The Comparative Effectiveness Of Mineralocorticoid Receptor Antagonists And Aldosterone Synthase Inhibitors In The Treatment Of Essential Hypertension: A Systematic Review & Network Meta-analysis

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Background

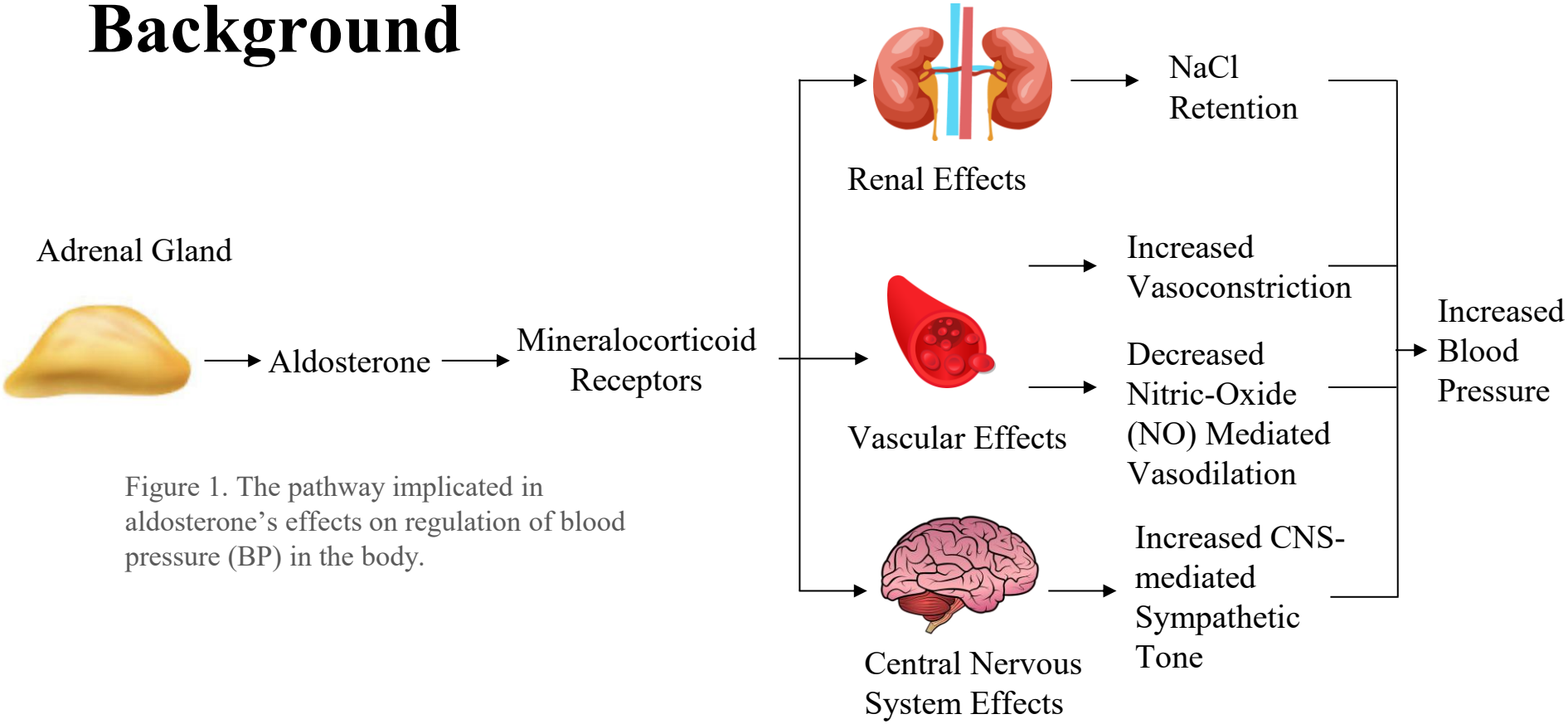
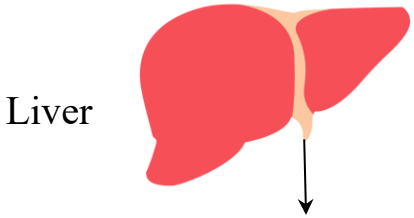
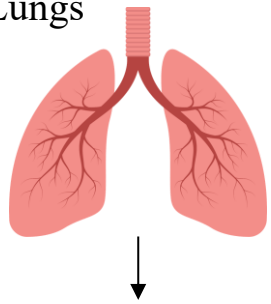


Figure 1. The pathway implicated in aldosterone's effects on regulation of blood pressure (BP) in the body.

