

What Is the Impact of Different Glucose-lowering Agents for Atrial Fibrillation Risk: A Systematic Review and a Network Meta-analysis

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Abstract

Background: The emergence of new glucose-lowering agents has brought revolutionary changes to the treatment of cardiovascular diseases. Diabetes is associated with atrial fibrillation (AF) and atrial flutter (AFL) progression, while whether or not glucose-lowering agents would bring a reduction of AF/AFL is not clear. We therefore evaluate the effect of different glucose-lowering agents on AF/AFL and made this network meta-analysis to identify the optimal treatment for diabetes patients to reduce AF/AFL events.

Methods: We searched PubMed, Embase, and the Cochrane Library until September 30 2020, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this network meta-analysis. The primary endpoint for our study was AF or AFL events. Only studies with a follow-up period of at least 12 months and reporting AF/AFL as clinical endpoints were included. Results from trials were presented as odds ratios (ORs) with 95% confidence intervals (CIs) and were pooled using a bayesian random-effects model.

Results: 5 eligible studies (9 glucose-lowering agents were analyzed including thiazolidinedione[TZD], metformin[Met], sulfonylurea[SU], insulin[Insu], dipeptidyl peptidase-4 inhibitor[DPP-4i], glucagon-like peptide-1 receptor agonist[GLP-1RA], sodium-glucose cotransporter 2 inhibitor[SGLT2i], alpha glucosidase inhibitor[AGI], and non-sulfonylurea[nSU]) consisting of 263583 patients with type 2 diabetes mellitus were included. Pooled results show that GLP1-RA, when compared to Met (OR 0.17, 95% CI 0.04-0.61), SU (OR 0.23, 95% CI 0.07-0.73), Insu (OR 0.20, 95% CI 0.07-0.86), and nSU (OR 0.18, 95% CI 0.04-0.66) significantly reduce AF/AFL events. In addition, DPP-4i could also reduce AF/AFL events when compared with nSU (OR 0.33, 95% CI 0.12-0.92).

Conclusion: The finding of our study indicated that GLP1-RA could be optimal glucose-lowering agent for diabetes patients to prevents AF/AFL. Met and insulin-providing therapy (insulin, sulfonylurea, or non-sulfonylurea) should be avoided to patients with high risk of AF/AFL.

Trial registration: We have registered in PROSPERO (international prospective register of systematic reviews (CRD42020212994) for this network meta-analysis

Background

As the world population ages, diabetes has become a major public health problem worldwide.[1, 2] Research indicated that diabetes-induced myocardial remodeling and changes in the electrical properties could bring a risk to develop cardiac arrhythmias, [3] and clinical data also identified diabetes as an independent risk factor for atrial fibrillation (AF) and atrial flutter (AFL).[4, 5] Recent years, new oral glucose-lowering agents has showed their revolutionary changes to the treatment of cardiovascular diseases. Evidence indicated additional cardiovascular benefit was associated with new oral glucose-lowering agents other than glucose-lowering effect.[6] Although the definite mechanisms of the non-glucose-lowering benefit are not clear, multiple salutary properties including, improved myocardial efficiency, improved oxygen delivery, reduction of inflammation and oxidative stress have been suggested

to exert potential direct cardiac protective effects.[7] Because aforementioned effect are also risk factors for the occurrence and development of AF/AFL, we hypothesized that new glucose-lowering agents with various characteristic would exert different effect on reducing the risk for AF/AFL events, and we made this network meta-analysis to identify the optimal treatment for diabetes patients to reduce AF/AFL events.

Methods

We have registered in PROSPERO (international prospective register of systematic reviews; (CRD42020212994) for this network meta-analysis which was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Supplement 1**).

Study Selection Criteria

Clinical research comparing different kind of glucose-lowering agents in diabetes patients in which clinical outcomes (primary or secondary endpoints) were AF/AFL were considered for our present meta-analysis. The inclusion criteria for our study included (1) Clinical research with at least 2 comparator arms; (2) study population of patients with diabetes; (3) AF/AFL were reported as primary or secondary endpoints; (4) AF/AFL events were reported in individual glucose-lowering agents arm. (5) follow-up of at least 12 months. We excluded review article, single arm studies, duplicate studies, mechanism research and article where AF/AFL were reported as side effects. No language, publication date, or publication status restrictions were applied. We also screened references of prior systematic reviews and meta-analyses for related studies.

