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Meta-Analysis

Time to Benefit of Surgery vs Targeted Medical Therapy for Patients With Primary Aldosteronism: A Meta-analysis

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Primary aldosteronism (PA) is one of the most common causes of hypertension (1). If left untreated, it increases the risk of cardiovascular, metabolic, and kidney disease, as well as premature mortality compared with other forms of hypertension (2-8). Importantly, highly effective disease-targeted treatments are available (ie, adrenalectomy and mineralocorticoid receptor antagonists), which can mitigate the risk of downstream complications (9-16).

While medical therapy is an option for all patients with PA, a considerable subset can be cured by adrenalectomy (17, 18). However, the decision of whether to proceed with the surgery is complex, dependent not only on unilateral

source of aldosterone excess, but also on patient preferences. As such, contextualizing the relative and absolute benefits of these treatments over time is crucial for informed decision-making.

Addressing this, we conducted a meta-analysis to examine the clinical outcomes of surgery vs medical therapy with respect to mortality, composite major adverse cardiovascular events (MACE, and its individual components), progression to chronic kidney disease, and incident diabetes mellitus. To help inform patients and providers of the expected long-term outcomes, we further meta-analyzed the time to benefit for these treatments.

Study Selection

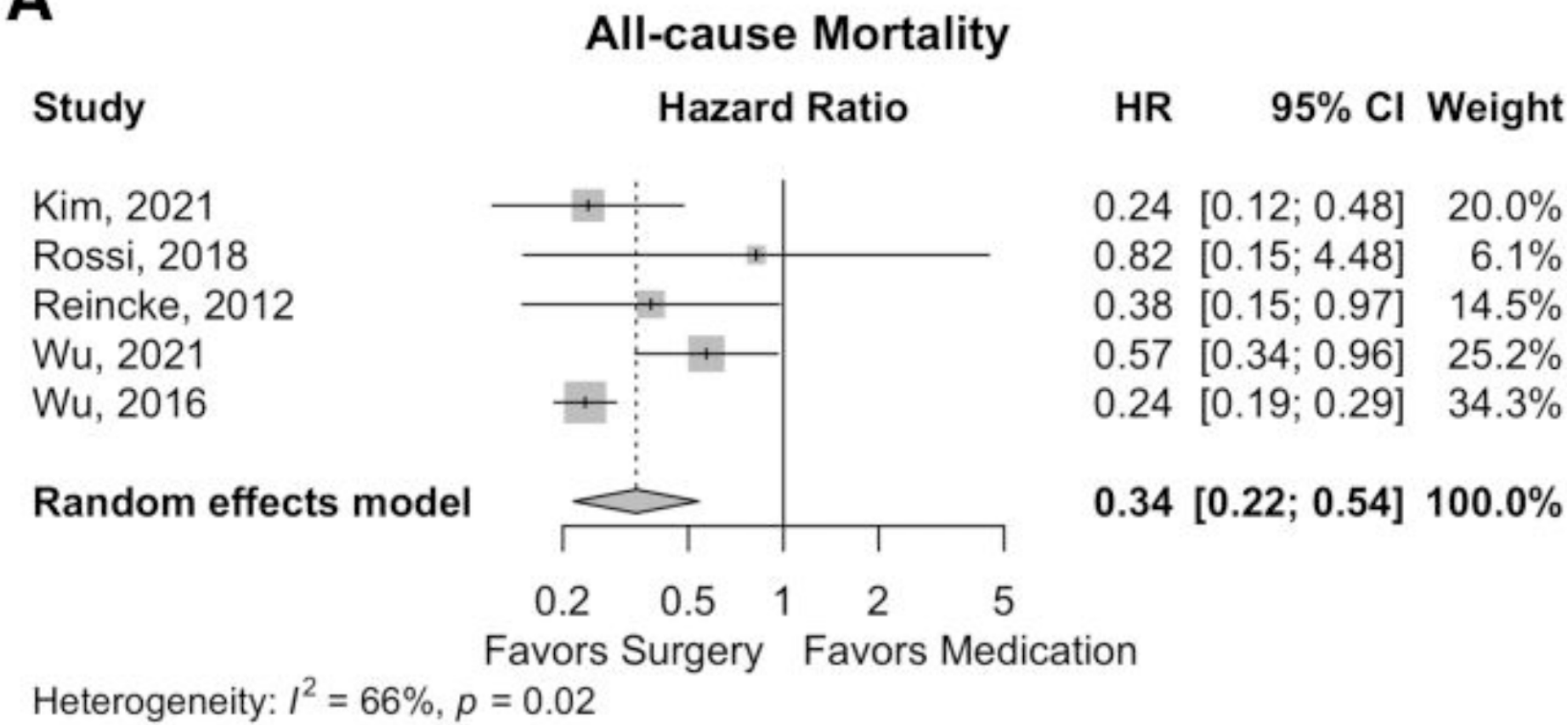
We included original studies identifying patients with PA who received treatment with either adrenalectomy or a mineralocorticoid receptor antagonist with reporting of 1 or more of the outcomes of interest (ie, all-cause mortality, cardiovascular mortality, MACE, myocardial infarction, stroke, atrial fibrillation, hospitalization for congestive heart failure, chronic kidney disease, and/or diabetes mellitus). Eligible study designs included randomized clinical trials, cohort studies, and cross-sectional studies. We excluded studies of nonhuman subjects, and those that did not directly compare surgery with medical therapy in patients with PA. Two reviewers (S.S., A.A.L.) independently screened titles and abstracts for eligibility. The full-text review was performed in duplicate with final inclusion of studies if the relative and/or absolute risk of adverse outcomes were reported (or could be manually calculated). Discrepancies were resolved by consensus.