Background





Cholesterol

Multiple Steps of Aldosterone Synthesis

11B-Hydroxylase (CYP11B1)

Renin

Angiotensin I

Angiotensin II

Corticosterone

Cortisol

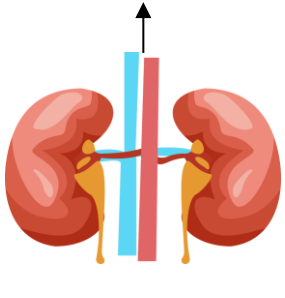


Figure 2. The biochemical pathways implicated in the actions of mineralocorticoid receptor antagonists (MRA) and Aldosterone-Synthase Inhibitors (ASI)

Second Generation Aldosterone Synthase Inhibitors (ASIs)

Aldosterone Synthase (CYP11B2)

Aldosterone

Mineralocorticoid Receptor Antagonist (MRA)

Mineralocorticoid Receptors

Objectives

- As there are currently few to no head-to-head trials that have compared MRAs and ASIs, the relative efficacy of each is unknown. We have performed, through a combination of direct and indirect comparisons, a systematic review and network meta-analysis to establish in adults with primary (non-secondary) hypertension (HTN) any differences in the following primary outcomes:
  - Changes in systolic blood pressure (sBP)
  - Changes in diastolic (dBP) blood pressure
  - Incidence of hyperkalemia

Methods

Search

Databases: MEDLINE, Embase, Cochrane CENTRAL, MEDLINE-In-Process, Scopus and Web of Science

Date Range: Inception - May 2025

Screening: With Covidence™, abstracts-titles were screened in duplicate as follows:

Inclusion Criteria	Exclusion Criteria
• Adult patients with HTN • ASI/ MRA • Randomized trial • Comparator • Reduction in SBP/DBP	• Pediatric patients • Known secondary HTN • Non-randomized trials • No comparator

Methods

Data Extraction: Data was extracted in duplicate as follows:

Demographic Data

- Publication year, Country
- Sample size
- Male (%), Age
- Taking 3+ antihypertensives (%)
- Baseline eGFR
- Baseline serum sodium, potassium

Primary Outcomes

- Change in SBP*
- Change in DBP*
- Incidence of Hyperkalemia

*sBP and dBP were preferentially analysed with ambulatory BP monitoring (ABPM) data, followed by home BP (HBPM), automated office BP (AOBP), and manual office BP (OBPM).

Methods

Risk of Bias

Reviewers worked independently and in duplicate to assess risk of bias using the Cochrane RoB 2.0 tool. The certainty of evidence was then evaluated using the Cochrane GRADE approach for network meta-analysis. The certainty of each comparison was then rated on the following scale.

Certainty in Evidence
High ++++
Moderate +++
Low ++
Very Low +

Based on →

(1) Risk of Bias
(2) Inconsistency
(3) Indirectness
(4) Publication Bias
(5) Intransitivity
(6) Incoherence (Difference between direct and indirect effects)
(7) Imprecision

Results: PRISMA[1-39]

