Eplerenone for Hypertension
A Cochrane Systematic Review and Meta-Analysis

Tina Tam, B.Sc.(Pharm); Aaron M Tejani, B.Sc.(Pharm), PharmD; Angus Kinkade, PharmD, MSc, ACPR; Anthony Tung, B.Sc.(Pharm), ACPR, BCPS, MBA; Sarah Masson, B.Sc.(Pharm), ACPR; May Wu, B.Sc.(Pharm); Sarah Stabler, B.Sc.(Pharm), ACPR, PharmD; Matthew Tsang, B.Sc.(Pharm), ACPR

Background

- Hypertension is defined in most guidelines as having a systolic blood pressure (SBP) ≥140 mm Hg and/or a diastolic blood pressure (DBP) ≥ 90 mm Hg
- Epidemiologic studies have shown increased blood pressure to be associated with increased incidences of stroke, ischemic heart disease, and vascular mortality
- Blood pressure is a surrogate goal of therapy for the prevention of hypertension-associated target-organ damage
- Lowering blood pressure below the target value of 140/90 mm Hg has not convincingly shown to reduce cardiovascular morbidity and mortality
- Eplerenone is an aldosterone receptor blocker
  - Eplerenone is indicated for the treatment of mild and moderate essential hypertension for patients who cannot be treated adequately with other agents

Objective

- To determine if eplerenone monotherapy provides a therapeutic advantage versus placebo for patients with essential hypertension

Methods

- Inclusion Criteria:
  - Studies: randomized controlled trials
  - Participants: adults (18 years and older) with essential hypertension
  - Intervention: oral eplerenone monotherapy
  - Comparator: placebo
- Primary outcomes:
  - All cause mortality
  - Number of patients experiencing at least one serious adverse event
  - Cardiovascular morbidity
- Secondary outcomes:
  - Number of patients who withdrew due to adverse events
  - Number of patients with at least one adverse event
  - Change in systolic blood pressure
  - Change in diastolic blood pressure
- Electronic databases:
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - MEDLINE, EMBASE, CINAHL, and the Hypertension Group specialized register
- Selection of studies
  - Results were screened based on title, abstracts, and/or full text by 2 independent reviewers
- Data extraction
  - Web-based systematic review program, Covidence, was used by 2 original independent reviewers on a standardized data extraction form
- Assessment of risk of bias
  - Parameters assessed by 2 independent reviewers using Covidence

Study ID	Outcomes of Interest					Protocol	Study Author Contact	Contact Record
	Primary Outcome	SBP	DBP	Any AE	Withdrawal due to AE			
Calhoun 2011	X	√	√	O	O	☐ Retrieved √ Information from trials registry ☐ Not retrieved	☐ Additional outcome data √ No additional data √ No response ☐ N/A	Email Jan 1, 2016
Flack 2003	X	√	√	√	√	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data ☐ No additional data √ No response ☐ N/A	Email Jan 3, 2016
Saruta 2004	X	√	√	O	O	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data ☐ No additional data √ No response ☐ N/A	Email Nov 14, 2015
Weinberger 2002	X	√	√	√	√	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data ☐ No additional data √ No response ☐ N/A	Email Jan 3, 2016
White 2003	X	√	√	√	√	☐ Retrieved ☐ Information from trials registry √ Not retrieved	☐ Additional outcome data √ No additional data ☐ No response ☐ N/A	Email Jan 3, 2016 (wwhite@uchc.edu) - clarification re: trial methods

√ Full reporting of results for treatment comparison of interest
X No reporting
O Partial reporting of results (i.e., only p-value, "non-significant")

Table 1: Summary of Data Extraction and Contact with Corresponding Authors

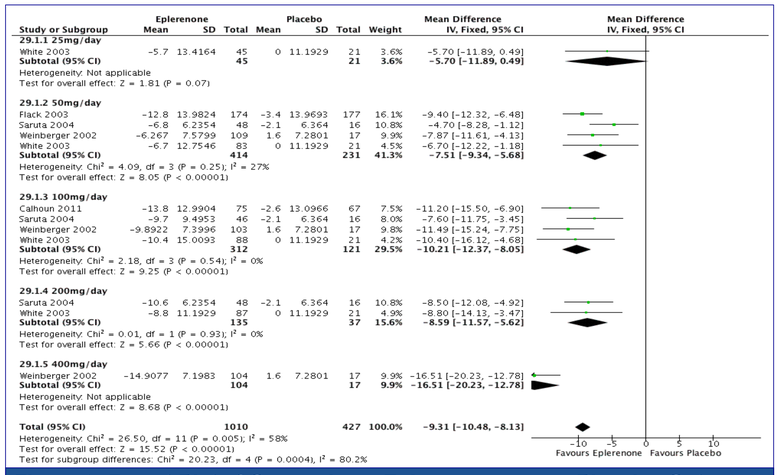

Figure 1: Forest Plot of Comparison: Eplerenone versus Placebo, Outcome: Systolic Dose Response