Results

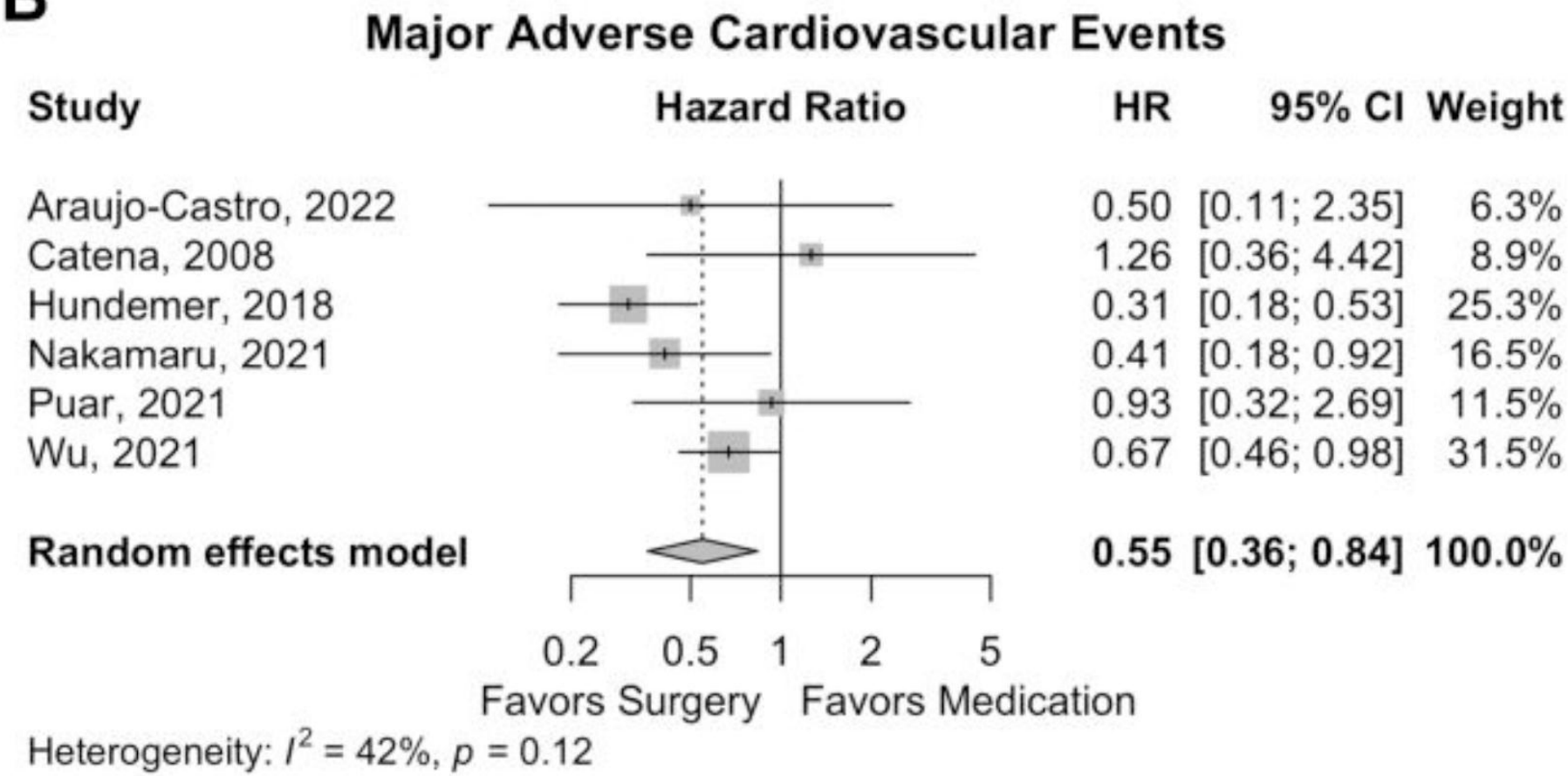
Characteristics of Included Studies

Sixteen studies included in the primary analysis (Table 1; Fig. S1 (20)) (2, 5, 6, 37-49). Of these, 5 studies assessed for all-cause mortality (42, 46-49), 1 for cardiovascular mortality (42), 6 for MACE (2, 5, 37, 43, 45, 48), 2 for myocardial infarction (6, 42), 3 for stroke (6, 38, 42), 4 for atrial fibrillation (40, 42, 47, 48), 3 for hospitalization related to congestive heart failure (6, 42, 48), 4 for progression to chronic kidney disease (37, 39, 41, 44), and 1 for diabetes mellitus (37). All of these were observational, nonrandomized studies. While the majority compared patients with unilateral vs bilateral PA (with the former commonly receiving surgery and the later medical therapy), there were 3 that exclusively enrolled patients with unilateral disease and reported their treatment-specific outcomes (43, 45, 48).

A


All-cause Mortality
Study
Hazard Ratio
HR
95% CI
Weight
Kim, 2021
0.24
[0.12; 0.48]
20.0%
Rossi, 2018
0.82
[0.15; 4.48]
6.1%
Reincke, 2012
0.38
[0.15; 0.97]
14.5%
Wu, 2021
0.57
[0.34; 0.96]
25.2%
Wu, 2016
0.24
[0.19; 0.29]
34.3%
Random effects model
0.34
[0.22; 0.54]
100.0%
0.2
0.5
1
2
5
Favors Surgery
Favors Medication
Heterogeneity: I^2 = 66%, p = 0.02

B


Major Adverse Cardiovascular Events
Study
Hazard Ratio
HR
95% CI
Weight
Araujo-Castro, 2022
0.50 [0.11; 2.35] 6.3%
Catena, 2008
1.26 [0.36; 4.42] 8.9%
Hundemer, 2018
0.31 [0.18; 0.53] 25.3%
Nakamaru, 2021
0.41 [0.18; 0.92] 16.5%
Puar, 2021
0.93 [0.32; 2.69] 11.5%
Wu, 2021
0.67 [0.46; 0.98] 31.5%
Random effects model
0.55 [0.36; 0.84] 100.0%
0.2
0.5
1
2
5
Favors Surgery
Favors Medication
Heterogeneity: I^2 = 42%, p = 0.12

Other Cardiovascular and Kidney Outcomes

There were only 2 studies that reported on the risk of myocardial infarction, and these broadly included nonfatal events and coronary revascularization (6, 42). Compared with medical therapy, patients who received surgery had a lower risk of adverse outcomes (HR, 0.63, 95% CI 0.34-1.19) with homogeneous results between studies ($P = .98$; $I^2 = 0\%$; Fig. S3A (20)).

Fig. S3A (20)).

