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Glycemic control efficacy of oral anti-diabetic drugs in treating type 2 diabetes: a protocol for network meta-analysis

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Keywords: protocol; type 2 diabetes; glycemic control; randomized controlled trials; network meta-analysis.

Word count: 1619

Abstract

Introduction:

There were three network meta-analyses on the efficacy of anti-diabetic drug combinations in treating type 2 diabetes. No network meta-analytic study has been published in medical journal to evaluate the efficacies of monotherapy. Current clinical guidelines (e.g. NICE clinical guidelines 66 and 87) are only based on the findings of limited clinical trials and pairwise meta-analysis. This study aims to fill this gap of research by conducting a Bayesian network meta-analysis to compare twelve anti-diabetic drugs, including metformin, pioglitazone, rosiglitazone, glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin and acarbose.

Methods and analyses:

Randomized controlled trials (RCT) on the drug therapy of type 2 diabetes with outcome measures including glycosylated hemoglobin (HbA1c) or fasting blood-glucose (FPG) will be included. The quality of inluced RTCs will be evaluated according to the Cochrane Collaboration's risk of bias tool. Overall effect sizes will be represented as mean differences with 95% credible intervals (CrI) for continuous outcome data. Pairwise meta-analysis in R software and Bayesian network meta-analysis in R and WinBUGS will be conducted to compare the efficacies of these drugs. Sensitivity analysis on the sample size of RCTs, contradiction analysis between pair and network meta-analyses, and publication bias analysis will be performed.

Ethics and dissemination:

Ethical approval is not required because this study include no confidential personal data and interventions on the patients. Network meta-analysis is based on the RCT reports of eligible drugs in treating type 2 diabetes. The results of this study will be disseminated by an open access and peer-reviewed publication.

Protocol registration:

PROSPERO CRD42014010567.

ARTICLE SUMMARY

Article focus

- This is a protocol of systematic review and network meta-analysis of randomized controlled trials on metformin, pioglitazone, rosiglitazone, glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin and acarbose in treating type 2 diabetes.

Key messages

- Included drugs will be evaluated by pairwise and a Bayesian network meta-analysis.
- Sensitivity analysis, contradiction analysis, and publication bias analysis will be conducted to compare the efficacy of drugs with glycosylated hemoglobin and fasting blood-glucose outcome measures.

Strengths and limitations of this study

- Network meta-analysis together with sensitivity analysis, contradiction analysis, and publication bias analysis will evaluate the efficacies of multiple anti-diabetic drugs.
- This study will provide evidence for clinical decision-makers to formulate better treatment of type 2 diabetes.
- This study is inherently retrospective and based on the published RCTs only.

INTRODUCTION

Glycemic control would prevent microvascular and macrovascular complications of type 2 diabetes patients [1-2]. Several categories of oral anti-diabetic drugs including biguanides, thiazolidinediones, sulfonylureas, meglitinides, DPP-4 inhibitors and alpha-glucosidase inhibitors are available for monotherapy of type 2 diabetes. Efficacies of these drugs should be monitored for post-marketing evaluation and referred for updates of clinical guidelines. Randomized control trials (RCTs) and their meta-analyses are used in testing the efficacies of different treatments [3]. However, head-to-head RCTs do not cover all direct comparisons between drugs. Network meta-analysis, also known as mixed treatment comparison, was developed to incorporate direct and indirect evidence from RCTs [3].

Although the National Institute for Health and Care Excellence (NICE) guideline [4] is a popular clinical guideline for diabetes care, there are still gaps to provide the necessary evidence of the glycemic control efficacy of oral anti-diabetic drugs for updating the guideline. Firstly, the evidence of the oral anti-diabetic drugs efficacies was mainly based on head-to-head RCTs and their meta-analyses. Secondly, efficacy ranking of the oral anti-diabetic drugs was still unknown from the guideline due to the lack of comprehensive multiple comparisons among these drugs. Network meta-analyses had been used in comparing the efficacies of oral anti-diabetic drugs [5-7]. A network meta-analysis published in 2011 aimed to compare the efficacies of anti-diabetic drugs added to metformin [5]. Others published in 2012 and 2014 aimed to compare the efficacies of anti-diabetic drugs adding to metformin [3-4]. While these studies compared the drug combination efficacy of different classes, the monotherapy efficacy of individual drug is not been compared in network meta-analysis. Thirdly, robustness of multiple comparisons is still needed to be evaluated. Therefore, network meta-analysis on the monotherapy efficacies of oral anti-diabetic drugs by incorporating direct and indirect evidence based on randomized controlled trials (RCT) is necessary [8].

Twelve popular drugs, including metformin, pioglitazone, rosiglitazone, glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin and acarbose, were selected from six oral anti-diabetic drug categories reported in the review [9] from the Agency for Healthcare Research and Quality. This study conducted a Bayesian network meta-analysis to compare the glycemic control efficacy of the selected anti-diabetic drugs.

OBJECTIVES

The objective of this study is to compare efficacies of popular anti-diabetic drugs by Bayesian network meta-analysis on RCTs.

METHODS AND ANALYSIS

Design

Systematic review and Bayesian network meta-analysis.

Information sources

Clinical trial reports will be searched from PubMed and Cochrane Library.