Search Strategy and Information Sources

We used keywords related to diabetes, atrial fibrillation, antihyperglycemic medications (thiazolidinedione, metformin, sulfonylurea, insulin, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, sodium-glucose cotransporter 2, alpha glucosidase inhibitor, and non-sulfonylurea) to searched PubMed/MEDLINE, Ovid/Embase and Cochrane databases from database inception through the final search date of September 30, 2020. The key words for search strategy are provided in the **Supplement 2**.

Two reviewers performed a systematic review, and disagreements were resolved in a panel discussion of 3 reviewers . Study selection involved screening of titles and abstracts followed by full-text evaluation of possible eligible studies.

Outcome Measures

The primary endpoint was AF/AFL defined by the diagnosis of AF/AFL based on the ICD-9-CM code of 427.31; ICD-8-CM code of 427.93, 427.94, 427.3 or ICD-10-CM code of I48, in either an in-patient or outpatient department at least once.

Data Collection Process

Two reviewers independently extracted data on the study design, baseline characteristics, interventions, and outcomes. Any disagreements of collected information between the 2 reviewers were reconciled through discussion.

Quality Assessment and Publication Bias

Two independent reviewers performed the qualitative assessment using Cochrane Collaboration tool (in the **Supplement 3**). Given the limited number of publications, we did not assess the risk of publication bias.

Statistical Analysis

We fitted a bayesian random-effects network meta-analysis model to simultaneously compare multiple glucose-lowering agents. We estimated odds ratios (ORs) of the treatment effects of the 2 individual glucose-lowering agents and the associated 95% credible intervals (CrIs) using Markov chain, Monte Carlo algorithms. All analyses were conducted using the gemtc package (version 0.8-7) and rjags package (version 4-10) in R, version 3.6.1 (The R Foundation). We assumed that the direct and indirect

evidence for a treatment comparison had no discrepancy, called evidence consistency. To account for effect heterogeneity across trials, we allowed random effects to net-work meta-analysis and measured the magnitude of heterogeneity. We used the package's default setting including noninformative prior distributions with 4 parallel chains, where each chain consists of 50 000 samples after a 20 000-sample burn-in.

To evaluate and rank regimens, we calculated rank probabilities (ie, probability of an AGM being the best, second-best, or worst for an outcome) and the Surface under the Cumulative Ranking (SUCRA). The SUCRA is a numerical summary that accounts for both magnitude and uncertainty of the estimated effect for each regimen. A larger SUCRA value indicates better performance for the outcome

We also made several sensitive analysis to show an class-effect of new oral glucose-lowering agents, detailed results of sensitive analysis can be found in **Supplement 4**.

Results

Search Results

We have searched EMBASE, PubMed/Medline databases, and the Cochrane library for Randomized Controlled Trials (RCTs) and observational studies for our study purpose, and 199 individual studies were identified by using key words (**Supplement 2**) in our search strategies. After excluding duplicates, 182 studies were enrolled in next assessment. Of those, 170 studies were deemed irrelevant based on title and

abstract screening. Then, investigators (S.W.C and Z.W.C) viewed all full text copies of potential 12 relatively studies. A third investigator (D.C.H) resolved any discordance in assessments. However, 2 of them did not provide available data for further analysis and 10 studies were included for qualitative synthesis. Finally, the main analysis included 5 articles after excluding another 5 studies by carefully group-discussion. **(Figure 1)**

Study Characteristics

Trial design, population, treatment regimens, main results, and other characteristics of the 5 included studies are available in the **Supplement 5 and 6**.

Structure of NMA

Figure 2 displays the network of individual AGM used in the main analysis. We compared 9 treatment: thiazolidinedione (TZD), metformin (Met), sulfonylurea (SU), insulin (Insu), dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 receptor agonist (GLP-1RA), sodium-glucose cotransporter 2 inhibitor (SGLT2i), alpha glucosidase inhibitor (AGI), and non-sulfonylurea (nSU).

Network Meta-analysis Results for AF/AFL

The **Figure 3** shows the OR value comparing the effects of two different glucose-lowering agents on AF/AFL events. Pooled results show that GLP1-RA, when compared to Met (OR 0.17, 95% CI 0.04-0.61), SU (OR 0.23, 95% CI 0.07-0.73), Insu (OR 0.20, 95% CI 0.07-0.86), and nSU (OR 0.18, 95% CI 0.04-0.66) significantly reduce AF/AFL events. In addition, DPP-4i could also reduce AF/AFL events when compared with nSU (OR 0.33, 95% CI 0.12-0.92). While, no significant results were found in other comparisons between 2 glucose-lowering agents.

