

BMJ Open Lorcaserin for prevention and remission of type 2 diabetes mellitus in people with overweight or obesity: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction High body mass index (BMI) is associated with risk of diabetes. Lorcaserin is a selective 5-hydroxytryptamine 2C agonist which exerts robust benefits on long-term weight loss by suppressing appetite among adults with overweight or obesity. The magnitude of efficacy of lorcaserin for preventing and remitting type 2 diabetes mellitus (T2DM) among those people remains undefined. Therefore, we plan to conduct this systematic review and meta-analysis to aggregate data from all published studies with regard to the issue to acquire reliable evidence.

Methods and analysis We will search various databases for relevant trials published up to June 2019. Randomised controlled trials investigating the efficacy of lorcaserin for preventing and remitting T2DM among overweight and obese population will be included. A standardised data form will be used to complete data search and extraction in duplicate. All discrepancies will be resolved by consensus. The primary outcome will be incidence of T2DM in patients with pre-diabetes. Secondary outcomes will include achievement of normoglycaemia in people with pre-diabetes, remission of hyperglycaemia in patients with diabetes, the proportion of patients with weight loss of at least 5% or 10% and hypoglycaemia incident. Data synthesis and statistical analysis will be performed for each outcome with Stata V.14.0.

Ethics and dissemination Ethics approval is not required. Results of our study will be submitted to a peer-review journal.

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INTRODUCTION

Over the past 40 years, the global prevalence of obesity has reached alarming proportions with rates nearly tripling.¹ As of 2016, 39% of adults all over the world were overweight (defined as body mass index (BMI) 25–29.9 kg/m²), and another 13% of adults were obese (BMI ≥30 kg/m²).¹ Obesity has been linked to the development and progression of dysglycaemia and type 2 diabetes mellitus (T2DM).² Analogously, the prevalence of diabetes is also rising globally,

Strengths and limitations of this study

- This study is the first systematic review and meta-analysis combining data from all available randomised controlled trials to evaluate the effectiveness of lorcaserin on diabetes prevention and remission among people with overweight or obesity.
- The study design is rigorous and complete, including systematic literature search, comprehensive evaluation of clinically important outcomes and proper assessment of quality of evidence.
- The quantity, methodological quality and heterogeneity of included studies may influence the results of this study.
- This meta-analytic review is limited by the inability to use individual participant data.

the number of people with diabetes grew from 153 million in 1980 to as many as 476 million in 2017, with T2DM accounting for 463 million.^{3–4} Approximately 29 million adults in America had T2DM in 2012, which is projected to increase to 100 million before 2050.^{5,6} In addition, an estimated 280 million adults globally, including 57 million in America, are considered to be patients with pre-diabetes.^{7–8} Pre-diabetes is an umbrella term, describing a blood glucose level that lies above normal but below that diagnosed for T2DM.⁹ People with defined pre-diabetic state are considered to be at high risk for the development of T2DM.^{10–12} Both diabetes and obesity raise the risk of cardiovascular disease, chronic kidney disease, neuropathy, stroke and cancers.^{13–20} The two conditions are also related to increased risk of all-cause mortality, the mortality burden of which nearly doubled in the past three decades.^{13,21} Globally, 6.53 million deaths and 171 million disability-adjusted life-years (DALYs) were attributed to high fasting plasma glucose in 2017, followed by high BMI (4.72 million

deaths and 148 million DALYs).²² Pharmacological agents for weight loss are recommended in guidelines as adjuncts to comprehensive lifestyle interventions in long-term weight management, which exert benefits on preventing progression to pre-diabetes and diabetes, reducing hypertension risk and improving lipid profiles,^{13 23} especially for those persons who fail in achieving sufficient weight loss with lifestyle interventions alone.²⁴