In the 3 studies that assessed for the risk of stroke (6, 38, 42), there was a nonsignificant difference between treatments overall, but with a pooled point estimate favoring surgery (HR 0.59, 95% CI 0.21-1.65; Fig. S3B (20)). In the 2 studies that reported a lower risk of stroke with surgery

Three studies assessed for the risk of hospitalization associated with congestive heart failure (6, 42, 48), collectively favoring surgery over medical therapy (HR 0.48, 95% CI 0.34-0.70) with no significant heterogeneity ($P = .44$; $I^2 = 0\%$; Fig. S3C (20)). Atrial fibrillation was reported as an outcome in 4 studies with no statistically significant difference between patients who received surgery vs those who were medically managed (HR 0.46, 95% CI 0.17-1.27; Fig. S3D (20)) (5, 40, 47, 48). Finally, 4 studies assessed for the

progression or development of chronic kidney disease (37, 39, 41, 44), and these showed a lower incidence among patients who received surgery (HR 0.62, 95% CI 0.39-0.98; Fig. S3E (20)). The observed statistical heterogeneity in the outcomes of atrial fibrillation and chronic kidney disease could not be explained by any of the key clinical characteristics or components of study quality.

Time to Benefit Analysis

Survival meta-analysis indicated that the benefit of surgery over medical therapy climbed steadily over time with a corresponding reduction in all-cause mortality (Fig. 2). In terms of time to benefit, after a median of 12.3 (95% CI 3.1-48.7) months following initial treatment, 1 death would be potentially prevented for every 200 patients treated with surgery instead of medical therapy (ARR = 0.005), or alternatively a median of 21.9 (95% CI 6.1-78.4) months would be needed to prevent 1 death for every 100 patients undergoing surgery compared to targeted medical therapy with aldosterone antagonists (ARR = 0.01) (Table S3 (20)).