(Odds ratio [95% credible intervals] between column and row treatment regimens are reported. Odds ratio smaller than 1 means that the odds of having AF/AFL risk for the column treatment regimen is lower than the row treatment regimen. Statistically significant results, where the 95% credible interval does not include 1, are in bold and italic. [Protective effect was labeled in orange and destructive effect was labeled in green])

Ranking of individual AGM

The **Table** showed SUCRA values for AF/AFL events. The AGM with the highest SUCRA value (ie, best performance) for AF/AFL outcomes was GLP1-RA (SUCRA of 95.67), followed by DPP-4i and SGLT2i with similar SUCRA (77.45 and 76.30 respectively).[The results for rank probability were shown in **Supplement 7**] All fitted models converged well and we did not find evidence that indicated statistical inconsistency in our NMA (**Supplement 8**).

Table SUCRA Values for individual glucose-lowering agents on AF/AFL

The larger the SUCRA value the better the glucose-lowering agent performance with respect to the AF/AFL outcome

Value	TZD	Met	SU	Insu	DPP-4i
AF/AFL	59.8	16.6	34.9	27.6	77.4
Value	GLP-1RA	SGLT2i	AGI	nSU	
AF/AFL	95.7	76.3	43.4	18.2	

Sensitive analysis

As shown in the **Supplement 4**, we performed a number of additional analyses. We found similar outcomes when using an NMA in which GLP1-RA were compared with Met or insulin-providing therapy (Insu, SU, or nSU).

Discussion

To our knowledge, this manuscript is the first net-work meta-analysis focusing on the effect of glucose-lowering agents on AF/AFL prognosis. Our results indicated that new oral glucose-lowering agents, especially GLP-1RA, showed property to lower AF/AFL events among diabetes population. The association between diabetes and atrial fibrillation has been demonstrated for decades.[3, 8, 9] The potential mechanism is complex with different pathophysiology, such as inflammation[10] and oxidative stress, which would affect structural, electromechanical and mechanical myocardial remodeling. [11] According to latest evidence,[12-16] new oral glucose-lowering agents are recommended as first-line prescription for diabetes patients with high risk for cardiovascular disease.[17] Mechanism beyond glucose-lowering might related to the reduction of cardiovascular risk.

The pooled results of our network meta-analysis comparing 9 glucose-lowering agents showed that GLP-1RA possessed the best property to prevent AF/AFL events among diabetes patients. Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted in the gut in response to meal ingestion, which increases insulin secretion and inhibits glucagon production, targeting pancreatic b-cells.[18] Therefore, GLP-1RA could improve hyperglycaemia. Some research show that GLP-1RA could reduce matrix metalloproteinase-2 levels[19], inhibit proliferation [20] and play role in anti-inflammatory effects.[21] In addition, GLP-1 receptor expression in ventricular cardiac myocytes [22] suggests that cardiac-direct actions of GLP-1RA may account for the reduction for AF/AFL events. However, in a separate study, [23] we did not find that GLP-1RA has a similar effect in reducing AF/AFL events, which may be due to the more prominent edge effect caused by the meta-analysis.

Our analysis indicated DPP-4i play a protective role against AF/AFL only when compared with Nsu, although Chang's [24]research showed an association between DPP-4i use and AF/AFL events reduction. DPP-4i is incretin-based glucose-lowering therapy, it can inhibit the degradation of GLP-1 and increase the

serum levels of GLP-1, which indirectly stimulate insulin secretion and enhance beta-cell function. Research showed that DPP-4i exert antiarrhythmic effects by increasing the threshold of ventricular fibrillation. [25, 26] This mechanism might related to the reduction of AF/AFL events in diabetes patients.

Our analysis did not show that SGLT2i perform an extra AF/AFL protective effect when compared with any other glucose-lowering agents. Significant reduction in re-hospitalization rate has been well clarified, and SGLT2i is recommended as first-line medication for diabetes patients. Although heart failure is associated with AF/AFL, SGLT2i did not decrease AF/AFL risk according to our results. This unexpecting results indicated that diuresis might paly critical role in improve cardiovascular outcomes, therefore protective effect on AF/AFL could be detected. [27]

We noticed that the SCURA values of Met, SU, Insu, nSU were the lowest (ie, worst performance) which were associated with increased risk for AF/AFL compared with GLP-1RA. Both SU, Insu and nSU are insulin-providing therapies, and they seemed inferior to new oral glucose-lowering drugs (DPP-4i, GLP-1RA, SGLT2i) in reducing adverse cardiovascular endpoints.[28, 29] This might be related to their single glucose-lowering effect.

