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The effects of incretin-based therapies on beta-cell function and insulin resistance in type 2 diabetes: a systematic review and network meta-analysis combining 360 trials

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ABSTRACT

Aim: To evaluate the comparative effects of incretin-based therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4Is), on beta-cell function and insulin resistance in patients with type 2 diabetes mellitus (T2DM).

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Materials and Methods: Medline, Embase, the Cochrane Library and www.clinicaltrials.gov were searched for randomized controlled trials (RCTs) with duration≥4 weeks. Network meta-analysis was performed, followed by subgroup analysis and meta-regression. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the quality of evidence. The outcome of interest includes homeostasis model assessment for β cell function (HOMA-β) and insulin resistance (HOMA-IR), fasting C-Peptide and fasting plasma glucose (FPG). Weighted mean difference (WMD) with 95% confidence interval (CI) was calculated as the measure of effect size.

Results: 360 RCTs (74% at least double-blinded) with 157,696 patients were included, comparing incretin-based therapies with other six classes of glucose-lowering drugs or placebo. Compared with placebo, significant increase of HOMA-β and fasting C-Peptide were detected for GLP-1RAs (WMD=20.31(95%CI: 16.34 to 24.39) with low quality, WMD=0.16ng/ml (95%CI: 0.03 to 0.29) with low quality) and DPP-4Is (WMD=9.90 (95%CI: 8.27 to 11.61) with moderate quality, 0.09ng/ml (95%CI: 0.04 to 0.14) with moderate quality) separately, while significant reduction of HOMA-IR and FPG were found in favour of GLP-1RAs (WMD=-0.67 (95%CI: -1.08 to -0.27) with low quality, -1.04mmol/L (95%CI: -1.26 to -0.83) with moderate quality) and DPP-4Is (WMD=-0.23 (95%CI: -0.38 to -0.08) with low quality, -0.77mmol/L (95%CI: -0.98 to -0.57) with moderate quality) respectively.

Conclusions: Incretin-based therapies not only show an increase of HOMA-β and fasting C-Peptide level, but also achieve a reduction of HOMA-IR and FPG in comparison with placebo. Even though GRADE evidences indicate low to moderate for most comparisons, incretin-based therapies seem to be advisable option for long term treatment to obtain preservation of β-cell function.

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Key words: Incretin-based therapies, type 2 diabetes, network meta-analysis, β-cell function, insulin resistance

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by a gradual deterioration of pancreatic beta cell function with insulin resistance (IR) [1-4]. The beta cell failure contributes to the worsening of hyperglycemia, while hyperglycemia itself is also detrimental for beta cell function leading to disease progression [5]. Therefore, it is critically important for glucose-lowering drugs that can preserve beta cell function in T2DM patients.

As a new class of glucose-lowering drugs, incretin-based therapies have been introduced for T2DM, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4Is). GLP-1 RAs mainly lower blood glucose by stimulating insulin secretion and inhibiting gastrointestinal motility, whereas DPP-4Is prevent the rapid degradation of GLP-1 through inhibition of DPP-4, thus enhancing pancreatic insulin secretion and suppressing pancreatic glucagon secretion [6,7]. Despite the increasing and widespread use of incretin-based therapies, substantial uncertainty about the beta-cell function and IR still exists in these therapies.

Although it has been proved that GLP-1 is associated with increased beta-cell mass and improved beta-cell function in some rodent models and vitro studies, the beneficial effects of incretin-based therapies for beta-cell function and IR in humans is yet unclear [8-12]. The homoeostasis model assessment (HOMA) indexes (HOMA-β and HOMA-IR), fasting C-peptide and fasting plasma glucose (FPG) are important indicators measuring beta-cell function and IR in vivo. Due to limited sample size and relative large variation of these indexes, results of different trials were inconsistent with underpowered. Although two meta-analyses are available until now, both of them were pairwise comparison between DPP-4Is and all other comparators (combining placebo and other active controls into one class) [13,14]. From a clinical point of view, these types of comparisons may potentially dilute the

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true effect of DPP-4Is due to mixed controlled groups and threaten the validity of results. So far there is also lack of evidence comparing incretin-based therapies with other glucose-lowering treatments regarding beta-cell function and insulin resistance in a trial network.

Therefore, we aimed to collect all RCTs comparing incretin-based therapies with placebo or other glucose-lowering drugs among T2DM patients for at least 4 weeks and conduct a network meta-analysis to assess the comparative effects on beta-cell function and insulin resistance of individual classes of glucose-lowering agents.

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2 MATERIALS AND METHODS

This study is registered on International Prospective Register of Systematic Review PROSPERO, number CRD 42018094042. The study was conducted according to the PRISMA-NMA checklist.

2.1 Data sources and Searches

Medline, Embase and the Cochrane Central Register of Controlled Trials were searched from inception to June 23th, 2017 (Web Appendix 1 for full details about the search strategy). Clinical trial registry (such as www.clinicaltrials.gov) was 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 quadruple-blind, triple-blind, double-blind, single-blind or open-label) written in English and with available data on β-cell function and insulin resistance in which incretin-based therapies (including GLP-1RAs and DPP-4Is) compared with other active drugs or placebo in patients with T2DM were included. The duration of trials was at least 4 weeks. For studies that were longer than 4 weeks, final endpoint data were used for the analysis. The outcome of interest includes HOMA-β, HOMA-IR, fasting C-Peptide and FPG. The eligibility of studies for inclusion criteria was assessed independently by four reviewers (SSW, JY, SQY and FS) in duplicate. Any discrepancies were resolved by consensus between the four independent reviewers.