Search strategies

Drug names, synonyms of type 2 diabetes (e.g. type 2 diabetes, type II diabetes and non-insulin-dependent diabetes) and "random*" will be used as keywords to search titles or abstracts for eligible RCTs from major databases including PubMed, Cochrane Library, ScienceDirect, and EMBASE. For example, the following search strategy will be used in searching PubMed:

1. metformin
2. type 2 diabetes
3. random*
4. 1 in title or abstract
5. 2 in title or abstract
6. 3 in title or abstract
7. 4 and 5 and 6

Eligibility criteria

The retrieved reports will be screened according to the checklist of eligibility (Appendix 1) and the eligibility criteria shown below including participants, interventions, controls, types of study, and other criteria.

► Participants

Inclusion: the participants must be adults aged at least 18 suffering from and requiring treatment for type 2 diabetes. Exclusion: the participants suffering from other diabetes disease conditions or aged less than 18.

► Interventions

Inclusion: any RCT that evaluates the efficacy of these twelve drugs. Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs or placebo.

► Controls

Inclusion: any RCT that evaluates the efficacy of these twelve drugs other than the drug of intervention or placebo. Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs.

► Types of study

Inclusion: only RCTs will be included. Exclusion: Observational cohort and case-control studies, case reports, experimental studies and reviews will be excluded.

► Other criteria

Other inclusion criteria: the RCTs must report complete efficacy data of glycosylated hemoglobin (HbA1c) or fasting blood-glucose (FPG) of each treatment. Follow-up periods or durations in RCTs are at least 4 weeks. Other exclusion criteria are (a) duplicated or redundant studies, and (b) combined treatments with multiple drugs.

Study selection

Reviewers will screen all titles or abstracts or full texts for database records independently according to the eligibility criteria. Disagreements between reviewers will be resolved by consensus. Selection process of relevant studies retrieved from databases will be shown in a PRISMA-compliant [10] flowchart (Figure 1).

Data extraction and quality assessment

Data of the study characteristics and the clinical outcome measures will be extracted. The data extracted from the RCTs are: (a) authors; (b) publication year; (c) sample sizes; (d) interventions of both arms; (e) dosages of both arms; (f) treatment outcome measures including glycosylated

hemoglobin (HbA1c) and fasting blood-glucose (FPG). The data will be standardized (Table 1). The quality of eligible studies will be evaluated according to the Cochrane Collaboration's risk of bias tool for assessing risk of bias (Table 2) [11]. Radar chart (or star chart) [12] will be used to summary the results.

Outcome measures

Outcome measures of anti-diabetic efficacy include mean changes of HbA1c (primary outcome) and FPG (secondary outcome) from baseline and their corresponding variation.

Statistical analysis

Pairwise meta-analysis of the included RCTs with random effect model [13-14] due to the expected heterogeneity will be conducted. Mean difference (MD) will be used to synthesis the continuous outcome data: mean changes from baseline of the HbA1c (%) and FPG (mol/L) in both arms. I^2 was used to estimate the heterogeneity [15]. Networks will be generated to visualize the results of pairwise meta-analysis and the current evidence from the included RCTs.

Network meta-analysis (NMA) based on the Bayesian hierarchical model [3] will be performed to compare the efficacy of selected drugs. Placebo will be used as common comparison [16] in NMA. Relative MD to the placebo will be output to assess the efficacy. The probability of each drug being ranked in each position based on HbA1c will be computed [17]. Kendall's test will be used to test the correlation between the relative MD and the ranking position.

Sensitivity analysis based on the sample size of the RCTs will be conducted when RCTs with sample size less than 50 are excluded. Begg's test [18] and Egger's test [19] will be used to evaluate the publication bias. Agreement will be computed to assess the consistency between pairwise and network meta-analyses.

R software [20] will be used to implement the analysis workflow. Package "metafor" [21] will be used to conduct pairwise meta-analysis. Package "igraph" [22] will be used to visualize the networks. Package "fmsb" [23] will be used to visualize the results of risk of bias assessment. Package "GeMTC" [24], "R2WinBUGS" [25] in R and WinBUGS [26] will be used to conducted network meta-analysis. Package "ggplot2" [27] will be used to visualize the distribution of ranking probability distribution. P Values lower than 0.05 will be considered statistically

significant.

ETHICS AND DISSEMINATION

Ethical issues

No ethical approval is required because this study include no confidential personal data and interventions with the patients.

Publication plan

This protocol has been registered (Registration number: CRD42014010567) with the PROSPERO (International Prospective Register of Systematic Reviews) [28]. The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA-compliant guideline. Details of this systematic review and network meta-analysis will be submitted to one of the BMJ journal.

Contributions

SL conceived the study. SL and YL designed the study. YL and YJ tested the feasibility of the study. YJ, YL, and SL wrote the protocol and approved the final manuscript.

Funding

The study is part of the "Open systematic reviewing of clinical trials" project supported by a research grant (MYRG190-Y3-L3-ICMS11-LSW) received from the University of Macau.

Competing interests

None declared.

Provenance and peer review

Not commissioned; external peer review.

Table Legends

Table 1. Summary of the included RCTs.

Table 2. RCT quality assessment with the Cochrane Collaboration's risk of bias tool.