We noticed that former studies concerned more on the benefits of AGM on major adverse cardiovascular events (death, myocardial infarction and stroke), few of them pay attention to arrhythmic endpoints. Our pooled results provide a perspective that diabetes patients might benefit from different glucose-lowering agents in reducing AF/AFL events, and clinicians should choose glucose-lowering agents according to the risks classification for arrhythmia.

There are some limitations in our manuscript: (1) Because few studies focus on arrhythmia endpoints, only 1 RCT was enrolled in our network meta-analysis, this may affect the results. (2) Although all patients in our study suffered diabetes, the glucose-lowering therapy was decided by clinician experience and local medical policy, which leads to differences in patient baselines between studies.

Conclusion

The finding of our study indicated that GLP1-RA could be optimal glucose-lowering agent for diabetes patients to prevents AF/AFL. Met and insulin-providing therapy (insulin, sulfonylurea, or non-sulfonylurea) should be avoided to patients with high risk of AF/AFL.

Abbreviations

atrial fibrillation and atrial flutter =AF/AFL ; Preferred Reporting Items for Systematic Reviews and Meta-Analyses =PRISMA; odds ratios =ORs; confidence intervals =CI; Thiazolidinedione=TZD, Metformin=Met, Sulfonylurea=SU, Insulin=Insu, Dipeptidyl peptidase-4 inhibitor=DPP-4i, Glucagon-like peptide-1 receptor agonist=GLP-1RA, Sodium-glucose cotransporter 2 inhibitor=SGLT2i, Alpha glucosidase inhibitor=AGI, non-sulfonylurea=nSU; Surface under the Cumulative Ranking =SUCRA; Randomized Controlled Trials =RCTs;

Declarations

Ethics approval and consent to participate: Not available

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests: The authors have no conflicts of interest to declare

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Authors' contributions: S.W.C, study concept and design, acquisition, analysis and interpretation of data, statistical analysis, drafting of the manuscript; Z.W.C, critical revision of manuscript; critical analysis and interpretation of data; G.L.H, data analysis and manuscript revision. D.C.H, study concept and design, critical revision of manuscript; study supervision, statistical analysis.