2.3 Data extraction and quality assessment

Data were extracted using ADDIS software [15] 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 (mean change from baseline and corresponding standard deviation of each treatment group) and information

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on methodology. Four investigators (SSW, JY, SQY and ZRY) extracted data independently in duplicate. Risk of bias of included studies was assessed according to Cochrane risk of bias tool (ROB tool) [16]. Since our outcome measures (HOMA-β, HOMA-IR, fasting C-Peptide and FPG) were all obtained from objective laboratory tests, detection bias was the same for all four outcomes, so we only performed risk of bias assessment once. 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 [17].

2.4 Data Synthesis and Analysis

Methods for direct treatment comparisons

Standard pairwise meta-analysis was performed using DerSimonian-Laird random effects model. Weighted mean difference (WMD) with 95% confidence interval (CI) of each outcome was calculated as effect measure. 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 omitting open label studies.

Methods for indirect and mixed comparisons

A random-effects network meta-analysis within a Bayesian framework [18] was then performed. WMD for each outcome 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,

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which was considered as secondary endpoint. 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.

Examination of assumptions in network meta-analysis (consistency, transitivity and heterogeneity)

To check the assumption of consistency in the entire analytical network, a design-by-treatment approach was used [19]. A loop-specific approach was used to evaluate the presence of inconsistency locally in each closed loop. The node splitting method and heatmap were 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 [20] 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. The transitivity assumption underlying network meta-analysis was evaluated by comparing the distribution of clinical variables which could act as effect modifiers across treatment comparisons.

Publication bias, subgroup analyses and meta-regression

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 [20]. 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 network meta-analysis was conducted according to trial duration, age group, HbA1c% level, years of T2DM, sample size, quality of study and sponsorship. Univariable and multivariable network

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meta-regression in the context of Bayesian framework was further conducted to examine the potential modification effects of trial duration, age, diabetes duration and HbA1c. Besides, since the trials included were with different duration, sensitivity analysis of network meta-analysis was narrowed into trials with longer duration (≥24weeks) to validate the robustness of the results.

All analyses were conducted using R 3.5.0 (gemtc package, network meta-analysis, assessment of global heterogeneity, network meta-regression, and SUCRA graphs), and STATA 13.0 (pairwise meta-analysis, estimation of inconsistency, transitivity and local heterogeneity, funnel plot).

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3 RESULTS

3.1 Study characteristics

Overall, 360 trials met the inclusion criteria (Web appendix 2 for full reference list). Flow chart of trials selection was shown in Figure 1. Nine treatments were analyzed, including incretin-based therapies (11 different DPP-4Is and 7 different GLP-1RAs), six other active glucose-lowering drugs [metformin, insulin, sulfonylurea, thiazolidinediones, alpha-glucosidase inhibitor (AGI) and sodium-glucose co-transporter 2(SGLT-2)] and placebo. 91.9% (331/360) of trials were two-arm studies and only 29 were multiple-arm studies (Appendix 3). Overall, 157,696 patients contributed to the whole analysis, of which, 68241, 42242, 15397 and 135333 patients contributed to four outcomes of HOMA-β, HOM-IR, fating C-Peptide and FPG, respectively (Figure 2 for evidence network). Appendix 3 summarized the characteristics of the included trials. Publication year varied from 2004 to 2017. Trial duration ranged from 4 to 235 weeks with a median follow-up of 24 weeks [interquartile range (IQR): 16-30 weeks]. The mean age of included patients was 56.2 years [standard deviation (SD) 4.99], the median duration of diabetes at baseline was 6.6 years (IQR: 4.6-8.8) and the mean baseline HbA1c level was 8.1% (SD 0.7%). The mean baseline HOMA-β and HOMA-IR was 45.4±15.4 and 4.5±1.9, respectively (Web appendix 4). Of the 360 trials included, DPP-4 Is and GLP-1RAs were studied in 252 and 135 trials, respectively, and 17 trials involved both DPP-4Is and GLP-1RAs simultaneously. Among 252 trials concerning DPP-4 Is, sitagliptin, vildagliptin, linagliptin, alogliptin and saxagliptin, were the most common studied drugs, with 110, 52, 26, 25 and 23 trials, respectively. In view of the 135 RCTs on GLP-1RAs, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, taspoglutide and semaglutide were studied in 45, 42, 17, 9, 14, 7 and 3 trials separately.

3.2 Methodological quality and risk of bias results

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In terms of quality of included studies, allocation concealment was not clearly reported in 15.0% of the cases. By contrast, the methods for randomization, blinding of participants and personnel and incomplete outcome data were appropriately described in the large majority of studies (90.5%, 75.2% and 97.9%, respectively). 23.5% of trials were open label and 93.9% did not have selective reporting (the remaining 5.8% was unclear due to no related protocol). Blinding of outcome assessment was generally low risk of bias as all 4 outcomes were obtained from objective laboratory tests. Additionally, 78.9% of trials were funded by company and only 2.4% did not report the funding sources (Web appendix 5 for risk of bias assessment). Overall, the risk of bias across evidence network was relatively low.

3.3 Results of pairwise meta-analysis

The effects of incretin-based therapies and other active glucose-lowering drugs on beta-cell function and insulin resistance from pairwise meta-analyses were shown in Figure 3. GLP-1RAs and DPP-4 Is were associated with a significant increase of HOMA-β (WMD=20.98 (95%CI: 14.54, 27.41) and 9.97 (95%CI: 8.00, 11.94) respectively) and a significant reduction of HOMA-IR (WMD=-0.60 (95%CI: -1.20, -0.10) and -0.23 (95%CI:-0.42, -0.05) respectively) compared with placebo. In addition, DPP-4Is could slightly increase fasting C-Peptide level versus placebo (WMD=0.09ng/ml, 95%CI: 0.04, 0.14). Significant decrease was found in terms of FPG level among GLP-1RAs, DPP-4Is, and other active comparators versus placebo with ranges from -2.33 to -0.83mmol/L.