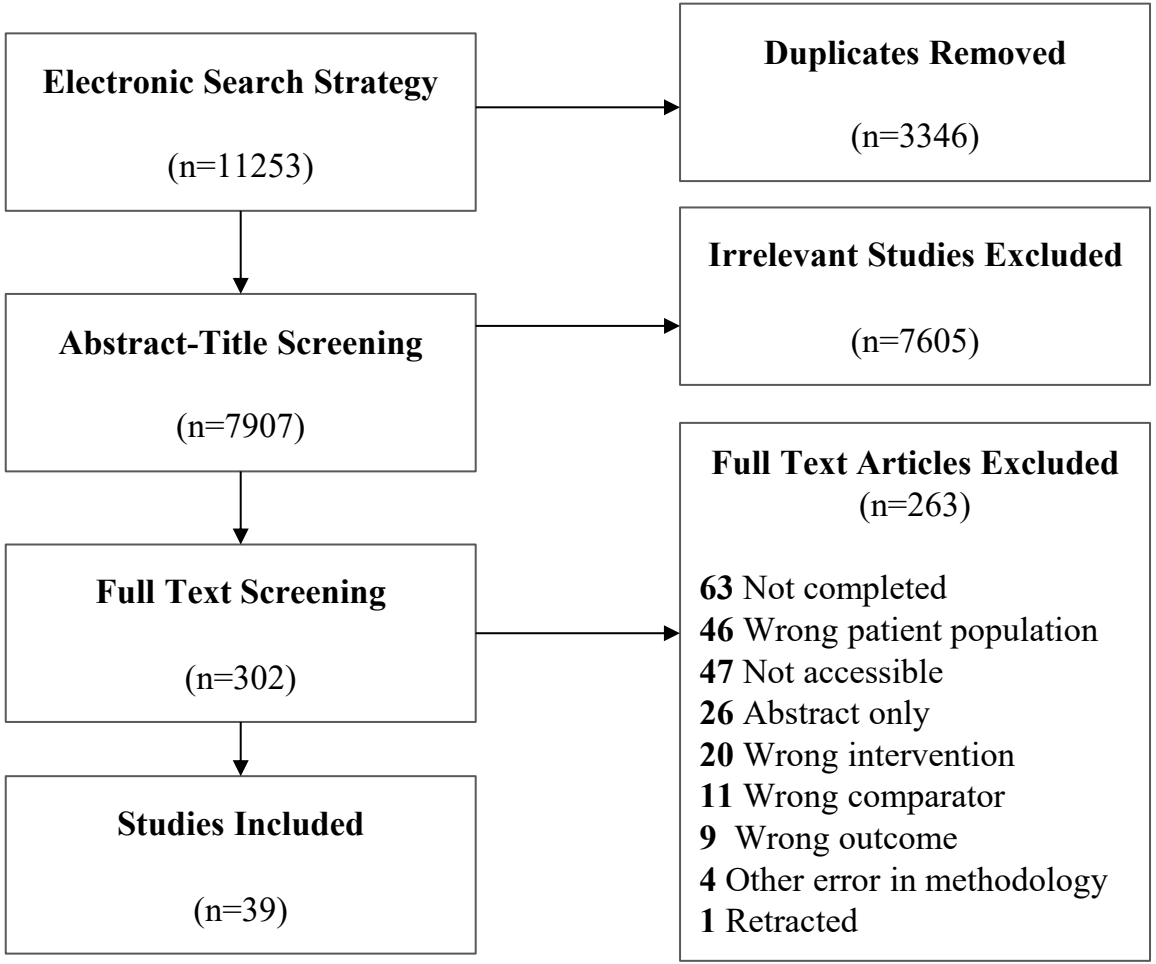


Figure 3: PRISMA flow diagram of screened, included or excluded studies

Results: [1-39]

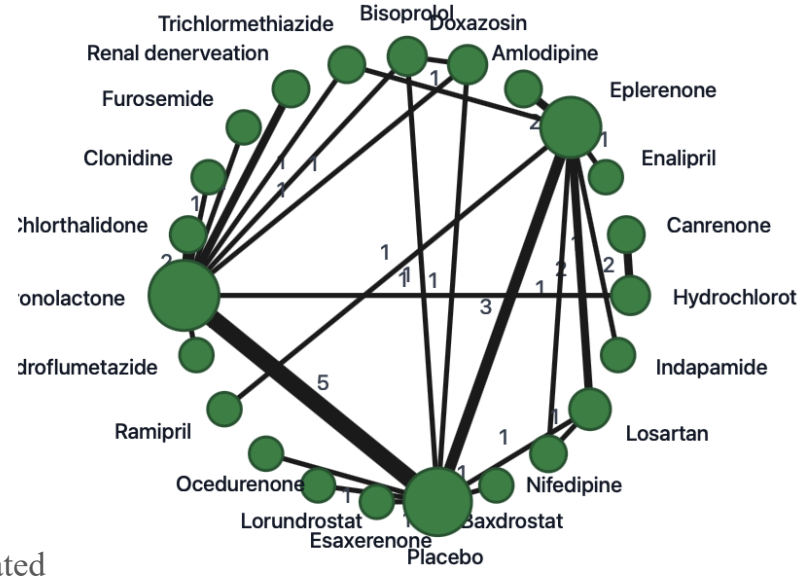


Figure 4: Example of a generated network diagram

Results: [1-39]

Comparison	Mean Difference Combined ΔSBP (95% CI)	Mean Difference Combined ΔDBP (95% CI)	Certainty
Spironolactone	-11.13 (-14.09 to -8.16)	-4.32 (-5.42 to -3.22)	Low
Eplerenone	-9.39 (-10.09 to -8.56)	-5.08 (-5.47 to -4.69)	Low
Esaxerenone	-9.48 (-11.60 to -7.35)	-4.89 (-6.56 to -3.22)	Low
Ocedurenone	-8.47 (-14.76 to -2.18)	-4.85 (-8.89 to -0.81)	Low
Lorundrostat	-7.23 (-9.67 to -4.79)	-3.50 (-13.39 to 6.39)	Low
Baxdrostat	-7.19 (-14.79 to 0.41)	-2.32 (-7.60 to 2.96)	Low

Table 1: The mean difference in combined ΔSBP/DBP in comparison to placebo

Results: [1-39]

Comparison	Relative Risk (95% CI)	Certainty
Spironolactone	3.26 (2.01 to 5.28)	Low
Eplerenone	0.62 (0.16 to 2.43)	Low
Esaxerenone	2.68 (0.93 to 7.68)	Low
Ocedurenone	2.99 (0.69 to 13.01)	Low
Lorundrostat	4.88 (0.52 to 46.10)	Low
Baxdrostat	5.10 (0.29 to 88.10)	Low

Table 2: The relative risk of incidence of hyperkalemia in comparison to placebo

Discussion

- Thus, current evidence suggests equivalent BP-lowering effectiveness among MRAs and second-generation ASIs in primary hypertension, making the MRAs and ASIs evaluated reasonable options for managing HTN. This conclusion is important for physicians as:
    - ASIs do not exert any non-aldosterone-mediated activation of the MR particularly the myocardium.
    - ASIs should exert protection against non-genomic aldosterone-mediated deleterious effects

Discussion

- In terms of the incidence of hyperkalemia, **Eplerenone** may confer a lower—though imprecisely estimated— risk of hyperkalemia compared with other agents and could be preferred in patients at heightened risk.

Thank you! Questions?

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