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Figures

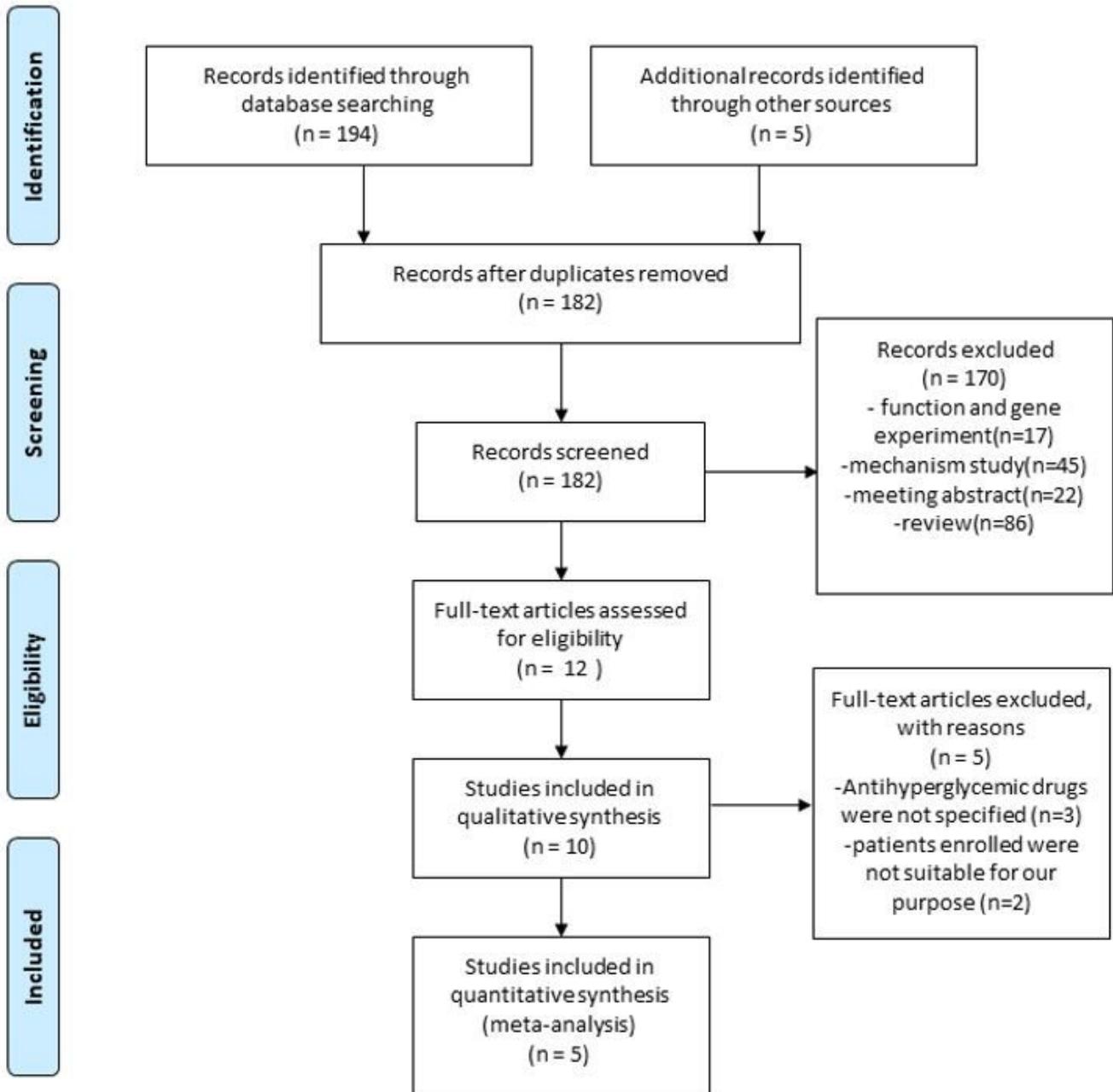


Figure 1

Flow chart for studies selection

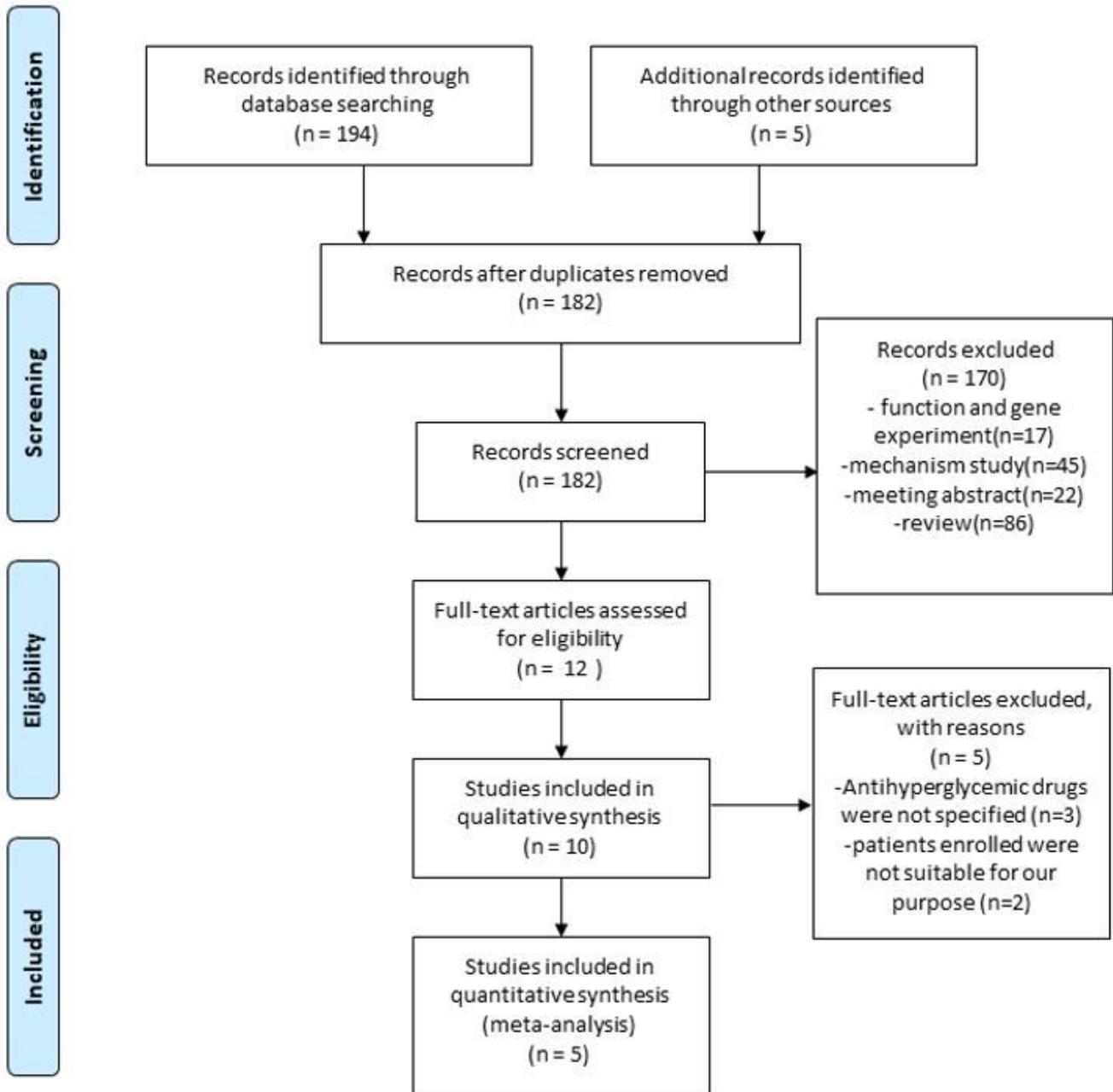


Figure 1

Flow chart for studies selection

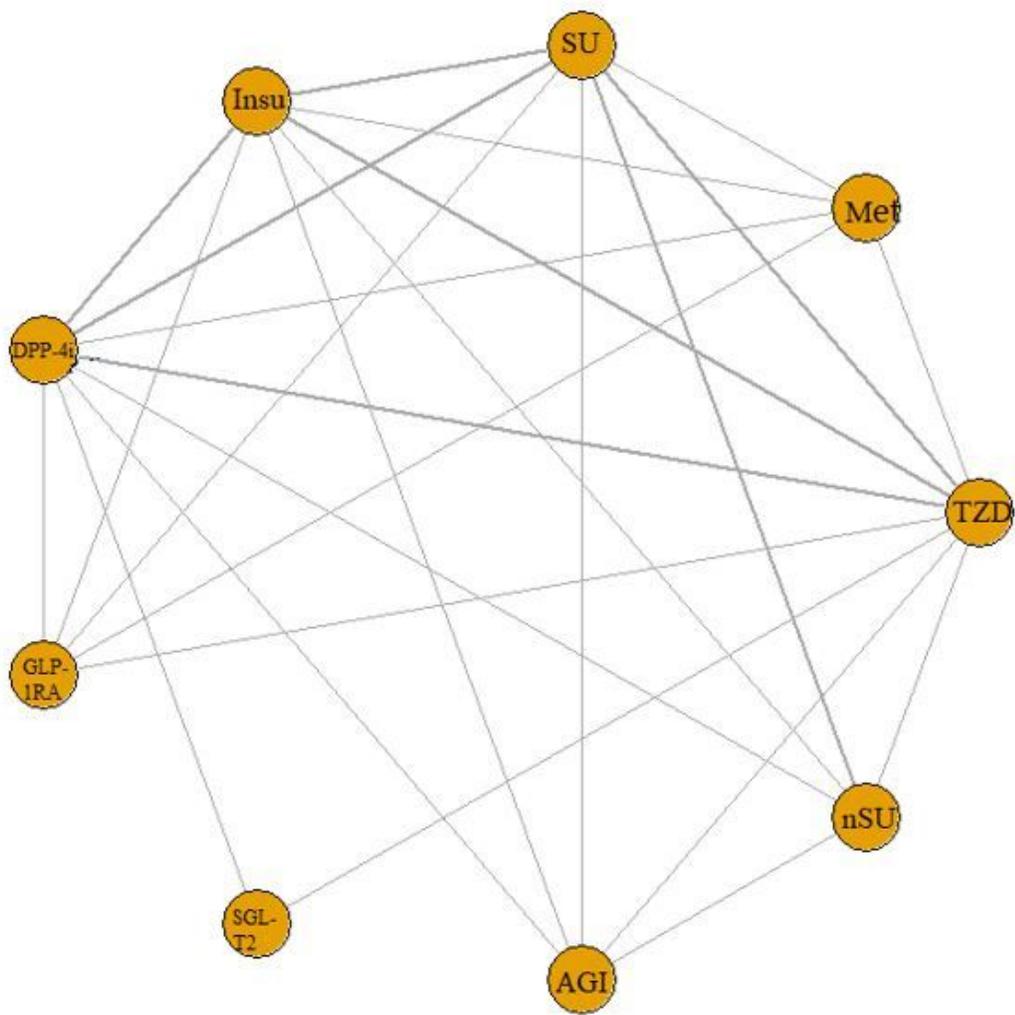


Figure 2

Network of treatment strategy

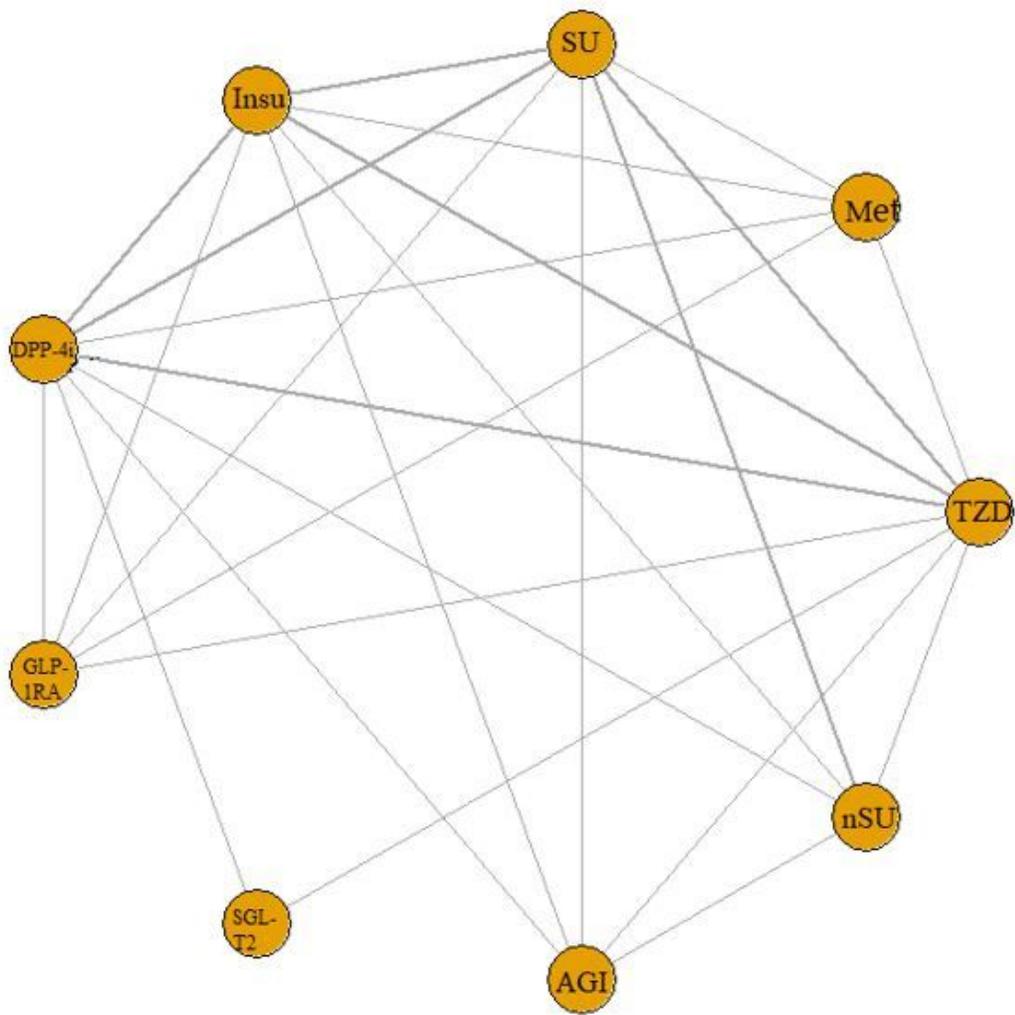


Figure 2

Network of treatment strategy

	TZD	Met	SU	Insu	DPP-4i	GLP-1RA	SGLT2i	AGI	nSU
TZD		0.43 (0.15-1.50)	0.60 (0.26-1.50)	0.53 (0.25-1.90)	1.40 (0.61-3.40)	2.60 (0.86-9.50)	1.40 (0.52-3.90)	0.71 (0.21-2.50)	0.46 (0.16-1.30)
Met	2.30 (0.67-6.70)		1.40 (0.43-4.20)	1.20 (0.46-4.70)	3.20 (0.97-9.60)	6.00 (1.60-23.0)	3.20 (0.74-12.0)	1.60 (0.36-3.80)	1.10 (0.26-3.80)
SU	1.70 (0.66-3.80)	0.72 (0.24-2.30)		0.87 (0.42-2.90)	2.30 (0.95-5.40)	4.30 (1.40-15.0)	2.30 (0.69-7.30)	1.20 (0.36-3.80)	0.76 (0.30-1.80)