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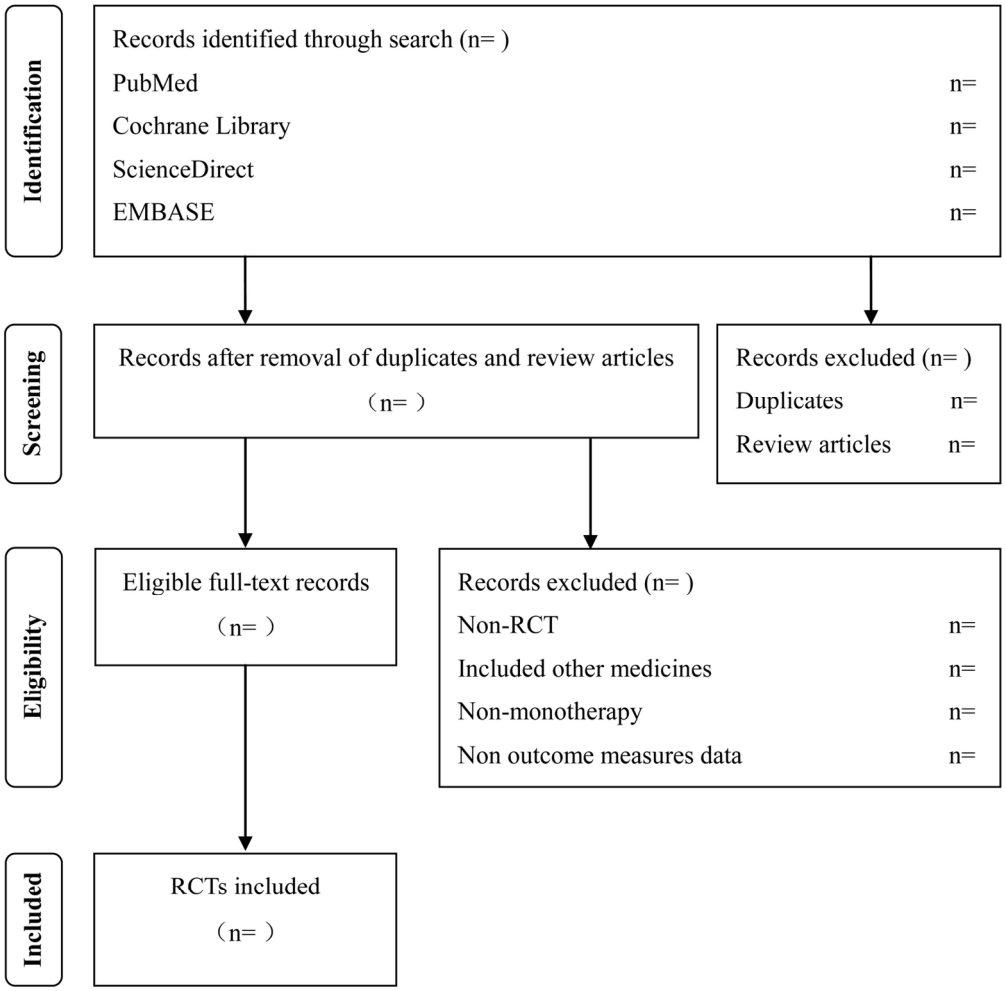
Table 1. Summary of the included RCTs.

Study	Sample size	Treatment duration	Drug 1 dosage	Drug 2 dosage	Drug 3 dosage	HbA1c	FPG
RCT 1							
RCT 2							
RCT 3							
RCT 4							
RCT 5							
…							

Table 2. RCT quality assessment according to the Cochrane Collaboration's risk of bias tool.

	RCT 1	RCT 2	RCT 3	RCT 4	RCT 5	…
Random sequence generation						
Allocation concealment						
Blinding of participants and personnel						
Blinding of outcome assessment						
Incomplete outcome data						
Selective reporting						
Other sources of bias						

Each item of included RCT will be evaluated at low risk, unclear risk and high risk of bias based on the Cochrane Collaboration's risk of bias tool [11].



Flowchart of study selection
145x142mm (300 x 300 DPI)

Appendix 1: Checklist of eligibility.

The study will be excluded when there is a negative ("No") answer to any of following questions:

1. Is the study a randomized controlled trial?

Yes ____

No ____

Unclear ____

2. Are the participants suffering from type 2 diabetes?

Yes ____

No ____

Unclear ____

3. Is the intervention under treatment with any one of selected twelve anti-diabetic drugs?

Yes ____

No ____

Unclear ____

4. Is the control under treatment with any one of selected twelve anti-diabetic drugs other than the drug of intervention or placebo?

Yes ____

No ____

Unclear ____

5. Do the outcome measures include at least one of glycosylated hemoglobin or fasting blood-glucose for each treatment?

Yes ____

No ____

Unclear ____

6. Is the follow-up periods at least four weeks?

Yes ____

No ____

Unclear ____

7. Is the study a non-duplicated and non-redundant publication?

Yes ____

No ____

Unclear ____

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Keywords: protocol; type 2 diabetes; glycemic control; randomized controlled trials; network meta-analysis.

Word count: 1580

Abstract

Introduction:

The past studies of network meta-analysis focused on evaluating drug combinations in treating type 2 diabetes, not evaluating anti-diabetic drugs in monotherapy. Clinical guidelines (e.g. NICE clinical guidelines 66 and 87) were only based on the findings of individual clinical trials and pairwise meta-analysis in evaluating monotherapy. This study aims to fill this gap of research by conducting a Bayesian network meta-analysis to compare major anti-diabetic drugs, including metformin, glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin, and SGLT-2 inhibitors.