As a highly selective serotonin 2C receptor agonist on proopiomelanocortin neurons, lorcaserin is effective for weight loss by regulating appetite in adults with obesity.²⁵ Based on data by three main clinical trials, including behavioural modification and lorcaserin for overweight and obesity management (BLOOM) study, BLOOM in patients of diabetes mellitus study and behavioural modification and lorcaserin second study for obesity management study, the US Food and Drug Administration initially approved lorcaserin as a new adjunctive prescription drug to lifestyle modification (reduced-calorie diet and increased physical activity) for the treatment of obesity in 2012, bringing new hope for people with obesity.^{25–27} Lorcaserin, considered as a safe and well tolerable drug, could achieve statistically significant weight loss and improve cardiometabolic parameters.²⁸ Additionally, long-term data from a recent large randomised trial suggested that lorcaserin could reduce the risk of microvascular complications without an increased incidence of major adverse cardiovascular events.^{29 30} Thus, lorcaserin demonstrates superiority to several pharmacological weight-loss agents associated with various cardiovascular or neuropsychiatric complications.^{31–33}

In recent years, there is an increasing interest regarding the prevention of progression of pre-diabetes to diabetes and remission of hyperglycaemia, and meanwhile lorcaserin has now been investigated in several trials^{29 34–36} in patients with type 2 diabetes or pre-diabetes and obesity. Results from these trials suggest that lorcaserin could help with achieving clinically meaningful weight loss, promoting reversion to euglycaemia and preventing progression to T2DM in patients with obesity.^{29 34–36} However, there is a paucity of comprehensive evidence of randomised controlled trials (RCTs) with respect to this topic. Our meta-analytic review aims to combine data from all relevant RCTs of lorcaserin to acquire reliable estimates regarding specific metabolic efficacy and safety outcomes on preventing and remitting T2DM in patients with obesity.

METHODS

Study design

This protocol is reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.^{37 38} This study will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.³⁹

Study registration

According to PRISMA-P and PRISMA guidelines, this study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO). We anticipate to conduct this review from January to June 2019.

Eligibility criteria

Population

Eligible patients will be adults (older than 18 years) who have T2DM or pre-diabetes with coexisting obesity. Definitions of pre-diabetes and diabetes could be based on any recognised standard diagnosis criteria, for instance, the American Diabetes Association guidelines.

Interventions and comparators

We plan to investigate the comparisons of lorcaserin versus placebo.

Outcomes

The primary outcome will be incidence of T2DM in patients with pre-diabetes. Secondary outcomes will include achievement of normoglycaemia among pre-diabetic patients, remission of hyperglycaemia in patients with diabetes, the proportion of patients who lost $\geq 5\%$ or 10% body weight among people with pre-diabetes or diabetes and incidence of hypoglycaemia in patients with diabetes. Definitions for these outcomes should be established and described in eligible trials.

Type of studies

RCTs will be included in our study. Retrospective or prospective observational cohort studies, cross-section studies, case-control studies and reviews will be excluded.

Search strategy

We will conduct a comprehensive systematic search of the following databases from inception date to June 2019, including PubMed, Embase, Web of Science, the Cochrane library, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Moreover, a restriction on the language of publication to English will be placed. Relevant keywords and their combinations will be applied in the search strategy, for instance, diabetes, T2DM, pre-diabetes, pre-diabetic state, glucose intolerance, impaired glucose, diabetic, dysglycaemia, hyperglycaemia, lorcaserin, obesity, obese, overweight, conversion, delay and prevent. A complete search strategy of PubMed database is provided in online supplementary. All potentially eligible studies will be considered for review. In addition, using the reference lists of key articles, including retrieved included studies, meta-analyses and systematic reviews, we will also do a manual search for other relevant eligible trials.

Selection of studies

According to the predefined inclusion criteria, titles and abstracts of all records retrieved in the literature search will be scanned by two review authors. Trials that met the inclusion criteria will be retrieved for further assessment.

All potentially relevant articles will be investigated via scrutinising full text. The PRISMA flow diagram of study selection will be used to depict trial identification and exclusion process. Disagreements at study selection will be resolved by discussion and consensus.