3.4 Results of network meta-analysis

Results of the network meta-analysis are reported in Figure 4-5. An improvement effect of HOMA-β was detected for GLP-1RAs versus placebo (WMD=20.31, 95%CI: 16.34, 24.39), metformin (WMD=13.98, 95%CI: 8.01, 19.94), TZD (WMD=16.45, 95%CI: 8.72, 24.14) and AGI (WMD=17.17,

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95%CI: 9.82, 24.37) individually, while no such evident effect was observed when compared with other active comparators. As for DPP-4Is, the improvement effect was found when compared with placebo (WMD=9.90, 95%CI: 8.27, 11.61) and AGI (WMD=6.78, 95%CI: 0.55, 12.61). However, HOMA-β was significantly lowered when compared with GLP-1RAs (WMD=-10.4, 95%CI: -14.49, -6.28), SGLT-2 (WMD=-12.53, 95%CI: -24.27, -0.47) and SU (WMD=-10.04, 95%CI: -14.80, -5.28).

Regarding to HOMA-IR, both GLP-1RAs and DPP-4Is could reduce insulin resistance compared with SU (WMD=-1.07(95%CI: -1.59, -0.56), -0.63(95%CI: -0.98, -0.28)) and placebo (WMD=-0.67(95%CI:-1.08, -0.27), -0.23(95%CI:-0.38, -0.08)), respectively. As for other active comparators, metformin (WMD=-0.77) and TZD (WMD=-1.53) were associated with reduction of HOMA-IR versus placebo, whereas SU seemed the increased risk of insulin resistance versus placebo (WMD=0.40).

In terms of fasting C-Peptide, the increase was statistically significant for GLP-1RAs (WMD=0.16ng/ml, 95%CI:0.03, 0.29) and DPP-4Is (WMD=0.09ng/ml, 95%CI:0.04, 0.14) compared with placebo, whereas TZD was associated with reduction of fasting C-Peptide versus placebo (WMD=-0.29ng/ml). In comparison with TZD, both GLP-1RAs and DPP-4Is indicated increased level of fasting C-Peptide with 0.45ng/ml (95%CI:0.24, 0.66) and 0.38ng/ml (95%CI:0.22, 0.54), respectively. Besides, no significant association was found among any other comparison.

As for FPG, all of the active treatments except AGI showed significantly decrease compared with placebo [range from -0.77(DPP-4Is) to -1.94mmol/L (Insulin)]. Among all active comparators, insulin significantly reduced FPG compared with other active comparators except SGLT-2 and TZD [range from -0.27(DPP-4Is) to -2.47mmol/L (AGI)]. Additionally, GLP-1RAs indicated significantly reduction of FPG compared with DPP-4Is (WMD=-0.27mmol/L, 95%CI:-0.52, -0.02).

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According to the contribution plots of the network (Web appendix 6), the comparison of placebo (treatment 1) versus GLP-1RAs (treatment 3) or DPP-4 Is (treatment 2) had the largest contribution in all 4 entire networks with 13.1% and 48.4% for HOMA-β, 8.1% and 54.8% for HOMA-IR, 14.0% and 62.0% for fasting C-Peptide, 18.8% and 34.1% for FPG, respectively.

3.5 Transitivity, inconsistency and heterogeneity

Assessment of transitivity by box plots indicated that mean age, mean baseline HbA1c and mean duration of diabetes across treatment comparisons were relatively similar (Web appendix 7). The test of global inconsistency did not detect any significant difference between the consistency and inconsistency models for all 4 outcomes (p=0.354 for HOMA-β, p=0.717 for HOMA-IR, p=0.980 for fasting C-Peptide and p=0.613 for FPG, respectively). Test for local inconsistency showed that all loops were consistent for HOMA-β, HOMA-IR, fasting C-Peptide, and most loops were consistent for FPG (20/23 loops) since their 95% CIs included 1 according to the inconsistency plots (Web appendix 8 for assessment of inconsistency). The test of inconsistency from node-splitting model and heatmaps showed no significant difference in most comparisons for all 4 outcomes, only two comparisons for FPG had significant differences between direct and indirect comparisons (Web appendix 8 for assessment of inconsistency). The global I^2 was 87.9%, 97.4%, 35.7% and 93.0% for HOMA-β, HOMA-IR, fasting C-Peptide and FPG, respectively. Predictive interval plot indicated that 25.0%, 38.1%, 21.4% and 61.1% of the comparisons for HOMA-β, HOMA-IR, fasting C-Peptide and FPG were substantially affected by the estimated heterogeneity in the network (Web appendix 9 for assessment of heterogeneity). The common heterogeneity through the bayesian meta-analysis was 41.66 for HOMA-β, 0.19 for HOMA-IR, 0.01 for fasting C-Peptide and 0.33 for FPG. At visual inspection, funnel plots for all four outcomes (Web appendix 10 for comparison-adjusted funnel plot)

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were relatively quite symmetric and did not suggest any significant risk of publication bias in our sample of included studies.

3.6 SUCRA and ranking of all treatments

Web appendix 11 showed the mean values of SUCRA for providing the hierarchy ranking of different treatments on HOMA-β, HOMA-IR, fasting C-Peptide and FPG. According to SUCRA, GLP-1RAs ranked first, third, second and third on improvement of HOMA-β, HOMA-IR, fasting C-Peptide and FPG among all treatments with probability of 86.4%, 70.3%, 81.1% and 74.1%, whereas DPP-4Is had a probability of 47.6%, 41.3%, 64.1% and 29.1% to rank fifth, fifth, third and seventh for each corresponding outcome above. However, considering not all trials were included (trials with active comparator like metformin, insulin, SU and SGLT-2 were not included), the ranking might be by highly biased and interpretation should be made with caution.

