

# BMJ Open Drug efficacy in treating stable angina pectoris: a protocol for network meta-analysis of randomised controlled trials

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## ABSTRACT

**Introduction:** There were 11 pairwise meta-analysis on the efficacy of  $\beta$ -blockers (including atenolol, propranolol, bisoprolol, metoprolol and nadolol), calcium channel blockers (including amlodipine, diltiazem, felodipine, nifedipine and verapamil), and nitrates (including isosorbide dinitrate, isosorbide mononitrate and nitroglycerin) in treating stable angina pectoris. No network meta-analytic study has been published to evaluate the efficacies of these antianginal drugs. Current clinical guidelines (eg, National Institute of Health and Care Excellence (NICE) clinical guideline 126) 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 all these antianginal drugs.

**Methods and analyses:** Randomised controlled trials (RCT) on the drug therapy of stable angina pectoris with multiple outcome measures, selected from symptomatic relief, ECG tests, exercise tests, heart rates and blood pressures, etc, will be included. Overall effect sizes will be represented as mean differences with 95% credible intervals (CrI) for continuous outcome data and as ORs with 95% CrI for dichotomous outcome data. Bayesian network meta-analysis by WinBUGS will be conducted to compare the efficacies of these drugs. Sensitivity analysis on the quality of RCTs and subgroup analysis on the category of included drugs will be performed.

**Ethics and dissemination:** Ethical approval is not required because this study includes no confidential personal data and interventions on the patients. Network meta-analysis is based on the RCT reports of eligible drugs in treating stable angina pectoris. The results of this study will be disseminated by an open access and peer-reviewed publication.

**Trial registration number:** PROSPERO CRD42014007113.

## INTRODUCTION

Stable angina pectoris is experienced as trans-sternal or retrosternal pressure or a choking sensation or pain that may radiate to

## Strengths and limitations of this study

- Network meta-analysis together with sensitivity analysis, subgroup analysis and consistency analysis will evaluate the efficacies of multiple anti-anginal drugs.
- This study will provide evidence for clinical decision-makers to formulate better treatment of stable angina pectoris.
- This study is inherently retrospective and based on the published randomised controlled trials only.

the left arm, jaw, neck or back.<sup>1</sup> Its treatment is mainly relief of symptoms with antianginal medications or revascularisation procedures.<sup>1</sup> The antianginal medications especially for monotherapy are selected from three groups of antianginal chemical drugs including  $\beta$  blockers (BBs), calcium channel blockers (CCBs) and nitrates.<sup>2</sup> In the UK the most frequently prescribed BBs are atenolol, propranolol, bisoprolol, metoprolol and nadolol.<sup>2</sup> The most frequently prescribed CCBs are amlodipine, diltiazem, felodipine, nifedipine and verapamil.<sup>2</sup> The most frequently prescribed nitrates are isosorbide dinitrate, isosorbide mononitrate and nitroglycerin.<sup>2</sup> Although clinical guidelines<sup>2, 3</sup> have suggested that these three group drugs can be used to alleviate angina symptoms and BBs or CCBs can be offered as the first-line treatment for stable angina, there is still no definitive evidence to support the efficacy profiles of antianginal drugs. Their efficacies have not been thoroughly evaluated by comprehensive pairwise meta-analysis, let alone the network meta-analysis for comparing multiple drugs.

Available meta-analysis of randomised and crossover trials comparing BBs, CCBs and nitrates suggested that BBs provide similar clinical outcomes and are associated with

fewer adverse events (AEs) than CCBs for patients with stable angina pectoris.<sup>4</sup> Meta-analysis of efficacy of monotherapy compared with combined antianginal drugs for treating stable angina pectoris suggested that the combined therapy with CCBs and BBs is more effective than monotherapy.<sup>5</sup> A systematic review and meta-analysis of randomised trials with nitrates for stable angina pectoris suggested that long-term administration of nitrates is beneficial for angina prophylaxis and improves exercise performance but might be ineffective for improving quality of life.<sup>6</sup> Another systematic review and meta-analysis of randomised controlled trials (RCTs) on long-term BBs for stable angina pectoris suggested that BBs may decrease the rates of death and unstable angina when compared with no treatment but are no more effective than other antianginal agents on prophylaxis of myocardial ischaemia.<sup>7</sup> Meta-analysis of randomised trials of BBs for stable angina suggested that BBs do not have statistically significant impact on mortality versus placebo or versus other active comparators.<sup>8</sup> The latest meta-analysis on antianginal drugs was published in 2012.<sup>8</sup> All of these systematic reviews performed only pairwise meta-analysis to compare efficacies of antianginal drugs.