Insu	1.90 (0.53-3.90)	0.84 (0.20-2.20)	1.20 (0.34-2.40)		2.60 (0.77-5.50)	5.00 (1.20-14.0)	2.70 (0.56-7.20)	1.40 (0.28-3.90)	0.88 (0.21-2.10)
DPP-4i	0.73 (0.30-1.60)	0.31 (0.10-1.00)	0.44 (0.19-1.00)	0.38 (0.18-1.30)		1.90 (0.60-6.60)	1.00 (0.36-2.70)	0.52 (0.16-1.70)	0.33 (0.12-0.92)
GLP-1RA	0.38 (0.10-1.20)	0.17 (0.04-0.61)	0.23 (0.07-0.73)	0.20 (0.07-0.86)	0.53 (0.15-1.70)		0.53 (0.12-2.10)	0.27 (0.06-1.20)	0.18 (0.04-0.66)
SGLT2i	0.73 (0.26-1.90)	0.31 (0.08-1.30)	0.44 (0.14-1.50)	0.38 (0.14-1.80)	0.99 (0.37-2.70)	1.90 (0.47-8.60)		0.52 (0.12-2.20)	0.33 (0.09-1.30)
AGI	1.40 (0.40-4.70)	0.61 (0.14-2.80)	0.85 (0.26-2.80)	0.74 (0.25-3.50)	1.90 (0.59-6.40)	3.70 (0.85-18.0)	1.90 (0.45-8.40)		0.65 (0.18-2.30)
nSU	2.20 (0.74-6.20)	0.94 (0.26-3.80)	1.30 (0.56-3.30)	1.10 (0.47-4.70)	3.00 (1.10-8.70)	5.70 (1.50-24.0)	3.00 (0.80-11.0)	1.50 (0.44-5.50)	