3.7 GRADE evaluation on quality of evidence

According to GRADE, the quality of evidence ranged between very low and high, but was rated as low and moderate for most comparisons. In terms of GLP-1RAs versus placebo, the quality was low for HOMA-β, HOMA-IR and fasting C-Peptide whereas moderate for FPG. As for DPP-4Is versus placebo, the quality was moderate for HOMA-β, fasting C-Peptide and FPG while low for HOMA-IR (Web appendix 12 for contribution summary of risk of bias assessment and Web appendix 13 for quality of evidence according to GRADE framework). Quality of evidence was low for overall ranking of treatment for HOMA-β, fasting C-Peptide and FPG whereas moderate for HOMA-IR (Web appendix 13).

3.8 Sensitivity analyses, subgroup analyses and meta-regression analyses

In addition, sensitivity analysis of network meta-analysis by narrowing into trials with duration

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≥24weeks confirmed the beneficial β-cell function effect and improved insulin resistance of GLP-1RAs and DPP-4Is versus placebo, which were in agreement with those previous produced (Web appendix 14 for sensitivity analysis). Subgroup analyses demonstrated that the beneficial β-cell function and insulin resistance effects of GLP-1RAs and DPP-4Is versus placebo was more evident in patients with HbA1c level<8.0% and T2DM duration<5 years (Web appendix 15 for subgroup analysis). Multivariable meta-regression indicated that for GLP-1RAs versus placebo, HOMA-β would increase by 37.7% and HOMA-IR would decrease by 1.67% for per 10 years change of age, 1.54% for per 1.0% increase of HbA1c and meanwhile 7.96% for per week longer of treatment duration (Web appendix 16 for meta-regression analysis). Besides, findings of network meta-analysis only with trials at low risk of bias also confirmed the effects of GLP-1RAs and DPP-4Is on improving β-cell function compared with placebo (Web appendix 15 for subgroup analysis).

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4 DISCUSSION

Aside from adequate glycaemia control, increasing attention is being paid to the preservation of β-cell function and improvement of insulin resistance of glucose-lowering drugs. Our network meta-analysis with 360 trials and 157,696 patients suggested that incretin-based regimens, both GLP-1RAs and DPP-4Is, were associated with beneficial effects of β-cell function and improved insulin resistance compared with placebo.

Several large-scale trials [21-23], including United Kingdom Prospective Diabetes Study (UKPDS) [21] and A Diabetes Outcome Progression Trial (ADOPT) [22], have proved that the worsening of glycemic control in T2DM is due to progressive decline of beta-cell function through an apoptosis-induced decline in beta-cell mass [24]. Thus, it highlights the importance of preserving β-cell function and improving insulin resistance in the management of T2DM. Our results were consistent with several large clinical trials for GLP-1RAs and DPP-4Is separately [25-27]. In a trial specifically designed for the effect on β-cell function, exenatide (a GLP-1 receptor agonist) was demonstrated to improve β-cell function measured not only by static index (HOMA-B, fasting C-Peptide) but also by dynamic tests (hyperglycaemic clamps), and the favorable effect was sustained up to three years [25]. Similarly, SAVOR-TIMI 53 trial indicated that saxagliptin (a DPP-4 inhibitor) was associated with an increase of 6.0% in HOMA-β, which may postpone the usual decline of β-cell function, thereby slow down diabetes progression [26]. Another pooled analysis [27] from six vildagliptin trials showed that the improvement of β-cell function would be attenuated by longer duration of T2DM, which was also in line with our subgroup analysis results.

In addition, the beneficial effect on β-cell function and insulin resistance of incretin-based therapies are biologically reasonable [11, 12, 28-31]. Both GLP-1RAs and DPP-4Is might exert a favorable effect

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through GLP-1 mediated role, which has been proved both in vitro and pre-clinical models of T2DM. GLP-1 was associated with improved survival of human islets and increased β-cell mass by stimulating β-cell differentiation and proliferation [28,29]. Moreover, GLP-1 may prevent endoplasmic reticulum stress and reduce oxidative, inflammation and apoptosis in human islets [11, 12, 30, 31]. Thus, it may reflect clinically relevant benefit in β-cell function and insulin resistance. To date, several long-term prospective trials specifically designed for β-cell preservation, such as RISE Adult Medication Study [32] (Restoring Insulin Secretion, NCT01779362), are currently in patients' recruitment phase. Thus, it will take several years to confirm whether this protective effect on β-cell function and insulin resistance was true or not.

One worthy to be noted, it should be recognized that HOMA is a measure of static insulin sensitivity and β-cell function, not giving information about the stimulated state compared with clamps tests. So it provides limited information on β-cell function[33]. However, as a simple tool, HOMA might be more appropriate for use in large epidemiological studies to assess the effects of treatments or investigate natural history of diabetes, although clamps are often considered as the "golden standard". Besides, it has been proved good correlation between results from HOMA and clamps [34].

A major strength of our study is the comprehensive search and analysis of β-cell function profiles of incretin-based therapies compared with placebo and other antidiabetic treatments in a whole network with high quality. Furthermore, we carried out sensitivity analyses by including trials with duration ≥ 24weeks, the results were consistently significant, which indicated that our findings were robust. Meanwhile, we also conducted detailed subgroup analyses and meta-regression by study characteristics (age group, trial duration, HbA1c% level, years of T2DM, sample size, quality of study and sponsorship) to address the heterogeneity of studies. Additionally, we assessed the quality of evidence

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and incorporate it into explaining the results by the GRADE framework.

Several limitations, however, should be mentioned. First, most trials included were not specially designed to evaluate the effect of incretin-based therapies on β-cell function profiles. Nearly 80% of the studies were funded by the manufacturer of the investigational drug. Thus, the results should be interpreted with caution. Secondly, some comparisons were assessed as low quality in GRADE framework, which might restrict the interpretation of results. Finally, we did not have access to original trials' 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.