Data collection process

Two review authors will independently extract data of all eligible studies with the use of a standardised data form in duplicate. The following data will be extracted from all selected studies: trial characteristics (author, year of publication, country setting, study design and trial duration), participant characteristics (mean age, percent of male, race, baseline weight, BMI and glycemic parameters), dose and frequency of lorcaserin and predefined primary and secondary outcomes. Any disagreement will be resolved by consensus or recourse to a third reviewer. We will contact authors by e-mails to acquire more information if the data are insufficient in the original article.

Assessment of methodological quality

The Cochrane tool for assessing risk of bias will be used to evaluate the methodological quality of included RCTs by two review authors working independently. The assessment details include seven domains as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.⁴⁰ Based on the description details of eligible studies, each domain will be defined as being at high, low or unclear risk of bias. We will settle all discrepancies in quality evaluation through consensus and consultation with a third reviewer.

Data synthesis and statistical analysis

Stata V.14.0 (StataCorp) will be used to carry out all statistical analyses. We will pool mean differences with 95% CIs for the effect of continuous outcomes across trials. The overall estimates of the risk ratios and their associated 95% CIs will also be calculated for categorical outcomes. A p value of no more than 0.05 will be considered as statistically significant. Results will be synthesised by a random-effects model to adequately account for the heterogeneity among included studies. The heterogeneity across included trials will be assessed by I^2 statistic. Heterogeneity will be considered to be low ($I^2 < 25\%$), moderate ($I^2 = 25\% - 50\%$) or high ($I^2 > 75\%$).⁴¹ Potential publication bias will be evaluated by funnel plots, and also assessed by the Egger and Begg tests if no less than 10 studies are pooled.⁴²

Sensitivity and subgroup analyses

A sensitivity analysis will be conducted by excluding studies with high risk of bias. In addition, the leave-one-out sensitivity analysis will also be performed to evaluate the stability of results. Moreover, subgroup analysis will be conducted according to BMI ($25 - 29.9 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$). Outcome data on adults (18–64 years) and elderly population (aged 65 years or older) will be

analysed separately. Gender and ethnicity will also be considered for subgroup analyses if the data permit.

Quality of evidence

The grading of recommendations assessment, development and evaluation (GRADE) approach will be applied to rate the overall quality of evidence with respect to each outcome of our findings.⁴³ The GRADE method categorises the quality of evidence into four levels as follows: very low, low, moderate and high. Several reasons will influence the confidence of evidence, including reporting bias, study limitations, indirectness of evidence, inconsistency of results and imprecision.

Patient and public involvement

Patients and public will be not involved in the study.

Ethics and dissemination

The meta-analytic review will not analyse confidential patient data, thus formal ethics approval is not required. Our results will be reported in line with the framework laid out in the PRISMA guidelines. The findings from our study will be submitted to a peer-reviewed journal.

DISCUSSION

Over the recent years, lorcaserin has gained increasing popularity in weight management among patients with obesity, with additional evidence from trials suggesting proven benefits on preventing progression of pre-diabetes to T2DM and remission of hyperglycaemia. Our study will be the first systematic review and meta-analysis to assess effectiveness and safety of lorcaserin for preventing and remitting of type 2 diabetes in the population with adiposity. The conclusions of this study are of benefit to patients with coexisting pre-diabetes or T2DM and obesity, guideline developers and clinicians. Nevertheless, we should acknowledge several potential limitations of this study. Trial-level data will be aggregated instead of individual participant data. Moreover, differences in inclusion criteria, definitions of endpoints and methodological quality among included studies may cause considerable heterogeneity. Additionally, common to any meta-analysis, the quantity of included studies may influence the findings of this study. To include more relevant studies and provide more reliable evidence, we will conduct a comprehensive systematic search of various databases. In the case of limited number of available trials, we will present a narrative review simultaneously and interpret the findings of our study cautiously.

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Contributors WF and YJ were the guarantors. HZ, ML and JW contributed to study design. JW, ML and ZL drafted the protocol. GH and ML registered the protocol and designed the search strategy. HZ, WF, YJ and PZ revised the protocol. All authors reviewed and approved the final manuscript.

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