Methods and analyses:

Randomized controlled trials (RCT) on the drug therapy of type 2 diabetes with outcome measures including glycosylated hemoglobin (HbA1c) or fasting blood-glucose (FPG) will be included. The quality of included RTCs will be evaluated according to the Cochrane Collaboration's risk of bias tool. Traditional pairwise meta-analysis and Bayesian network meta-analysis will be conducted to compare the efficacies of anti-diabetic drugs. Sensitivity analysis on the sample size of RCTs, meta-regression analysis on the follow-up periods, dosages, and baselines of outcome measure, contradiction analysis between pairwise and network meta-analyses, and publication bias analysis will be performed.

Ethics and dissemination:

Ethical approval is not required because this study includes no confidential personal data and interventions on the patients. Pairwise and network meta-analyses are based on the published RCT reports of eligible drugs in treating type 2 diabetes. The results of this study will be disseminated by a peer-reviewed publication.

Protocol registration:

PROSPERO CRD42014010567.

ARTICLE SUMMARY

Strengths and limitations of this study

- Network meta-analysis together with sensitivity analysis, contradiction analysis, and publication bias analysis will evaluate the efficacies of multiple anti-diabetic drugs.
- This study will provide evidence for clinical decision-makers to formulate better treatment of type 2 diabetes.
- This study is inherently retrospective and based on the published RCTs only.

INTRODUCTION

Glycemic control would prevent microvascular and macrovascular complications of type 2 diabetes [1-2]. Several categories of oral anti-diabetic drugs including biguanides, thiazolidinediones, sulfonylureas, meglitinides, DPP-4 inhibitors and alpha-glucosidase inhibitors are available for monotherapy of type 2 diabetes. Efficacies of these drugs should be monitored for post-marketing evaluation and for updates of clinical guidelines. However, the latest National Institute for Health and Care Excellence (NICE) guidelines [3-4] for treating type 2 diabetes did only include the randomized control trials (RCTs) and their meta-analyses published before 2010.

Even if the clinical guidelines were up to date, there are still gaps to be filled among the current pieces of evidence for the glycemic control efficacy of oral anti-diabetic drugs. Firstly, the current evidence for the oral anti-diabetic drugs efficacies was only limited number of head-to-head RCTs and meta-analyses, including the most comprehensive study by the Agency for Healthcare Research and Quality [5], that cannot cover all possible comparisons among individual drugs. Under this situation, network meta-analysis that can integrate the evidence from direct and indirect comparisons [6] would be applicable. Secondly, efficacy ranking of the oral anti-diabetic drugs was still unknown. The drug recommendation by the clinical guidelines was not based on comprehensive and systematic studies for comparing multiple drugs. This gap also suggests an imminent need for network meta-analysis that can rank all evaluated interventions [7].

While network meta-analysis was used in comparing the efficacies of oral anti-diabetic drugs, the available network meta-analyses [8-10] evaluated only treatments combined with metformin. The monotherapy efficacies of individual drugs have not been studied by network meta-analysis.

This study conducted a Bayesian network meta-analysis [11] to compare the glycemic control efficacy of popular oral anti-diabetic drugs, including metformin, glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin, and SGLT-2 inhibitors.

OBJECTIVES

The objective of this study is to compare efficacies of popular anti-diabetic drugs by Bayesian network meta-analysis on RCTs.

METHODS AND ANALYSIS

Design

Systematic review and Bayesian network meta-analysis.

Information sources

Clinical trial reports will be searched from PubMed and Cochrane Library.

Search strategies

Drug names, synonyms of type 2 diabetes (e.g. type 2 diabetes, type II diabetes and non-insulin-dependent diabetes) and "random*" will be used as keywords to search titles or abstracts for eligible RCTs from major databases including PubMed, Cochrane Library, ScienceDirect, and EMBASE as well as FDA medical reviews, clinicaltrials.gov website. The search is scheduled between August and October in 2014. For example, the following search strategy will be used in searching PubMed:

1. metformin
2. type 2 diabetes
3. random*
4. 1 in title or abstract
5. 2 in title or abstract
6. 3 in title or abstract
7. 4 and 5 and 6

Eligibility criteria

The retrieved reports will be screened according to the checklist of eligibility (Appendix 1) and the eligibility criteria shown below including participants, interventions, controls, types of study, and other criteria.

► Participants

Inclusion: the participants must be adults aged at least 18 suffering from and requiring treatment for type 2 diabetes. Exclusion: the participants suffering from other diabetes disease conditions or aged less than 18.

► Interventions

Inclusion: any RCT that evaluates the efficacy of these drugs. Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs or placebo.

► Controls

Inclusion: any RCT that evaluates the efficacy of these drugs other than the drug of intervention or placebo. Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs.

► Types of study

Inclusion: only RCTs will be included. Exclusion: Observational cohort and case-control studies, case reports, experimental studies and reviews will be excluded.

► Other criteria

Other inclusion criteria: the RCTs must report complete efficacy data of glycosylated hemoglobin (HbA1c) or fasting blood-glucose (FPG) of each treatment. Follow-up periods or durations in RCTs are at least 4 weeks. Other exclusion criteria are (a) duplicated or redundant studies, and (b) combined treatments with multiple drugs.

Study selection

Reviewers will screen all titles or abstracts or full texts for database records independently according to the eligibility criteria. Disagreements between reviewers will be resolved by consensus. Selection process of relevant studies retrieved from databases will be shown in a PRISMA-compliant [12] flowchart (Figure 1).

