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INPLASY

Aldosterone-related sodium-retention pathway therapies for resistant hypertension: a network meta-analysis of randomized controlled trials

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670099

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 July 2026 and was last updated on 25 July 2026.

INTRODUCTION

Review question / Objective This review aims to compare the short-term blood pressure-lowering effects of pharmacological treatments that act on the aldosterone-related sodium-retention pathway in adults with resistant hypertension. The review will evaluate mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, and epithelial sodium channel blockade using a drug-level network meta-analysis of randomized controlled trials.

Condition being studied Resistant hypertension is a high-risk hypertension phenotype in which blood pressure remains uncontrolled despite multidrug therapy or requires multiple agents to achieve control. Aldosterone-related sodium retention and volume expansion are considered important contributors to this condition. Several drug classes targeting this pathway are available or under investigation, including mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, and epithelial sodium channel blockers.

METHODS

Search strategy The search strategy will combine terms related to resistant hypertension, randomized trials, and eligible aldosterone-pathway drugs. Search terms will include resistant hypertension, uncontrolled hypertension, refractory hypertension, spironolactone, eplerenone, amiloride, baxdrostat, lorundrostat, osilodrostat, aldosterone synthase inhibitor, CYP11B2 inhibitor, mineralocorticoid receptor antagonist, ENaC blocker, randomized, placebo, and double-blind.

Participant or population Adults with resistant hypertension will be included. Resistant hypertension will be defined as uncontrolled blood pressure despite treatment with at least three antihypertensive agents, including a diuretic. Trials enrolling broader hypertensive populations will be

considered only when resistant hypertension subgroup data are separately extractable.

Intervention Eligible interventions will include pharmacological agents targeting aldosterone-related sodium retention, including spironolactone, eplerenone, amiloride, baxdrostat, lorundrostat, osilodrostat, and other eligible drugs within the same therapeutic pathway if they meet the predefined study criteria.

Comparator Eligible comparators will include placebo or another eligible active drug within the predefined treatment network.

Study designs to be included Randomized controlled trials.

Eligibility criteria Studies will be eligible if they:
1. enrolled adults with resistant hypertension or provided extractable resistant hypertension subgroup data;
2. evaluated at least one eligible aldosterone-pathway pharmacotherapy;
3. used placebo or another eligible active treatment as comparator;
4. reported extractable blood pressure outcome data; and
5. were randomized controlled trials.
Studies will be excluded if they enrolled only selected disease-specific resistant hypertension populations, such as chronic kidney disease, dialysis-dependent kidney failure, obstructive sleep apnea syndrome, heart failure, or other populations in which disease-specific mechanisms or background therapies could substantially modify treatment effects.

Information sources We will search PubMed, Embase, Cochrane CENTRAL, Cochrane Reviews, and ClinicalTrials.gov from database inception to July 20, 2026. Reference lists of included studies and relevant reviews will also be screened for additional eligible trials.

Main outcome(s) The primary outcome will be change in office systolic blood pressure from baseline.

Additional outcome(s) Secondary outcomes will include change in office diastolic blood pressure, 24-hour ambulatory systolic blood pressure, and 24-hour ambulatory diastolic blood pressure.

Data management Two reviewers will independently extract study-level data using a standardized form. Extracted items will include study characteristics, participant characteristics, resistant hypertension definition, background antihypertensive therapy, intervention and comparator details, dose, follow-up duration, blood pressure measurement method, and outcome data. Disagreements will be resolved by discussion or consultation with another reviewer.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers using the Cochrane Risk of Bias 2 tool for randomized trials. The assessed domains will include the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result.

Strategy of data synthesis A frequentist network meta-analysis will be conducted when the evidence network is connected and outcome data are sufficient. Treatment effects for continuous blood pressure outcomes will be expressed as mean differences with 95% confidence intervals. Drug-level nodes will be used as the primary framework. When multiple doses of the same drug are reported within a study, dose arms may be combined into a single drug-level node to avoid double-counting shared comparators. Office and ambulatory blood pressure outcomes will be analyzed separately.

Subgroup analysis A mechanism-based class-level analysis may be performed for the primary outcome by grouping mineralocorticoid receptor antagonists and aldosterone synthase inhibitors.

Sensitivity analysis Sensitivity analyses will be conducted to assess the robustness of the primary findings, including alternative model assumptions, alternative assumptions for imputed change-score standard deviations, and study design-related analyses when applicable.

Language restriction No language restrictions will be applied during the literature search.

Country(ies) involved Taiwan.

Other relevant information No.

Keywords resistant hypertension; aldosterone synthase inhibitor; mineralocorticoid receptor antagonist; Epithelial sodium channel blocker; network meta-analysis; blood pressure.

Dissemination plans The findings will be submitted for publication in a peer-reviewed journal and may be presented at scientific meetings.

Contributions of each author

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