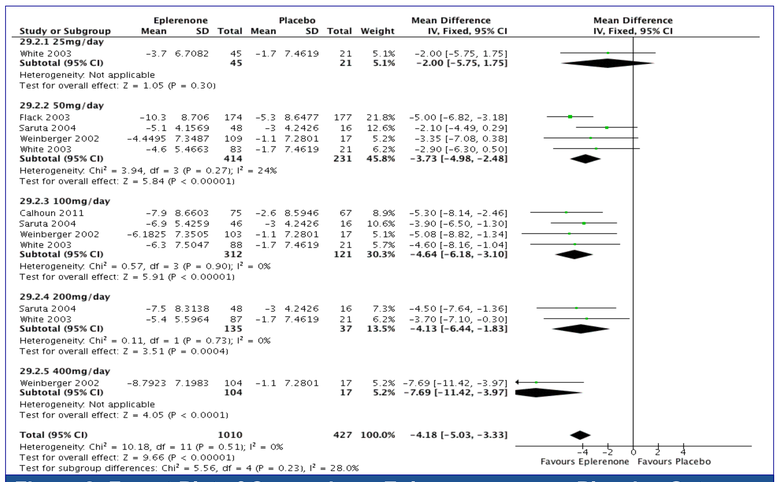

Figure 2: Forest Plot of Comparison: Eplerenone versus Placebo, Outcome: Diastolic Dose Response

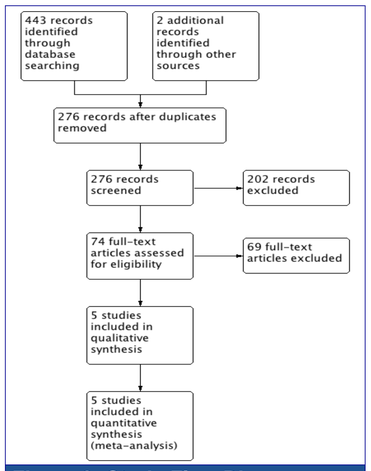

Figure 3: Study Flow Diagram

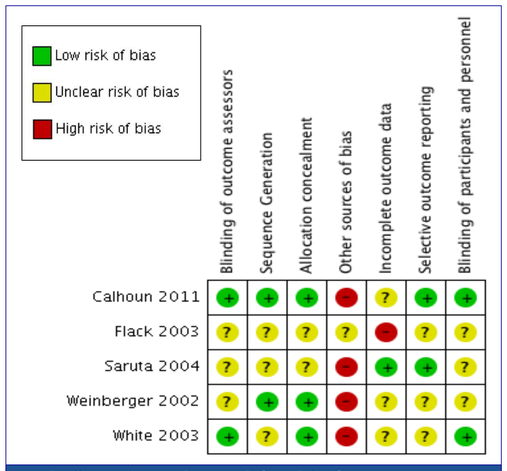

Table 2: Methodological Quality Summary

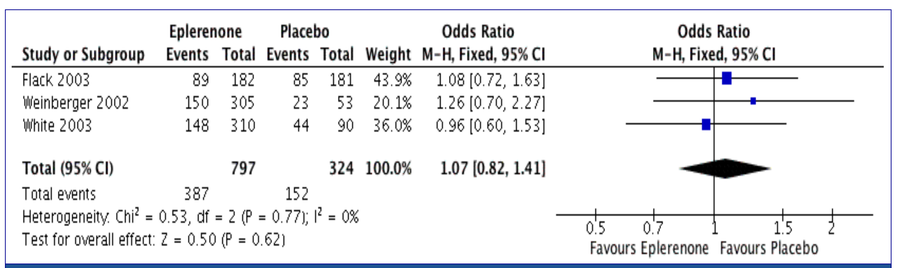

Figure 4: Forest Plot of Comparison: Eplerenone versus Placebo, Outcome: Number of Patients with At Least One Adverse Event

Discussion

- Goal of therapy for hypertension is not to lower blood pressure
  - Blood pressure is a surrogate marker for cardiovascular risk
- Implications of risk of bias
  - Blood pressure lowering effects of eplerenone are likely over estimates due to high/unclear risk of bias in included studies
- Limitations
  - None of the included trials reported any of our clinically meaningful end points as defined in our primary outcomes
  - Extensive efforts to acquire unpublished data from trial investigators, clinical trial registries, and trial sponsors did not yield any usable information

Conclusions

- Insufficient evidence for therapeutic advantage versus placebo
  - Impact of eplerenone on clinical outcomes of cardiovascular mortality and morbidity remains unknown
- High risk of selective outcome reporting in included studies for clinically important outcomes
- No obvious dose response noted for blood pressure lowering effect

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