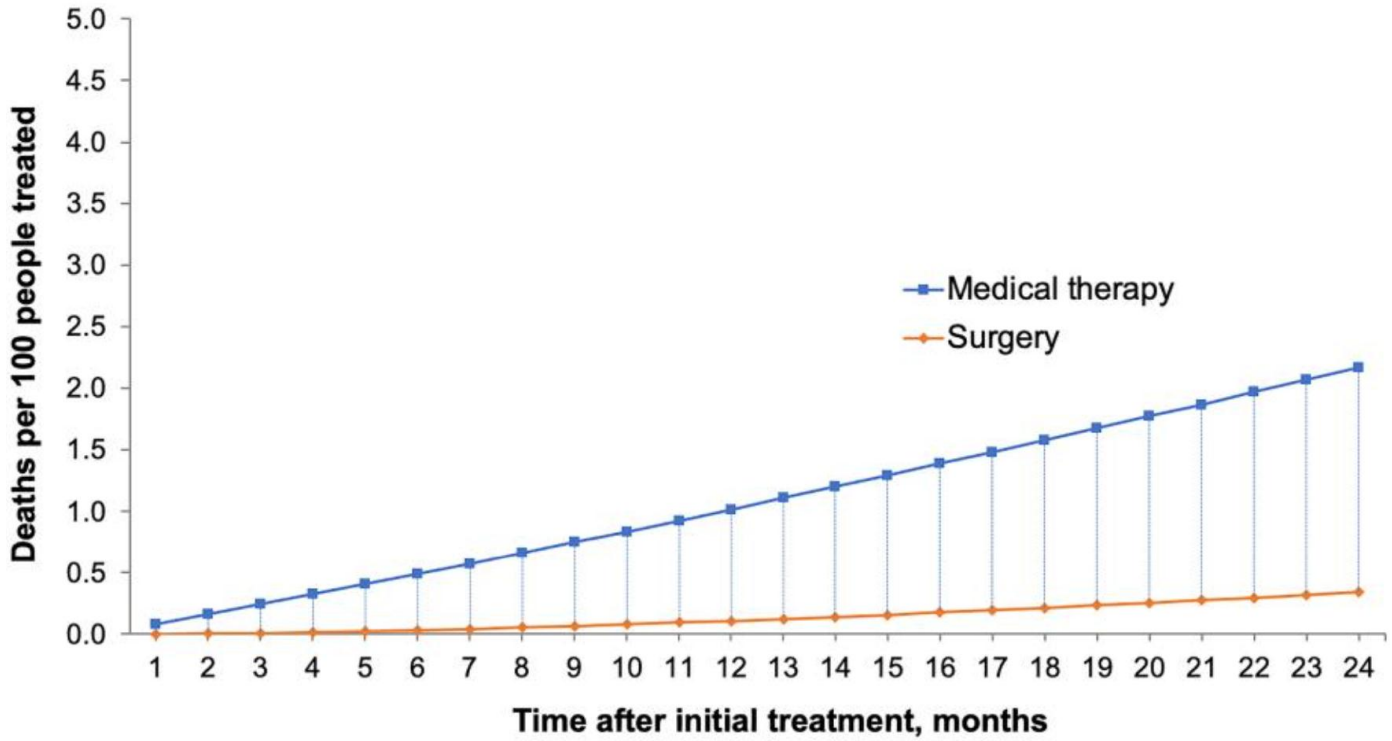


Figure 2. Pooled survival curves from studies examining the association between treatment type and all-cause mortality. The difference between curves is equal to the number of deaths prevented per 100 people treated with surgery compared with medical therapy.

Discussion

In this study, we found that surgery was consistently better than medical therapy for patients with PA across a variety of important clinical outcomes. Surgery was associated with an overall 66% relative reduction in the risk of death and 45% in the risk of MACE compared to medical therapy. These findings remained robust, even after accounting for the impact of potential residual confounding. When contextualized in absolute terms, the number needed to treat (with surgery vs medical therapy) was 200 patients over 12 months to prevent 1 death. As presented, these absolute risk reductions correspond to large treatment effects with clinically important benefits realized soon after surgery.

The excess risks of cardiovascular, kidney, and metabolic disease in patients with PA are, at least in part, independent of blood pressure control (4, 8, 54), owing to the increased

endothelial dysfunction, inflammation, and fibrosis that occur with supraphysiologic aldosterone activity (55, 56). Therefore, it should not be inherently surprising that surgery is associated with an overall better prognosis than medical therapy. The former can permanently reverse the underlying abnormality by definitively removing the source of aldosterone excess, whereas effectiveness of the latter is subject to ongoing drug adherence and adequate dosing long-term to ensure relatively complete blockade of excess aldosterone (5, 40).

Moreover, long-term medical therapy carries certain risks that may limit treatment adherence and tolerability for certain patients. For instance, treatment with spironolactone may lead to antiandrogenic side-effects in men (eg, gynecomastia) or progestin-like side-effects in women (eg, menstrual irregularities) (57). While newer agents (eg, eplerenone) may have a more favorable side-effect profile, they are also considerably more costly (58). Common to all mineralocorticoid receptor antagonists, there is a risk of hyperkalemia, particularly in patients with chronic kidney disease, though the absolute risks are likely small in patients with PA (59). Side-effects notwith-

standing, even under ideal circumstances, treatment with mineralocorticoid receptor antagonists cannot completely mitigate against the deleterious effects of aldosterone that are independent of the mineralocorticoid receptor. However, medical therapy with emerging selective aldosterone synthase inhibitors (60), which inhibit aldosterone production, may be a promising alternative to surgery that would be theoretically as effective and potentially available in the near future.

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Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

