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Comparative efficacy of statin and antihypertensive agent combinations: a network meta-analysis of randomized controlled trials

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ABSTRACT

Hypertension and dyslipidemia often co-occur, significantly increasing the risk of cardiovascular mordbidity and mortality. Statins and antihypertensive agents are commonly simultaneously administered, although it remains unclear which drug combination provides the optimal balance between safety and efficacy. The present network meta-analysis aims to gather current literature in the field and provide a hiearchy of statin-antihypertensive drug combinations, aiming to identify the most effective one in terms of lipid and blood pressure lowering, without increasing the rates of adverse effects.

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1 Background: Hypertension often occurs concomitantly with dyslipidemia, increasing the risk of adverse cardiovascular outcomes. These two entities both contribute on endothelial dysfunction and insulin resistance and thus can act synergistically in promoting atherosclerotic disease. For this reason, lipid-lowering drugs, especially statins are commonly co-administered with antihypertensives drugs, although the optimal combination providing the highest efficacy and safety remains unclear.

2 Study design: The network meta-analysis will be conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses (PRISMA-NMA) guidelines.

3 Search strategy: Medline, Scopus, CENTRAL, Web of Science and Clinicaltrials.gov will be systematically searched from inception. Google Scholar will be searched to provide grey literature coverage. The full reference list of the retrieved

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studies will also be searched to identify potential additional sources (“snowball” method). Search will be based on Medical Subject Headings (MeSH) terms ("Hydroxymethylglutaryl-CoA Reductase Inhibitors", “Antihypertensive Agents”, “Angiotensin Receptor Antagonists", "Angiotensin-Converting Enzyme Inhibitors", "Calcium Channel Blockers") combined with a list of antihypertensive agents. No date or language restrictions will be applied.

4 Study selection: Population: Adult patients with essential hypertension and dyslipidemia Intervention: Co-administration of a statin and an antihypertensive agent Comparator: Statin or antihypertensive agent monotherapy Outcomes: Systolic blood pressure and serum low-density lipoprotein (LDL) will be the primary outcomes. Serum high-density lipoprotein (HDL) and triglycerides, as well as adverse effects will be evaluated as secondary outcomes. Study type: Randomized controlled trials Exclusion criteria: Observational studies, case series, case-reports, animal studies, review articles, treatment with 3 or more agents concomitantly, pediatric patients, serious medical conditions (e.g. severe heart failure, serious cerebrovascular accident, myocardial infraction, liver failure, end-stage kidney disease).

5 Data extraction Data extraction will be performed independently by two researchers. The following data will be extracted: name of first author, publication date, country, study design, inclusion and exclusion criteria, indication for treatment, type of drug, dosage regimens, patients’ number, gender, age, body mass index, smoking and comorbidities (e.g. diabetes mellitus, coronary artery disease, peripheral artery disease).

6 Quality assessment The quality of the included studies will be evaluated using the Cochrane risk of bias tool for randomized controlled trials, which takes into account the following domains: random sequence generation, blinding, allocation concealment, incomplete outcome and selective reporting. The quality of evidence will be assessed with the Confidence In Network Meta-Analysis (CINeMA) approach, which is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and evaluates the potential presence of within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence.

7 Data analysis The mean change of systolic blood pressure and LDL before and after treatment will be extracted. In case that studies provide adjustment for covariates, the least mean square mean change will be used. A random-effects frequentist network meta-analytic model will be fitted to provide pooled estimates of mean difference. Confidence intervals (CI) will be set at 95%. League tables will be created, depicting the relative effects for all comparisons. Treatments will be ranked according to their P-scores, which ranged from 0 to 1. Heterogeneity will be quantified by calculating the inconsistency index (I2) and between-study variance ($\tau 2$), while its impact on outcomes will be assessed by estimating the 95% prediction intervals (PI). Publication bias will be assessed by examining the possible presence of small-study effects through the visual inspection of comparison-adjusted funnel plots. The plausibility of the transitivity assumption will be tested by comparing the distributions of potential confounders across studies grouped by comparison. The global consistency of network will be statistically assessed with the design-by-treatment interaction test.

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