cardiovascular effect of GLP-1RAs versus placebo was more evident in patients with HbA1c level $\geq 8.5\%$, DM duration ≥ 10 years and older age (see Web appendix 15 for subgroup analysis). Univariate meta-regression indicated that the risk of cardiovascular events would decrease 33% for per 1% change of HbA1c (see Web appendix 16 for meta-regression analysis). Besides, findings of network meta-analysis only with trials at low risk of bias also confirmed the protective effect for GLP-1RAs and neutral effect for DPP-4 inhibitors when compared with placebo (see Web appendix 15 for subgroup analysis).

4. Discussion

Our network meta-analysis with 281 trials and 180,000 patients suggested that GLP-1RAs were associated with decreased risk of cardiovascular events compared with placebo and sulfonylurea, while DPP-4 inhibitors had a neutral effect on cardiovascular profiles in comparison with placebo and other

traditional anti-diabetic drugs. Aside from adequate glycaemia control, increasing attention is being paid to the cardiovascular safety of incretin-based therapies recently. EXSCEL study also showed the incidence of major adverse cardiovascular events did not differ significantly between patients with exenatide and those with placebo ²⁶.

Four large cardiovascular trials ²⁷⁻³⁰ for DPP-4 inhibitors and GLP-1RAs separately also failed to detect the favorable effect on cardiovascular events. The apparent inconsistency may be due to the limited sample size of those trials. The sample size of the four trials was 16,492, 5,380, 14,671 and 6,068, respectively, which was much smaller than the sample size of 180,000 patients in our analysis. As cardiovascular endpoint was a rare outcome, the limited sample size of each trial may be underpowered to assess the cardiovascular endpoint ^{3,31}. Moreover, the duration of those trials was relatively short (median follow-up of 1.5-3 years), making the beneficial cardiovascular effect not completely reflected ³². The United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI-1) trials all followed for up to 20-30 years to detect the significant reduction of cardiovascular risk in subjects initially treated with intensive glucose-lowering therapy ^{33, 34}. Therefore, the cardiovascular effect of incretin-based therapies may also require several years to achieve. Thirdly, participants in those trials were more complex multi-morbid with multifactorial interventions including anti-platelet, anti-hypertensive and lipid lowering agents, while patients included in our analysis were relatively healthier (50% and 70% of the trials without anti-hypertensive and lipid lowering therapy, respectively) ³². According to the comprehensive analysis of the effect of glycemic, blood pressure and cholesterol control on cardiovascular risk by Yudkin et al ³⁵, the number of subjects needed to treat for 5 years to prevent one cardiovascular event would be 44 with 1 mmol/l cholesterol lowering, 34 with a 10/5 mmHg reduction in blood pressure, and 119 with intensive

glucose lowering. Consequently, anti-hypertensive and lipid lowering treatments appear to have a greater impact than glucose lowering on cardiovascular events, making the favorable cardiovascular effect of incretin-based therapies less noticeable.

Nevertheless, several studies have supported the non-increasing effect of incretin-based therapies ³⁶⁻⁴⁰. Both GLP-1RAs and DPP-4 inhibitors might exert a favorable cardiovascular effect through anti-inflammatory mechanism, such as reductions in levels of tumor necrosis factor-alpha and mid-regional pro-adrenomedullin in patients with T2DM ³⁶. Moreover, incretin-based therapies have been shown to significantly reduce carotid intima-media thickness ³⁷, levels of albuminuria ^{36, 38}, epicardial adipose tissue ^{39, 40} and several cardiovascular risk biomarkers ^{36, 37} in patients with T2DM. Thus it may reflect clinically relevant benefit in cardiovascular events. To date, several long-term prospective trials (see Web appendix 17) specially designed for cardiovascular outcomes of incretin-based therapies, such as CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus, NCT01897532), are currently undergoing or in patients recruitment phase. Thus, it will take several years to confirm whether this protective effect on cardiovascular events, particularly for patients with higher HbA1c level, was true or not.

A major strength of our study is the comprehensive and substantial analysis of cardiovascular profiles of incretin-based therapies compared with placebo and other antidiabetic treatments separately in a whole trial network with high quality. In addition to the main analysis, we conducted detailed subgroup analyses and meta-regression by study characteristics (age group, trial duration, HbA1c% level, years of T2DM, sample size, quality of study, sponsorship and classification of incretin-based therapies) to address the clinical heterogeneity of studies. Furthermore, we carried out sensitivity analyses by using only MACE as the outcome and including only double-blind trials, the results were consistent, which indicated that

our findings were robust. Additionally, we assessed the quality of evidence and incorporate it into explaining the results by the GRADE framework.