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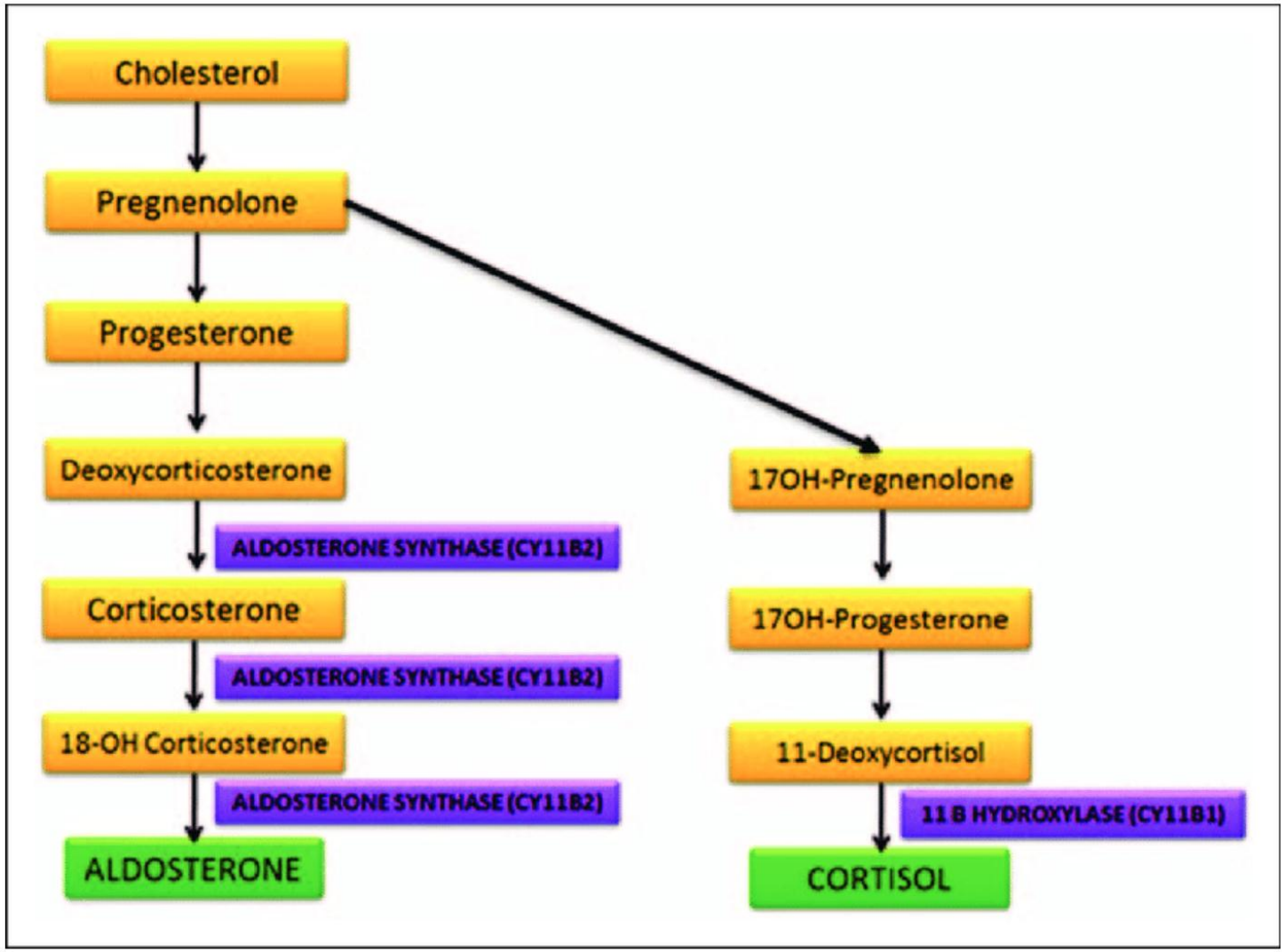