Data extraction and quality assessment

Data of the study characteristics and the clinical outcome measures will be extracted. The data extracted from the RCTs are: (a) authors; (b) publication year; (c) baseline of outcome measures; (d) sample sizes; (e) interventions of both arms; (f) dosages of both arms; (g) treatment outcome measures including glycosylated hemoglobin (HbA1c) and fasting blood-glucose (FPG). The data will be standardized (Table 1). The quality of eligible studies will be evaluated according to the Cochrane Collaboration's risk of bias tool for assessing risk of bias (Table 2) [13]. Radar chart (or star chart) [14] will be used to summary the results.

Outcome measures

Outcome measures of anti-diabetic efficacy include mean changes of HbA1c (primary outcome) and FPG (secondary outcome) from baseline and their corresponding variation.

Statistical analysis

Pairwise meta-analysis of the included RCTs with random effect model [15-16] due to the expected heterogeneity will be conducted. Mean difference (MD) will be used to synthesis the continuous outcome data: mean changes from baseline of the HbA1c (%) and FPG (mol/L) in both arms. I^2 was used to estimate the heterogeneity [17]. Networks will be generated to visualize the results of pairwise meta-analysis and the current evidence from the included RCTs.

Network meta-analysis (NMA) based on the Bayesian hierarchical model [8] will be performed to compare the efficacy of selected drugs. Placebo will be used as common comparison [18] in NMA. Relative MD to the placebo will be output to assess the efficacy. The probability of each drug being ranked in each position based on HbA1c will be computed [19]. Kendall's test will be used to test the correlation between the relative MD and the ranking position.

Sensitivity analysis based on the sample size of the RCTs will be conducted when RCTs with sample size less than 50 are excluded. Sensitivity analysis will also be conducted on different baselines. Meta-regression analyses will be conducted on the different follow-up periods and dosages for drugs of the included RCTs. Begg's test [20] and Egger's test [21] will be used to evaluate the publication bias. Agreement will be computed to assess the consistency between pairwise and network meta-analyses.

R software [22] will be used to implement the analysis workflow. Package "metafor" [23] will be used to conduct pairwise meta-analysis. Package "igraph" [24] will be used to visualize the networks. Package "fmsb" [25] will be used to visualize the results of risk of bias assessment. Package "GeMTC" [26], "R2WinBUGS" [27] in R and WinBUGS [28] will be used to conducted network meta-analysis. Package "ggplot2" [29] will be used to visualize the distribution of ranking probability distribution. P values lower than 0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

Ethical issues

No ethical approval is required because this study include no confidential personal data and interventions with the patients.

Publication plan

This protocol has been registered (Registration number: CRD42014010567) with the PROSPERO (International Prospective Register of Systematic Reviews) [30]. The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA-compliant guideline. The results of this systematic review and network meta-analysis will be submitted to a peer-reviewed journal for publication.

Contributions

SL conceived the study. SL, YL, and YJ designed the protocol. YL and YJ tested the feasibility of the study. YJ, YL, and SL wrote the protocol and approved the final manuscript.

Funding

The study is part of the "Open systematic reviewing of clinical trials" project supported by a research grant (MYRG190-Y3-L3-ICMS11-LSW) received from the University of Macau.

Competing interests

None declared.

Provenance and peer review

Not commissioned; external peer review.

Table legends

Table 1. Summary of the included RCTs.

Table 2. RCT quality assessment with the Cochrane Collaboration's risk of bias tool.

References

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Table 1. Summary of the included RCTs.

Study	Baseline	Sample size	Treatment duration	Drug 1 dosage	Drug 2 dosage	Drug 3 dosage	HbA1c	FPG
RCT 1								
RCT 2								
RCT 3								
RCT 4								
RCT 5								
…								

Table 2. RCT quality assessment according to the Cochrane Collaboration's risk of bias tool.

	RCT 1	RCT 2	RCT 3	RCT 4	RCT 5	…
Random sequence generation						
Allocation concealment						
Blinding of participants and personnel						
Blinding of outcome assessment						
Incomplete outcome data						
Selective reporting						
Other sources of bias						

Each item of included RCT will be evaluated at low risk, unclear risk and high risk of bias based on the Cochrane Collaboration's risk of bias tool [13].

Glycemic control efficacy of oral anti-diabetic drugs in treating type 2 diabetes: a protocol for network meta-analysis

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Keywords: protocol; type 2 diabetes; glycemic control; randomized controlled trials; network meta-analysis.

Word count: ~~16191~~1580

ARTICLE SUMMARY

~~Article focus~~

- ~~This is a protocol of systematic review and network meta-analysis of randomized controlled trials on metformin, pioglitazone, rosiglitazone, glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin and acarbose in treating type 2 diabetes.~~

~~Key messages~~

- ~~Included drugs will be evaluated by pairwise and a Bayesian network meta-analysis.~~
- ~~Sensitivity analysis, contradiction analysis, and publication bias analysis will be conducted to compare the efficacy of drugs with glycosylated hemoglobin and fasting blood-glucose outcome measures.~~

Strengths and limitations of this study

- Network meta-analysis together with sensitivity analysis, contradiction analysis, and publication bias analysis will evaluate the efficacies of multiple anti-diabetic drugs.
- This study will provide evidence for clinical decision-makers to formulate better treatment of type 2 diabetes.
- This study is inherently retrospective and based on the published RCTs only.