Figure 3

Pooled results for AF/AFL outcomes from network meta-analysis

	TZD	Met	SU	Insu	DPP-4i	GLP-1RA	SGLT2i	AGI	nSU
TZD		0.43 (0.15-1.50)	0.60 (0.26-1.50)	0.53 (0.25-1.90)	1.40 (0.61-3.40)	2.60 (0.86-9.50)	1.40 (0.52-3.90)	0.71 (0.21-2.50)	0.46 (0.16-1.30)
Met	2.30 (0.67-6.70)		1.40 (0.43-4.20)	1.20 (0.46-4.70)	3.20 (0.97-9.60)	6.00 (1.60-23.0)	3.20 (0.74-12.0)	1.60 (0.36-3.80)	1.10 (0.26-3.80)
SU	1.70 (0.66-3.80)	0.72 (0.24-2.30)		0.87 (0.42-2.90)	2.30 (0.95-5.40)	4.30 (1.40-15.0)	2.30 (0.69-7.30)	1.20 (0.36-3.80)	0.76 (0.30-1.80)
Insu	1.90 (0.53-3.90)	0.84 (0.20-2.20)	1.20 (0.34-2.40)		2.60 (0.77-5.50)	5.00 (1.20-14.0)	2.70 (0.56-7.20)	1.40 (0.28-3.90)	0.88 (0.21-2.10)
DPP-4i	0.73 (0.30-1.60)	0.31 (0.10-1.00)	0.44 (0.19-1.00)	0.38 (0.18-1.30)		1.90 (0.60-6.60)	1.00 (0.36-2.70)	0.52 (0.16-1.70)	0.33 (0.12-0.92)