Conclusions

GLP-1RAs and DPP-4Is not only show an increase of HOMA-β and fasting C-Peptide level, but also achieve a reduction of HOMA-IR and FPG in comparison with placebo, which seems to be a suitable option for long term treatment of T2DM patients to obtain preservation of β-cell function. However, majority of studies were funded by 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.

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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, SQY and ZRY extracted the data, SSW, ZRY, YZ and JY evaluated the RCTs quality. SSW, JY and FS assessed the quality of evidence by GRADE framework. SQY, YX and ZRY verified the data, LG and SSW analyzed the data. YH and ZLZ revised the manuscript. 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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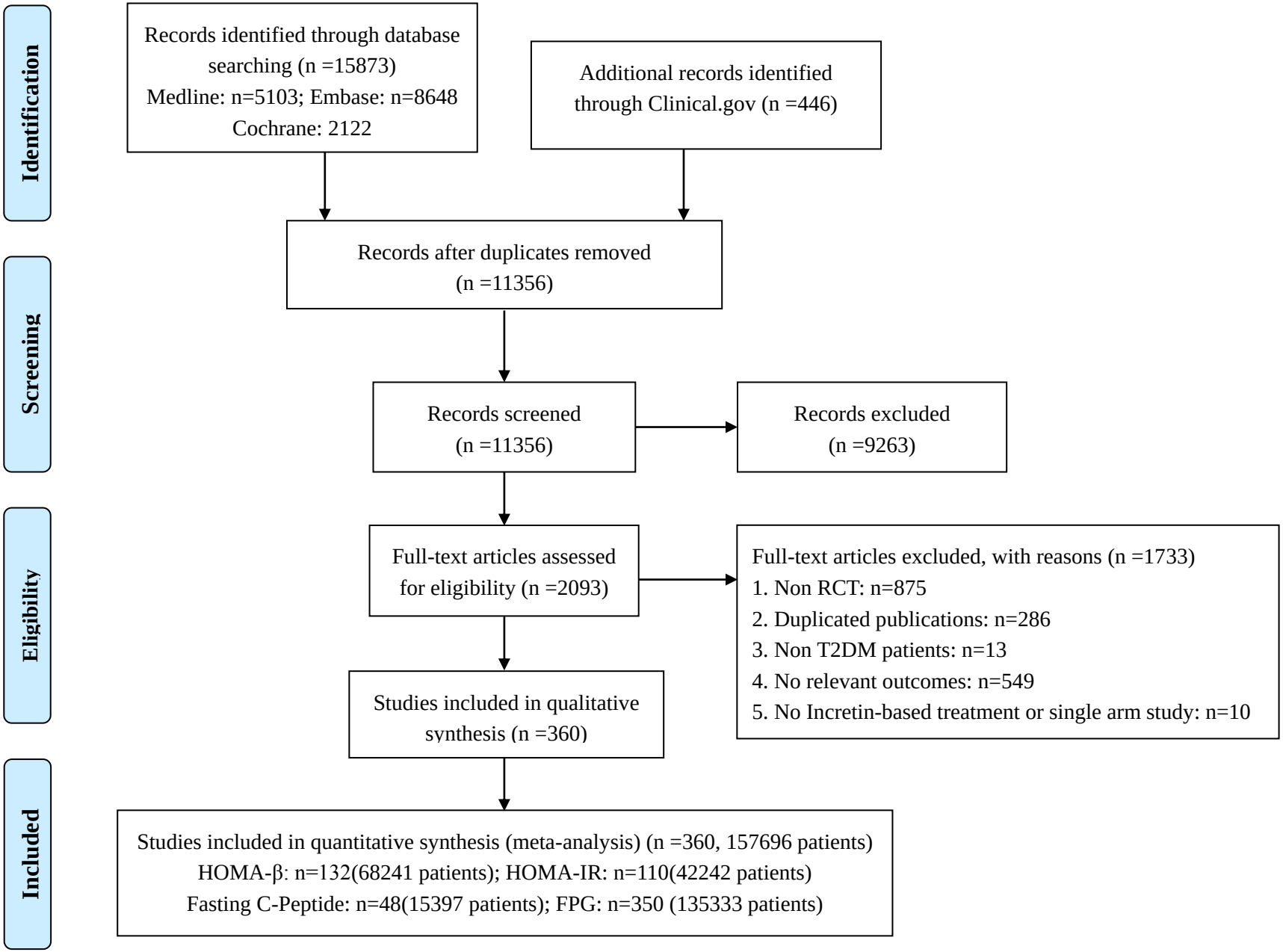

Figure 1. Flow chart of studies considered for inclusion.

HOMA-β: homeostasis model assessment for β cell function; HOM-IR: homeostasis model assessment for insulin resistance; FPG: fasting plasma glucose.