Abstract

Introduction:

~~There were three~~ The past studies of network meta-~~analyses~~analysis focused on ~~the efficacy of anti-diabetic~~ evaluating drug combinations in treating type 2 diabetes~~. No network meta-analytic study has been published~~, not evaluating anti-diabetic drugs in ~~medical journal to evaluate the efficacies of~~ monotherapy. ~~Current clinical~~Clinical guidelines (e.g. NICE clinical guidelines 66 and 87) ~~are~~ were only based on the findings of ~~limited~~individual clinical trials and pairwise meta-analysis~~.~~ in evaluating monotherapy. This study aims to fill this gap of research by conducting a Bayesian network meta-analysis to compare ~~twelve~~major anti-diabetic drugs, including metformin, ~~pioglitazone, rosiglitazone,~~ glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin, and ~~acarbose~~SGLT-2 inhibitors.

Methods and analyses:

Randomized controlled trials (RCT) on the drug therapy of type 2 diabetes with outcome measures including glycosylated hemoglobin (HbA1c) or fasting blood-glucose (FPG) will be included. The quality of ~~inluced~~included RTCs will be evaluated according to the Cochrane Collaboration's risk of bias tool. ~~Overall effect sizes will be represented as mean differences with 95% credible intervals (CrI) for continuous outcome data. Pairwise~~Traditional pairwise meta-analysis ~~in R software~~ and Bayesian network meta-analysis ~~in R and WinBUGS~~ will be conducted to compare the efficacies of ~~these~~anti-diabetic drugs. Sensitivity analysis on the sample size of RCTs, meta-regression analysis on the follow-up periods, dosages, and baselines of outcome measure, contradiction analysis between ~~pair~~pairwise and network meta-analyses, and publication bias analysis will be performed.

Ethics and dissemination:

Ethical approval is not required because this study ~~include~~includes no confidential personal data and interventions on the patients. ~~Network~~Pairwise and network meta-~~analysis is~~analyses are based on the published RCT reports of eligible drugs in treating type 2 diabetes. The results of this study will be disseminated by ~~an open access and~~a peer-reviewed publication.

Protocol registration:

PROSPERO CRD42014010567.

INTRODUCTION

Glycemic control would prevent microvascular and macrovascular complications of type 2 diabetes ~~patients~~ [1-2]. Several categories of oral anti-diabetic drugs including biguanides, thiazolidinediones, sulfonylureas, meglitinides, DPP-4 inhibitors and alpha-glucosidase inhibitors are available for monotherapy of type 2 diabetes. Efficacies of these drugs should be monitored for post-marketing evaluation and ~~referred~~ for updates of clinical guidelines. ~~Randomized~~However, the latest National Institute for Health and Care Excellence (NICE) guidelines [3-4] for treating type 2 diabetes did only include the randomized control trials (RCTs) and their meta-analyses ~~are used in testing the efficacies of different treatments [3]. However, head-to-head RCTs do not cover all direct comparisons between drugs. Network meta-analysis, also known as mixed treatment comparison, was developed to incorporate direct and indirect evidence from RCTs [3].~~published before 2010.

~~Although~~Even if the ~~National Institute for Health and Care Excellence (NICE) guideline [4] is a popular~~ clinical ~~guideline for diabetes care~~guidelines were up to date, there are still gaps to ~~provide~~ be filled among the ~~necessary~~ current pieces of evidence ~~of~~for the glycemic control efficacy of oral anti-diabetic drugs ~~for updating the guideline.~~ Firstly, the current evidence ~~of~~for the oral anti-diabetic drugs efficacies was ~~mainly based on~~ only limited number of head-to-head RCTs and ~~their~~ meta-analyses~~.~~, including the most comprehensive study by the Agency for Healthcare Research and Quality [5], that cannot cover all possible comparisons among individual drugs. Under this situation, network meta-analysis that can integrate the evidence from direct and indirect comparisons [6] would be applicable. Secondly, efficacy ranking of the oral anti-diabetic drugs was still unknown ~~from~~. The drug recommendation by the ~~guideline due to the lack of~~clinical guidelines was not based on comprehensive and systematic studies for comparing multiple ~~comparisons among these drugs. Network meta-analyses had been~~drugs. This gap also suggests an imminent need for network meta-analysis that can rank all evaluated interventions [7].

While network meta-analysis was used in comparing the efficacies of oral anti-diabetic drugs ~~[5-7]. A network meta-analysis published in 2011 aimed to compare the~~ , the available network meta-analyses [8-10] evaluated only treatments combined with metformin. The monotherapy efficacies of ~~anti-diabetic drugs added to metformin [5]. Others published in 2012 and 2014 aimed to compare the efficacies of anti-diabetic drugs adding to metformin [3-4]. While these studies~~

compared the drug combination efficacy of different classes, the monotherapy efficacy of individual drug is not been compared in network meta-analysis. Thirdly, robustness of multiple comparisons is still needed to be evaluated. Therefore, network meta-analysis on the monotherapy efficacies of individual drugs have not been studied by network meta-analysis.

This study conducted a Bayesian network meta-analysis [11] to compare the glycemic control efficacy of popular oral anti-diabetic drugs by incorporating direct and indirect evidence based on randomized controlled trials (RCT) is necessary [8].

Twelve popular drugs, including metformin, pioglitazone, rosiglitazone, glimepiride, glyburide, glipizide, repaglinide, nateglinide, sitagliptin, vildagliptin, saxagliptin, and acarbose, were selected from six oral anti-diabetic drug categories reported in the review [9] from the Agency for Healthcare Research and Quality. This study conducted a Bayesian network meta-analysis to compare the glycemic control efficacy of the selected anti-diabetic drugs.SGLT-2 inhibitors.