As the number (n) of available treatments increases, the required number ( $C_n^2$ ) of pairwise meta-analysis increases exponentially. Therefore, pairwise meta-analysis for comparing multiple treatments is labour-intensive and time-consuming. The Cochrane Handbook regards multiple treatment comparison (MTC) as a highly relevant and useful technique to evaluate and rank treatments, although the Handbook does not describe the methods for MTC.<sup>9</sup> Bayesian network meta-analyses were proposed for evaluating the efficacies of MTC.<sup>10 11</sup> The most related Bayesian meta-analytic study was on other classes of antianginal drugs (ie, trimetazidine vs other non-heart rate lowering antianginal medications) and was not monotherapy,<sup>12</sup> while the present study was on monotherapy with BBs, CCBs and nitrates.

This study is a comprehensive network meta-analysis on the efficacies of BBs, CCBs and nitrates in treating stable angina pectoris.

## OBJECTIVES

The objective of this study is to compare efficacies of common antianginal 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 major databases including PubMed, ScienceDirect, Cochrane Library and EMBASE.

## Search strategies

Keywords used in search strategies include 'angina' and 'random'. For example, the following search strategy will be used in searching PubMed and other English databases:

1. angina pectoris
2. random
3. 1 in MeSH terms
4. 2 in Text Word
5. 3 AND 4

## Eligibility criteria

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

- ▶ **Participants** Inclusion—the participants suffering from and requiring treatment for stable angina pectoris. Exclusion—the participants suffering from unstable angina pectoris or other complicated heart disease conditions.
- ▶ **Interventions** Inclusion—any RCT that evaluates the efficacy of these 13 drugs. Exclusion—any RCT that evaluates other drugs or combined treatments of multiple drugs.
- ▶ **Controls** Inclusion—any RCT that evaluates the efficacy of these 13 drugs other than the drug of intervention. 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—any RCT that includes outcome measures of symptomatic (SYM) relief, ECG tests, exercise tests, heart rates or blood pressures. Other exclusion criteria are (1) duplicated or redundant studies and (2) combined treatments with multiple drugs.

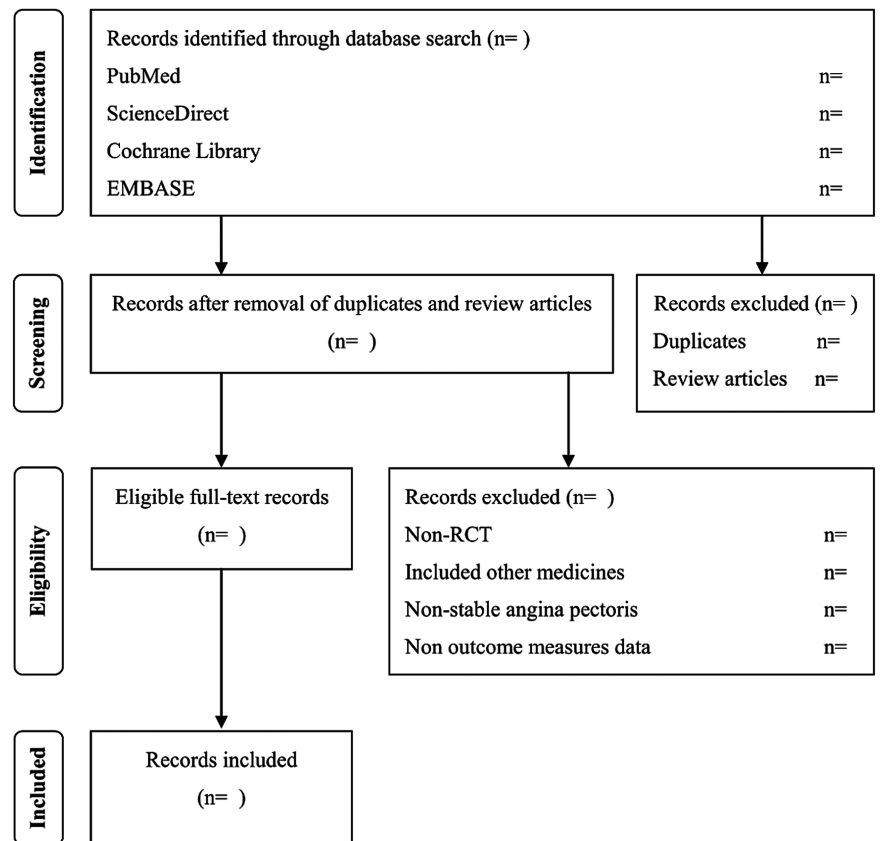
## Study selection

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

## Data extraction and quality assessment

Data items to be extracted from eligible RCTs: (1) publication years, (2) number of authors, (3) baseline comparison of participants between groups, (4) sample sizes, (5) treatment durations, (6) dosages of treatment, (7) AEs and (8) outcome measures including ECG tests, SYM relief, exercise tests, heart rates and blood pressures. The data will be standardised (table 1). The quality of eligible studies will be evaluated according to

**Figure 1** Process of study search and selection.



the Cochrane Collaboration's risk of bias tool for assessing risk of bias (table 2).<sup>9</sup>

### Outcome measures

Outcome measures of antianginal efficacy include ECG tests, SYM relief, exercise tests, heart rates and blood pressures.<sup>2-3</sup> Primary outcomes are ECG tests, SYM relief and exercise tests. Secondary outcomes are heart rates and blood pressures.