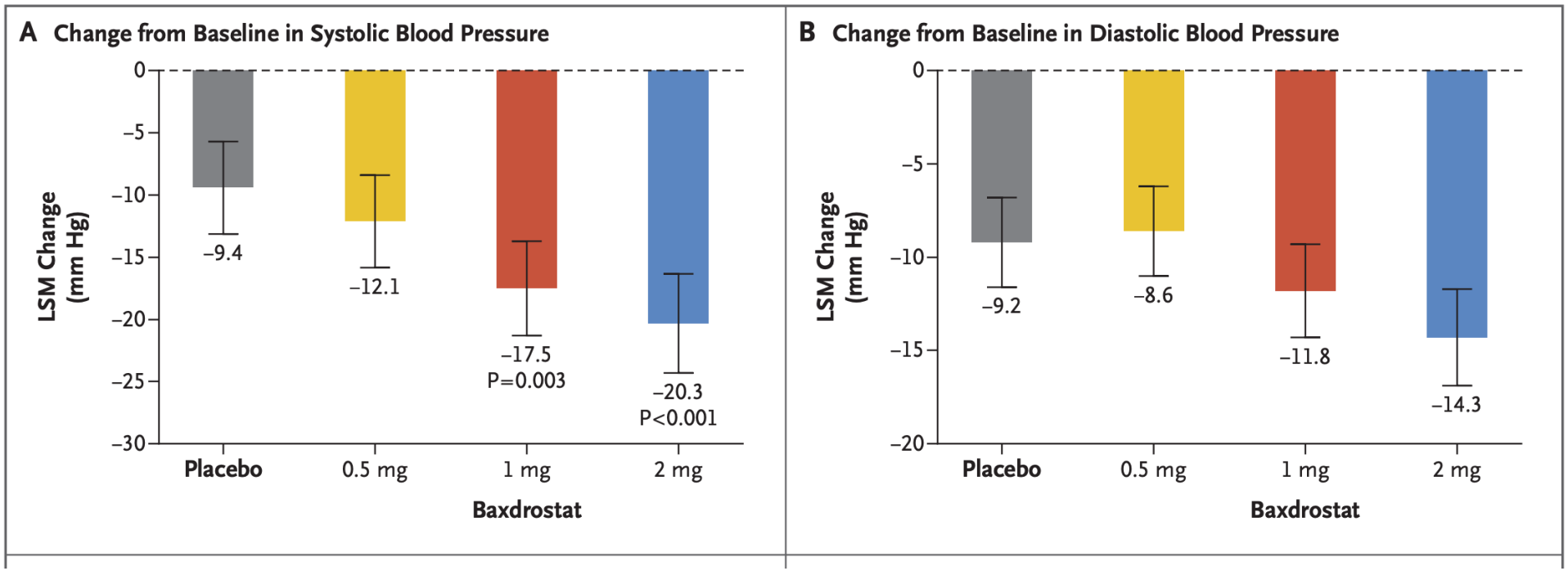
BACKGROUND