OBJECTIVES

The objective of this study is to compare efficacies of popular anti-diabetic drugs by Bayesian network meta-analysis on RCTs.

METHODS AND ANALYSIS

Design

Systematic review and Bayesian network meta-analysis.

Information sources

Clinical trial reports will be searched from PubMed and Cochrane Library.

Search strategies

Drug names, synonyms of type 2 diabetes (e.g. type 2 diabetes, type II diabetes and non-insulin-dependent diabetes) and "random*" will be used as keywords to search titles or abstracts for eligible RCTs from major databases including PubMed, Cochrane Library, ScienceDirect, and EMBASE, as well as FDA medical reviews, clinicaltrials.gov website. The

search is scheduled between August and October in 2014. For example, the following search strategy will be used in searching PubMed:

1. metformin
2. type 2 diabetes
3. random*
4. 1 in title or abstract
5. 2 in title or abstract
6. 3 in title or abstract
7. 4 and 5 and 6

Eligibility criteria

The retrieved reports will be screened according to the checklist of eligibility (Appendix 1) and the eligibility criteria shown below including participants, interventions, controls, types of study, and other criteria.

► Participants

Inclusion: the participants must be adults aged at least 18 suffering from and requiring treatment for type 2 diabetes. Exclusion: the participants suffering from other diabetes disease conditions or aged less than 18.

► Interventions

Inclusion: any RCT that evaluates the efficacy of these ~~twelve~~ drugs. Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs or placebo.

► Controls

Inclusion: any RCT that evaluates the efficacy of these ~~twelve~~ drugs other than the drug of intervention or placebo. Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs.

► Types of study

Inclusion: only RCTs will be included. Exclusion: Observational cohort and case-control studies, case reports, experimental studies and reviews will be excluded.

► Other criteria

Other inclusion criteria: the RCTs must report complete efficacy data of glycosylated hemoglobin

(HbA1c) or fasting blood-glucose (FPG) of each treatment. Follow-up periods or durations in RCTs are at least 4 weeks. Other exclusion criteria are (a) duplicated or redundant studies, and (b) combined treatments with multiple drugs.

Study selection

Reviewers will screen all titles or abstracts or full texts for database records independently according to the eligibility criteria. Disagreements between reviewers will be resolved by consensus. Selection process of relevant studies retrieved from databases will be shown in a PRISMA-compliant [~~10~~12] flowchart (Figure 1).

Data extraction and quality assessment

Data of the study characteristics and the clinical outcome measures will be extracted. The data extracted from the RCTs are: (a) authors; (b) publication year; (c) baseline of outcome measures; (d) sample sizes; (~~d~~e) interventions of both arms; (~~e~~f) dosages of both arms; (~~f~~g) treatment outcome measures including glycosylated hemoglobin (HbA1c) and fasting blood-glucose (FPG). The data will be standardized (Table 1). The quality of eligible studies will be evaluated according to the Cochrane Collaboration's risk of bias tool for assessing risk of bias (Table 2) [~~11~~13]. Radar chart (or star chart) [~~12~~14] will be used to summary the results.

Outcome measures

Outcome measures of anti-diabetic efficacy include mean changes of HbA1c (primary outcome) and FPG (secondary outcome) from baseline and their corresponding variation.

Statistical analysis

Pairwise meta-analysis of the included RCTs with random effect model [~~13-14~~15-16] due to the expected heterogeneity will be conducted. Mean difference (MD) will be used to synthesis the continuous outcome data: mean changes from baseline of the HbA1c (%) and FPG (mol/L) in both arms. I^2 was used to estimate the heterogeneity [~~15~~17]. Networks will be generated to visualize the results of pairwise meta-analysis and the current evidence from the included RCTs.

Network meta-analysis (NMA) based on the Bayesian hierarchical model [~~3~~8] will be

performed to compare the efficacy of selected drugs. Placebo will be used as common comparison [~~16~~18] in NMA. Relative MD to the placebo will be output to assess the efficacy. The probability of each drug being ranked in each position based on HbA1c will be computed [~~17~~19]. Kendall's test will be used to test the correlation between the relative MD and the ranking position.

Sensitivity analysis based on the sample size of the RCTs will be conducted when RCTs with sample size less than 50 are excluded. ~~Begg's test [18] and Egger's test [19~~Sensitivity analysis will also be conducted on different baselines. Meta-regression analyses will be conducted on the different follow-up periods and dosages for drugs of the included RCTs. Begg's test [20] and Egger's test [21] will be used to evaluate the publication bias. Agreement will be computed to assess the consistency between pairwise and network meta-analyses.

R software [~~20~~22] will be used to implement the analysis workflow. Package "metafor" [~~21~~23] will be used to conduct pairwise meta-analysis. Package "igraph" [~~22~~24] will be used to visualize the networks. Package "fmsb" [~~23~~25] will be used to visualize the results of risk of bias assessment. Package "GeMTC" [246], "R2WinBUGS" [~~25~~27] in R and WinBUGS [~~26~~28] will be used to conducted network meta-analysis. Package "ggplot2" [~~27~~29] will be used to visualize the distribution of ranking probability distribution. P ~~Values~~values lower than 0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

Ethical issues

No ethical approval is required because this study include no confidential personal data and interventions with the patients.