### Statistical analysis

Network meta-analysis will be conducted with WinBUGS V.1.4.3<sup>13</sup> and 'R2WinBUGS' package<sup>14</sup> in R software.<sup>15</sup>

A Bayesian random-effects model<sup>11-16</sup> will be adopted:

$$r_{Ti} \sim \text{Binomial}(p_{Ti}, n_{Ti}),$$

$$\log \text{it}(p_{Ti}) = \mu_i + \delta_{TCi},$$

$$\delta_{TCi} \sim \text{Normal}(d_{TC}, \sigma^2),$$

$$\mu_i \sim \text{Normal}(0, \sigma_\mu^2),$$

$$d_{TC} \sim \text{Normal}(0, \sigma_d^2),$$

$$\sigma \sim \text{Uniform}(0, s)$$

where T is the treatment (a specific arm) of the RCT; C the control (the baseline arm) of the RCT and  $T \neq C$ ; i the number index of RCT;  $r_{Ti}$  the number of success events in the treatment T in the  $i$ th RCT;  $p_{Ti}$  the probability of treatment response;  $n_{Ti}$  the number of all events in the treatment T in the  $i$ th RCT;  $\delta_{TCi}$  the

**Table 1** Summary of the included RCTs

Study	Sample size	Treatment duration	Drug 1 dosage	Drug 2 dosage	Drug 3 dosage	Outcome data	AEs
RCT 1							
RCT 2							
RCT 3							
RCT 4							
...							

AEs, adverse events; RCT, randomised controlled trials.

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

	RCT 1	RCT 2	RCT 3	RCT 4	...
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 is evaluated at low risk, unclear risk and high risk of bias based on the Cochrane Collaboration's risk of bias tool.<sup>9</sup> RCT, randomised controlled trials.

random effect of T relative to C in the  $i$ th RCT;  $d_{TC}$  the mean effect of T compared with C;  $\mu_i$  the actual effect of C in the  $i$ th RCT;  $\sigma^2$  the random effects variance of  $\delta_{TCi}$ ;  $\sigma_\mu^2$  the variance of  $\mu_i$  distribution, which is a numeric choice;  $\sigma_d^2$  the variance of  $d_{TC}$  distribution, which is a numeric choice;  $\sigma$  the SD of  $\delta_{TCi}$ ; and  $s$  the numeric choice of uniform prior.

This Bayesian model and WinBUGS codes are as specified in the research reports published by the Agency for Healthcare Research and Quality (AHRQ)<sup>11</sup> and the National Institute of Health and Care Excellence (NICE).<sup>17, 18</sup> Model fitness will be assessed with the deviance information criterion (DIC) and the posterior mean of the total residual deviance.<sup>19</sup> Deviance measures the fit of the model to the data using the likelihood function. The DIC is a statistic that measures Bayesian model fit and penalises the deviance by the model complexity. Variances and consistencies among all comparisons are assessed using the Brooks-Gelman-Rubin method under a random-effects model.<sup>20</sup> Bayesian models will be executed with the WinBUGS settings: chains at 4, refresh at 100, thinning intervals at 10 and update at 20 000. The overall effect size will be presented by ORs with their 95% credible intervals for dichotomous outcomes.<sup>21</sup> Continuous outcomes will be computed by mean differences with their 95% credible intervals.<sup>21</sup> The overall ranking will be determined by network meta-analysis according to overall effect sizes. The ranks are ranged between 1 and 13 (number of drugs). Rank 1 is the best and rank 13 is the worst.

Subgroup analysis will be performed based on the specified outcomes.<sup>18</sup> Sensitivity analyses will be performed on evidence quality evaluated by the Cochrane Collaboration's risk of bias tool. Consistency analysis will be performed with 'metafor' package<sup>22</sup> and 'combinat' package<sup>23</sup> in R software. Mann-Whitney-Wilcoxon test<sup>24</sup> and Kendall rank correlation<sup>25</sup> will be performed with statistical software R to determine the agreement among the rankings based on different outcome measures.  $p$  Values lower than 0.05 will be considered statistically significant.

**Publication plan** This protocol has been registered (Registration number: CRD42014007113) with the PROSPERO (International Prospective Register of

Systematic Reviews).<sup>26</sup> The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA guideline.<sup>27</sup> Details of this systematic review and network meta-analysis will be submitted to an open access and peer reviewed journal.

**Contributions** SL conceived the study. SL and YJ wrote the protocol and approved the final manuscript.

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**Competing interests** None.

**Provenance and peer review** Not commissioned; external peer review.

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