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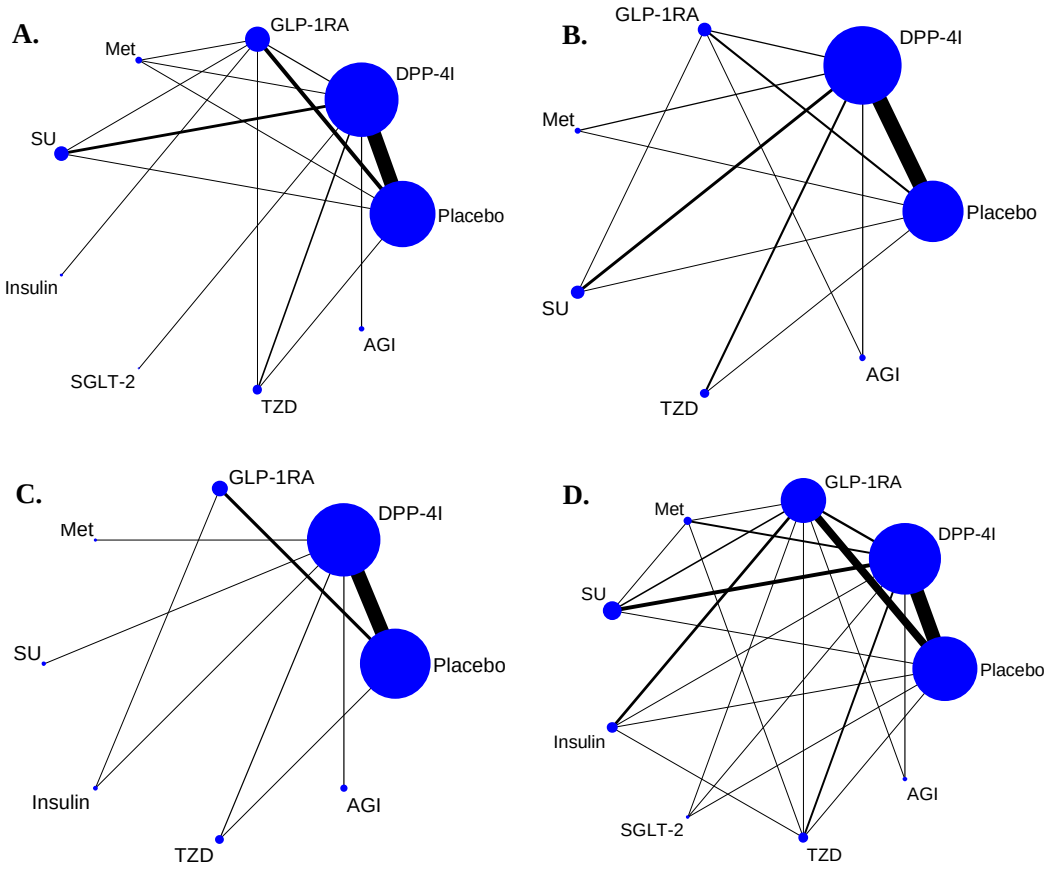

Figure 2. Evidence structure of eligible comparisons for network meta-analysis. A. HOMA-β. B. HOMA-IR. C. Fasting C-Peptide. D. FPG.

Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible RCTs. The width of the lines represents the cumulative number of RCTs for each pairwise comparison and the size of every node is proportional to the number of randomized participants (sample size). HOMA-β: homeostasis model assessment for β cell function; HOM-IR: homeostasis model assessment for insulin resistance; FPG: fasting plasma glucose; DPP-4I: dipeptidyl peptidase-4 inhibitors; GLP-1RA: Glucagon-like peptide-1 receptor agonists; SGLT-2: Sodium-Glucose co-Transporter 2; Met: metformin; SU: sulphanylureas; AGI: alpha-glucosidase inhibitor; TZD: thiazolidinediones.

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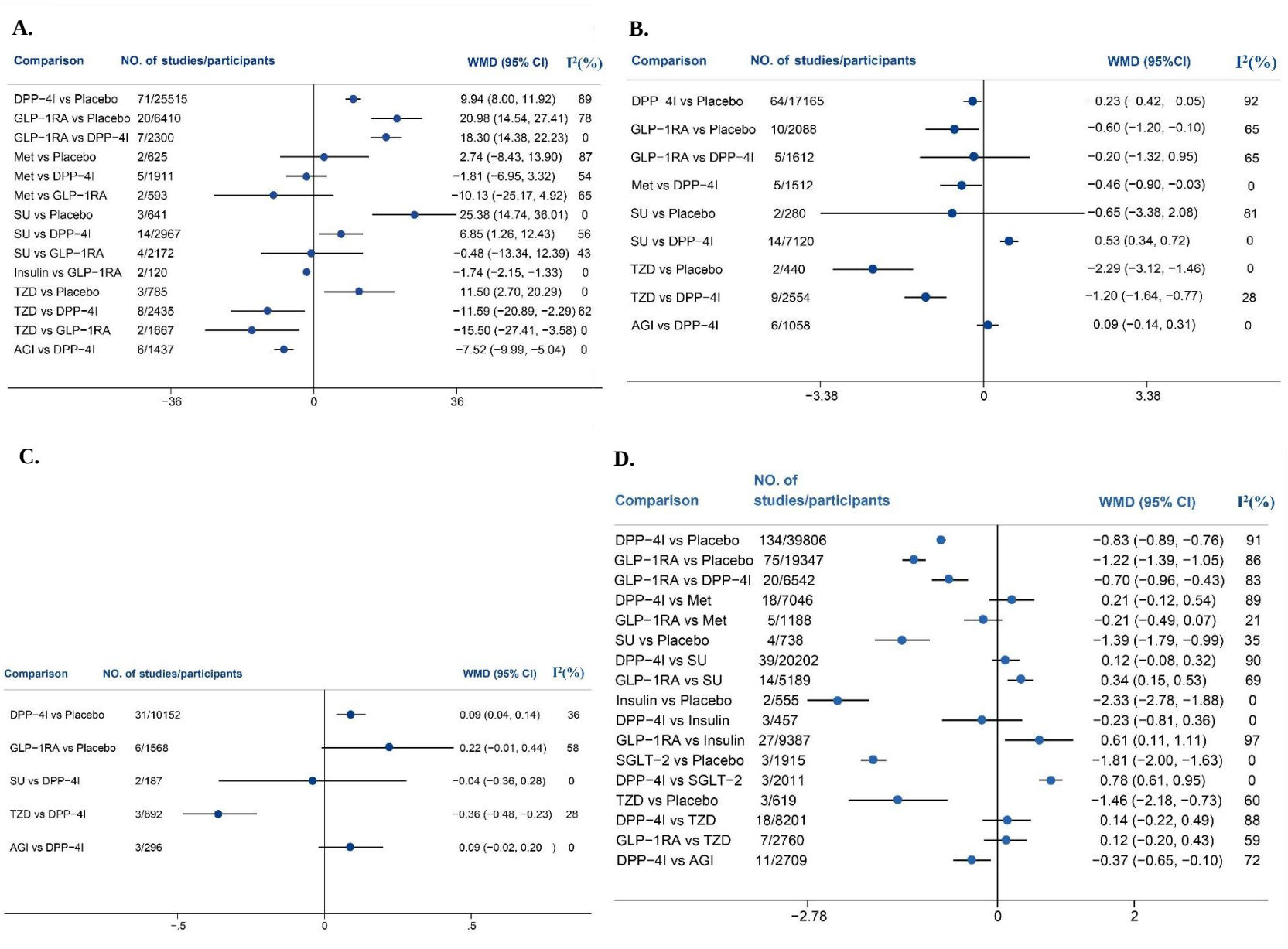