Publication plan

This protocol has been registered (Registration number: CRD42014010567) with the PROSPERO (International Prospective Register of Systematic Reviews) [~~28~~30]. The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA-compliant guideline. ~~Details~~The results of this systematic review and network

meta-analysis will be submitted to ~~one of the BMJ~~a peer-reviewed journal for publication.

Contributions

SL conceived the study. SL, YL, and ~~YL~~YJ designed the ~~study~~ protocol. YL and YJ tested the feasibility of the study. YJ, YL, and SL wrote the protocol and approved the final manuscript.

Funding

The study is part of the "Open systematic reviewing of clinical trials" project supported by a research grant (MYRG190-Y3-L3-ICMS11-LSW) received from the University of Macau.

Competing interests

None declared.

Provenance and peer review

Not commissioned; external peer review.

Table ~~Legends~~legends

Table 1. Summary of the included RCTs.

Table 2. RCT quality assessment with the Cochrane Collaboration's risk of bias tool.

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RCT 4								
RCT 5								
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Inserted Cells

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	RCT 1	RCT 2	RCT 3	RCT 4	RCT 5	…
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Blinding of participants and personnel						
Blinding of outcome assessment						
Incomplete outcome data						
Selective reporting						
Other sources of bias						

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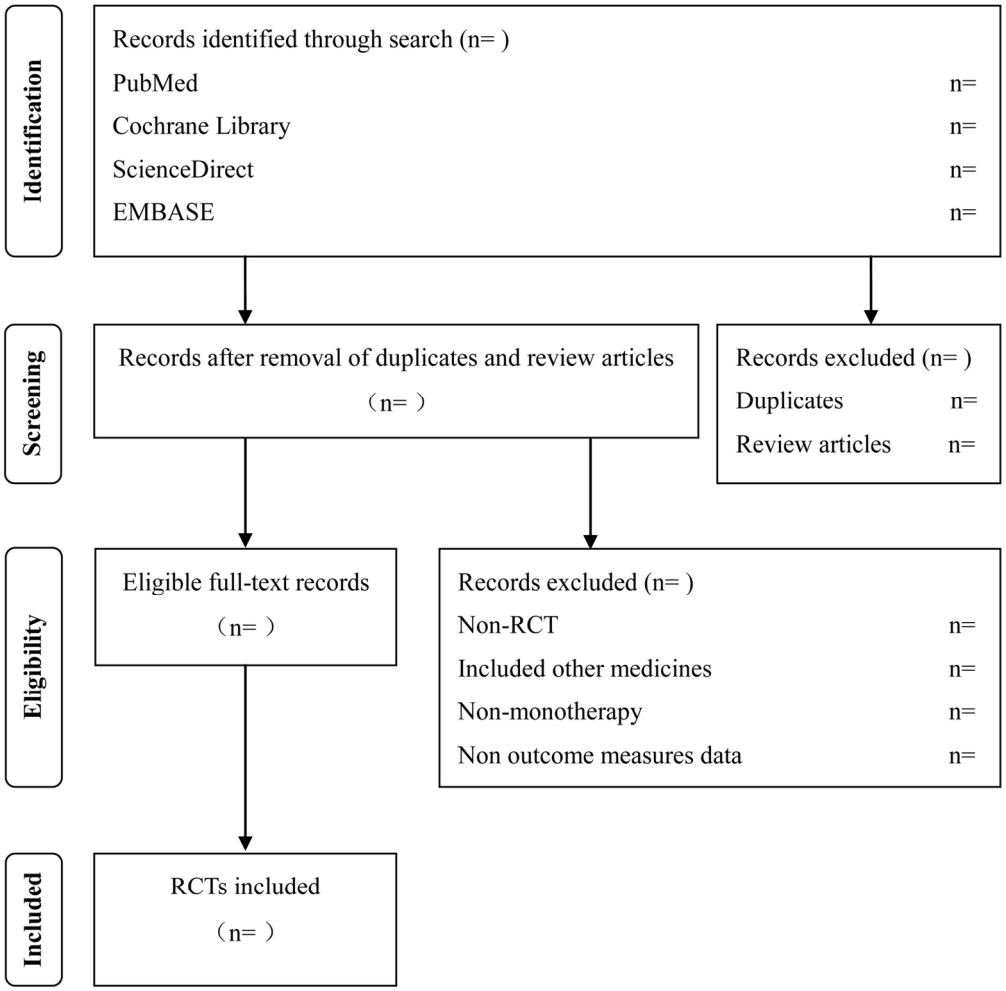

Flowchart of study selection
145x142mm (300 x 300 DPI)

Appendix 1: Checklist of eligibility.

The study will be excluded when there is a negative ("No") answer to any of following questions:

1. Is the study a randomized controlled trial?

Yes ____

No ____

Unclear ____

2. Are the participants suffering from type 2 diabetes?

Yes ____

No ____

Unclear ____

3. Is the intervention under treatment with any one of selected twelve anti-diabetic drugs?

Yes ____

No ____

Unclear ____

4. Is the control under treatment with any one of selected twelve anti-diabetic drugs other than the drug of intervention or placebo?

Yes ____

No ____

Unclear ____

5. Do the outcome measures include at least one of glycosylated hemoglobin or fasting blood-glucose for each treatment?

Yes ____

No ____

Unclear ____

6. Is the follow-up periods at least four weeks?

Yes ____

No ____

Unclear ____

7. Is the study a non-duplicated and non-redundant publication?

Yes ____

No ____

Unclear ____