Several limitations, however, should be mentioned and taken into account when interpreting the data from this study. First, most comparisons were assessed as low quality in the GRADE framework, which might restrict the interpretation of the results. Secondly, most trials included were not specially designed to evaluate the effect of incretin-based therapies on cardiovascular events. In nearly half of the trials, the outcome assessment (i.e. adjudication of cardiovascular events) was not blind and 90% of the studies were funded by the manufacturer of the investigational drug. Finally, we did not have access to original studies' data, so we could not perform an individual patient data meta-analysis to properly assess in our analyses potentially relevant effect modifiers such as, different baseline levels of diabetes duration and HbA1c or cardiovascular comorbidity (i.e. hypertension and hyperlipidemia).

5. Conclusions

GLP-1RAs not only show a similar risk of cardiovascular events in comparison with metformin, insulin, thiazolidinediones, alpha-glucosidase inhibitor and sodium-glucose co-transporter 2, but also appear to decrease the risk when compared with sulfonylurea or placebo, which seems to be a suitable option for long term treatment of type 2 diabetes mellitus. DPP-4 inhibitors seem to have a neutral effect when compared with placebo. However, the great majority of studies were funded by the pharmaceutical company marketing the investigational drug. Future guidelines should incorporate findings from this network meta-analysis, taking into account also the implications in terms of cost effectiveness for this new class of drugs.

Acknowledgements

We are grateful to all cooperating organizations and their staff whose hard work made this study possible.

AC is supported by the NIHR Oxford Cognitive Health Clinical Research Facility. ZRY is supported by the Cambridge Trust and the China Scholarship Council.

Funding

This study is funded by National Natural Science Foundation of China (81302508, 71673003). The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Author Contributions

FS and SYZ designed the study and drafted the manuscript. SSW, JY, TC and QXC extracted the data, SSW, ZRY, YZ and JY evaluated the RCTs quality. SSW, JY and FS assessed the quality of evidence by GRADE framework. TC, YX and ZRY verified the data, FS and SSW analyzed the data. FS, SYZ and AC interpreted the results, incorporated comments for the co-authors and finalized the manuscript. All authors approved the final version of the paper.

Conflicts of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no potential conflicts of interest relevant to this article.

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Table 1_ Ranking probability of different kinds of glucose-lowering drugs on cardiovascular events

Treatment	Cardiovascular events	
	SUCRA	Rank
Placebo	0.414	7
DPP-4I	0.629	3
GLP-1RA	0.699	1
Insulin	0.596	5
Met	0.501	6
SGLT-2	0.600	4
SU	0.217	8
AGI	0.632	2
TZD	0.212	9

Note: Ranking: probability of being the best treatment, of being the second best, the third best and so on, among the 8 treatments. SUCRA: surface under the cumulative ranking curve. DPP-4I: dipeptidyl peptidase-4 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; SGLT-2: sodium-glucose co-transporter 2; Met: metformin; SU: sulphonylureas; AGI: alpha-glucosidase inhibitor; TZD: thiazolidinediones.