Figure 3. Results of direct pairwise meta-analysis for each outcome. A. HOMA-β. B. HOMA-IR. C. Fasting C-Peptide. D. FPG. HOMA-β: homeostasis model assessment for β cell function; HOM-IR: homeostasis model assessment for insulin resistance; FPG: fasting plasma glucose; DPP-4I: dipeptidyl peptidase-4 inhibitors; GLP-1RA: Glucagon-like peptide-1 receptor agonists; Met: metformin; SU: sulphanylureas; AGI: alpha-glucosidase inhibitor; TZD: thiazolidinediones.

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DPP-4I	**0.27 (0.02, 0.52)**	0.09 (-0.37, 0.55)	0.66 (-0.18, 1.48)	0.03 (-0.27, 0.32)	**0.63 (0.14, 1.12)**	-1.30 (-3.09, 0.43)	**1.17 (0.67, 1.66)**	**-0.77 (-0.98, -0.57)**
-10.40 (-14.49, -6.28)	**GLP-1RA**	-0.18 (-0.66, 0.29)	0.39 (-0.44, 1.19)	-0.24 (-0.59, 0.11)	0.36 (-0.14, 0.85)	-1.57 (-3.38, 0.18)	**0.90 (0.47, 1.33)**	**-1.04 (-1.26, -0.83)**
3.58 (-1.58, 8.52)	**13.98 (8.01, 19.94)**	**Met**	0.57 (-0.37, 1.48)	-0.06 (-0.59, 0.47)	0.54 (-0.09, 1.18)	-1.40 (-3.22, 0.40)	**1.08 (0.44, 1.72)**	**-0.86 (-1.33, -0.38)**
-12.53 (-24.27, -0.47)	-2.09 (-14.51, 10.57)	**-16.14 (-28.87, -2.95)**	**SGLT-2**	-0.64 (-1.50, 0.25)	-0.03 (-0.98, 0.92)	**-1.97 (-3.91, -0.07)**	0.51 (-0.41, 1.44)	**-1.43 (-2.24, -0.60)**
-10.04 (-14.80, -5.28)	0.38 (-5.59, 6.32)	**-13.67 (-20.31, -6.64)**	2.46 (-10.50, 15.20)	**SU**	**0.60 (0.03, 1.16)**	-1.33 (-3.12, 0.46)	**1.14 (0.60, 1.68)**	**-0.80 (-1.15, -0.47)**
6.03 (-0.78, 12.92)	**16.45 (8.72, 24.14)**	2.44 (-5.93, 10.97)	**18.53 (4.72, 32.57)**	**16.09 (7.79, 24.34)**	**TZD**	**-1.94 (-3.81, -0.09)**	0.54 (-0.09, 1.16)	**-1.40 (-1.91, -0.89)**
6.78 (0.55, 12.61)	**17.17 (9.82, 24.37)**	3.13 (-4.84, 10.99)	**19.28 (5.78, 32.57)**	**16.83 (9.02, 24.59)**	0.69 (-8.41, 9.78)	**AGI**	**2.47 (0.68, 4.30)**	0.53 (-1.23, 2.34)
-8.66 (-19.11, 1.89)	1.78 (-8.12, 11.34)	**-12.23 (-23.36, -0.82)**	3.98 (-12.07, 19.78)	1.39 (-10.01, 12.82)	**-14.58 (-27.08, -2.31)**	**-15.40 (-27.47, -3.12)**	**Insulin**	**-1.94 (-2.42, -1.47)**
9.90 (8.27, 11.61)	**20.31 (16.34, 24.39)**	**6.34 (1.23, 11.55)**	**22.42 (10.35, 34.29)**	**19.98 (15.00, 24.88)**	3.88 (-3.03, 10.91)	3.13 (-3.07, 9.69)	**18.54 (8.18, 29.14)**	Placebo

Figure 4A. WMD (weighted mean difference) with 95%CI of network meta-analysis for HOMA-β and FPG.

Note: HOMA-β: homeostasis model assessment for β cell function; FPG: fasting plasma glucose; Results of network meta-analysis for HOMA-β and FPG were listed in the lower and upper 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: sulphanylureas; AGI: alpha-glucosidase inhibitor; TZD: thiazolidinediones.