GLP-1RA	0.38 (0.10-1.20)	0.17 (0.04-0.61)	0.23 (0.07-0.73)	0.20 (0.07-0.86)	0.53 (0.15-1.70)		0.53 (0.12-2.10)	0.27 (0.06-1.20)	0.18 (0.04-0.66)
SGLT2i	0.73 (0.26-1.90)	0.31 (0.08-1.30)	0.44 (0.14-1.50)	0.38 (0.14-1.80)	0.99 (0.37-2.70)	1.90 (0.47-8.60)		0.52 (0.12-2.20)	0.33 (0.09-1.30)
AGI	1.40 (0.40-4.70)	0.61 (0.14-2.80)	0.85 (0.26-2.80)	0.74 (0.25-3.50)	1.90 (0.59-6.40)	3.70 (0.85-18.0)	1.90 (0.45-8.40)		0.65 (0.18-2.30)
nSU	2.20 (0.74-6.20)	0.94 (0.26-3.80)	1.30 (0.56-3.30)	1.10 (0.47-4.70)	3.00 (1.10-8.70)	5.70 (1.50-24.0)	3.00 (0.80-11.0)	1.50 (0.44-5.50)	

Figure 3

Pooled results for AF/AFL outcomes from network meta-analysis

Supplementary Files

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- [Supplement.docx](#)
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