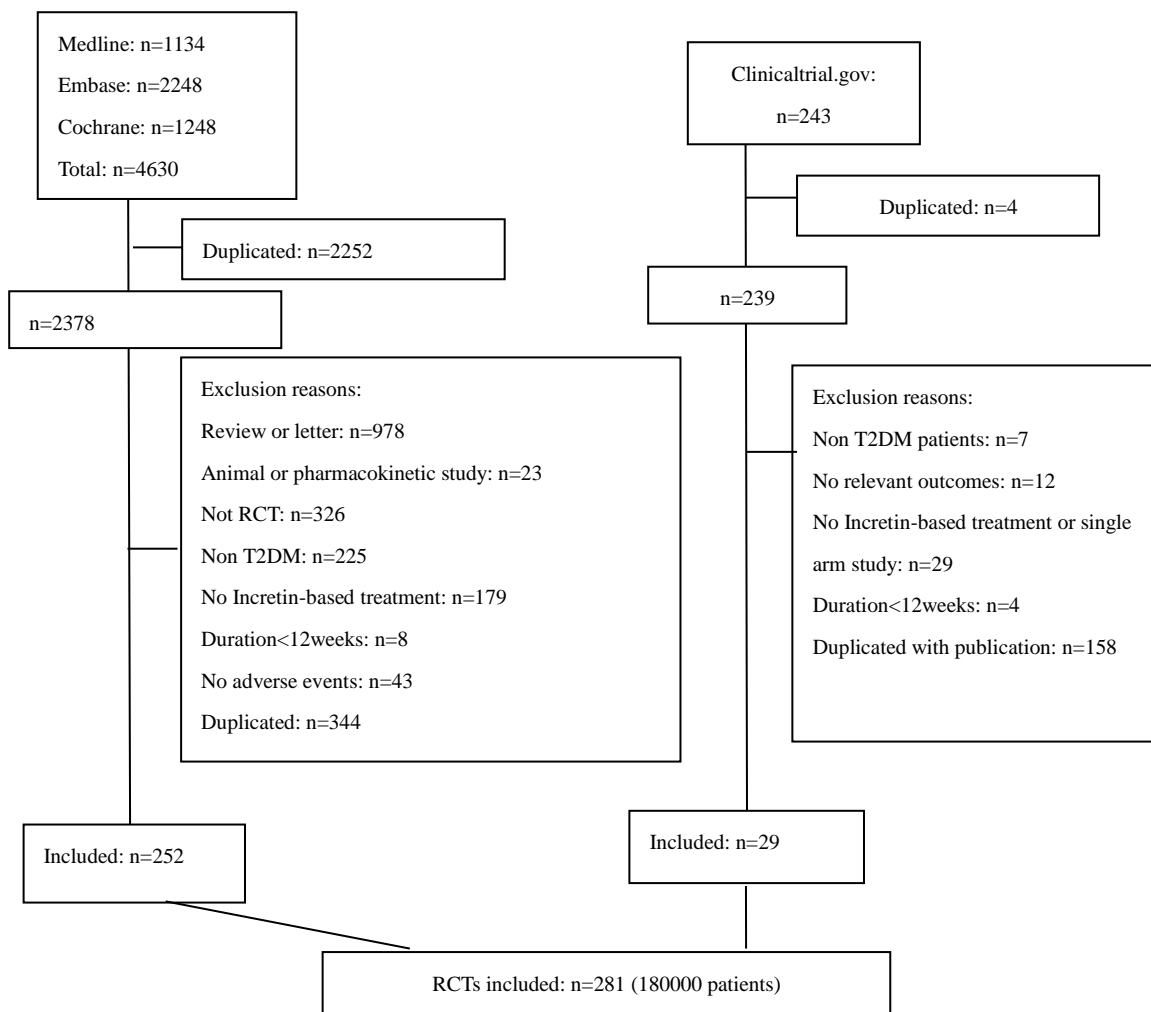


Figure 1. Flow chart of studies considered for inclusion. RCT: randomized controlled trial.

DPP-4I	0.91(0.49,1.67)	0.75(0.18, 3.03)	0.75(0.27,2.05)	1.03(0.40,2.63)	0.69(0.53,0.89)	1.15(0.39,3.44)	0.97(0.52,1.82)	0.95(0.89, 1.01)
1.03(0.90,1.18)	GLP-1RA	1.03 (0.65,1.64)	0.69 (0.14,3.38)	1.03 (0.40,2.63)	1.38 (0.82,2.32)	1.15 (0.39,3.45)	0.29 (0.12, 0.66)	0.89 (0.82,0.96)
1.02(0.65,1.59)	0.99(0.64,1.52)	Insulin	NA	NA	NA	NA	NA	1.27(0.21,7.78)
0.94(0.42,2.09)	0.91(0.40,2.04)	0.92 (0.37,2.30)	Met	NA	NA	NA	NA	NA
1.05(0.48,2.33)	1.02(0.46,2.28)	1.04 (0.42,2.57)	1.13 (0.36,3.48)	SGLT-2	NA	NA	NA	0.86 (0.28,2.68)
0.79(0.62,1.00)	0.76(0.59,0.99)	0.77 (0.47,1.27)	0.84 (0.36,1.94)	0.75 (0.33,1.71)	SU	NA	NA	0.65 (0.22,1.94)
1.15(0.39,3.44)	1.12(0.37,3.36)	1.13 (0.35,3.70)	1.23 (0.32,4.78)	1.09 (0.28,4.22)	1.47 (0.48,4.50)	AGI	NA	NA
0.74(0.47,1.17)	0.72(0.45,1.14)	0.73 (0.39,1.36)	0.79 (0.33,1.90)	0.70 (0.28,1.75)	0.94 (0.56,1.58)	0.64 (0.20,2.11)	TZD	0.84 (0.35,2.01)
0.92(0.83,1.01)	0.89(0.80,0.99)	0.90 (0.58,1.40)	0.98 (0.44,2.20)	0.87 (0.39,1.93)	1.17 (0.91,1.51)	0.80 (0.27,2.39)	1.24 (0.78,1.97)	Placebo

Figure 2. Odds ratio (OR) with 95%CI of network meta-analysis for cardiovascular events.

Note: Treatments were reported in alphabetical order. Results of direct comparisons were listed in the upper triangle, and the estimation was calculated as the row-defining treatment compared with the column-defining treatment. Results of network meta-analysis were listed in the lower triangle, and the estimation was calculated as the column-defining treatment compared with the row-defining treatment. NA: not available. DPP-4I: dipeptidyl peptidase-4 inhibitors; GLP-1RA: Glucagon-like peptide-1 receptor agonists; SGLT-2: Sodium-Glucose co-Transporter 2; Met: metformin; SU: sulphonylureas; AGI: alpha-glucosidase inhibitor; TZD: thiazolidinediones.