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DPP-4I	**0.45 (0.04, 0.87)**	NA	0.54 (-0.07, 1.16)	**-0.63 (-0.98, -0.28)**	**1.30 (0.80, 1.83)**	0.08 (-0.41, 0.58)	**-0.23 (-0.38, -0.08)**
-0.07 (-0.21, 0.07)	**GLP-1RA**	NA	0.10 (-0.64, 0.83)	**-1.07 (-1.59, -0.56)**	**0.86 (0.21, 1.50)**	-0.36 (-0.95, 0.21)	**-0.67 (-1.08, -0.27)**
0.18 (-0.18, 0.49)	0.24 (-0.10, 0.56)	**Insulin**	NA	NA	NA	NA	NA
0.09 (-0.25, 0.42)	0.16 (-0.21, 0.52)	-0.08 (-0.54, 0.43)	**Met**	**-1.17 (-1.89, -0.48)**	0.76 (-0.03, 1.56)	-0.46 (-1.25, 0.34)	**-0.77 (-1.40, -0.15)**
0.04 (-0.31, 0.38)	0.11 (-0.27, 0.48)	-0.13 (-0.59, 0.36)	-0.05 (-0.54, 0.42)	**SU**	**1.93 (1.33, 2.56)**	**0.71 (0.10, 1.31)**	**0.40 (0.03, 0.77)**
0.38 (0.22, 0.54)	**0.45 (0.24, 0.66)**	0.21 (-0.14, 0.58)	0.28 (-0.07, 0.66)	0.34 (-0.04, 0.72)	**TZD**	**-1.22 (-1.94, -0.51)**	**-1.53 (-2.07, -1.01)**
-0.10 (-0.28, 0.10)	-0.03 (-0.26, 0.21)	-0.27 (-0.63, 0.12)	-0.18 (-0.60, 0.20)	-0.13 (-0.53, 0.27)	**-0.47 (-0.72, -0.22)**	**AGI**	-0.31 (-0.82, 0.20)
0.09 (0.04, 0.14)	**0.16 (0.03, 0.29)**	-0.08 (-0.40, 0.27)	-0.00 (-0.34, 0.35)	0.05 (-0.30, 0.41)	**-0.29 (-0.45, -0.13)**	0.19 (-0.02, 0.38)	**Placebo**

Figure 4B. WMD (weighted mean difference) with 95%CI of network meta-analysis for fasting C-peptide and HOMA-IR.

Note: HOMA-IR: homeostasis model assessment for insulin resistance; Results of network meta-analysis for fasting C-peptide and HOMA-IR were listed in the lower and upper triangle, and the estimation was calculated as the column-defining treatment compared with the row-defining treatment. Since there is no trial reported HOMA-IR of the insulin group, so there is NA for the upper triangle. NA: not available. DPP-4I: dipeptidyl peptidase-4 inhibitors; GLP-1RA: Glucagon-like peptide-1 receptor agonists; Met: metformin; SU: sulphanylureas; AGI: alpha-glucosidase inhibitor; TZD: thiazolidinediones.

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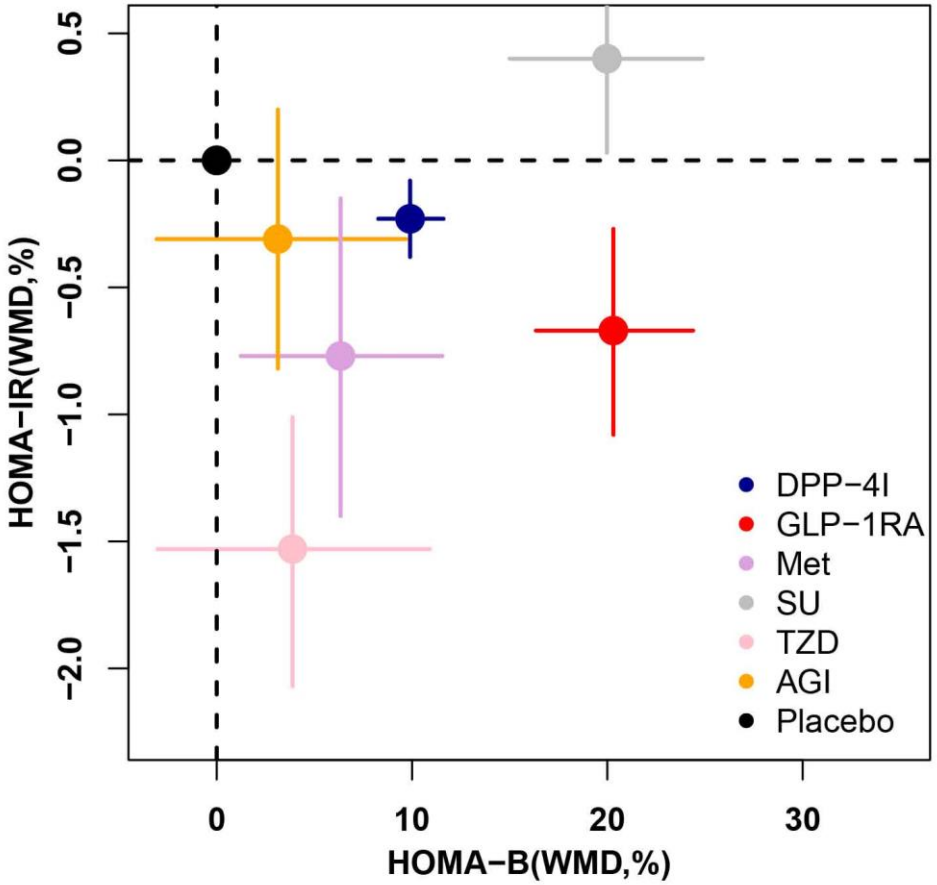

Figure 5. Two-dimensional graphs about HOMA-IR and HOMA-β in network analysis.
Data are reported as WMD in comparison with placebo, which is the reference drug. Error bars are 95% CI. Individual drugs are represented by different colored nodes. Since there was no data on HOMA-IR for SGLT-2 and insulin, we did not draw points for SGLT-2 and insulin. WMD: weighted mean difference; HOMA-IR: homeostasis model assessment for insulin resistance; HOMA-β: homeostasis model assessment for β-cell function; DPP-4I: dipeptidyl peptidase-4 inhibitors; GLP-1RA: Glucagon-like peptide-1 receptor agonists; SGLT-2: Sodium-Glucose co-Transporter 2; Met: metformin; SU: sulphanylureas; AGI: alpha-glucosidase inhibitor; TZD: thiazolidinediones.

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