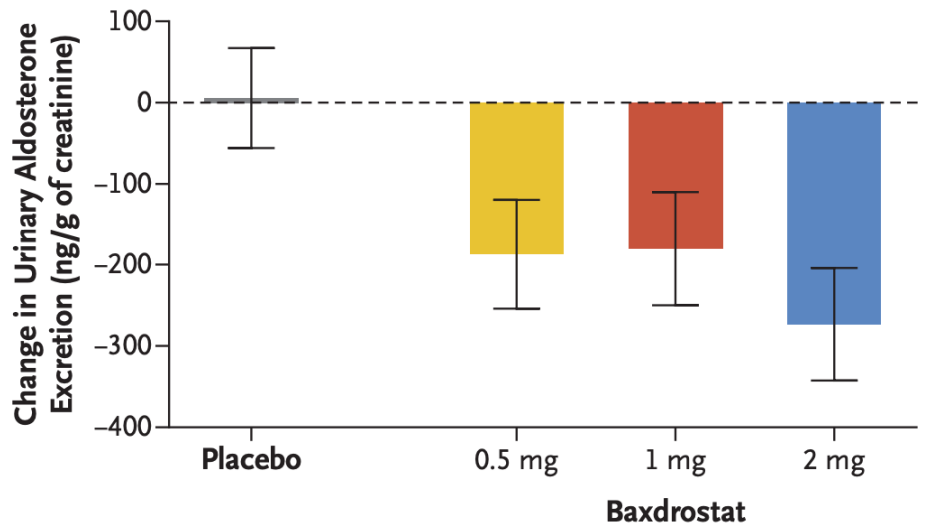
Aldosterone synthase controls the synthesis of aldosterone and has been a pharmacologic target for the treatment of hypertension for several decades. Selective inhibition of aldosterone synthase is essential but difficult to achieve because cortisol synthesis is catalyzed by another enzyme that shares 93% sequence similarity with aldosterone synthase. In preclinical and phase 1 studies, baxdrostat had 100:1 selectivity for enzyme inhibition, and baxdrostat at several dose levels reduced plasma aldosterone levels but not cortisol levels.



Schematic of adrenal steroid biosynthesis.

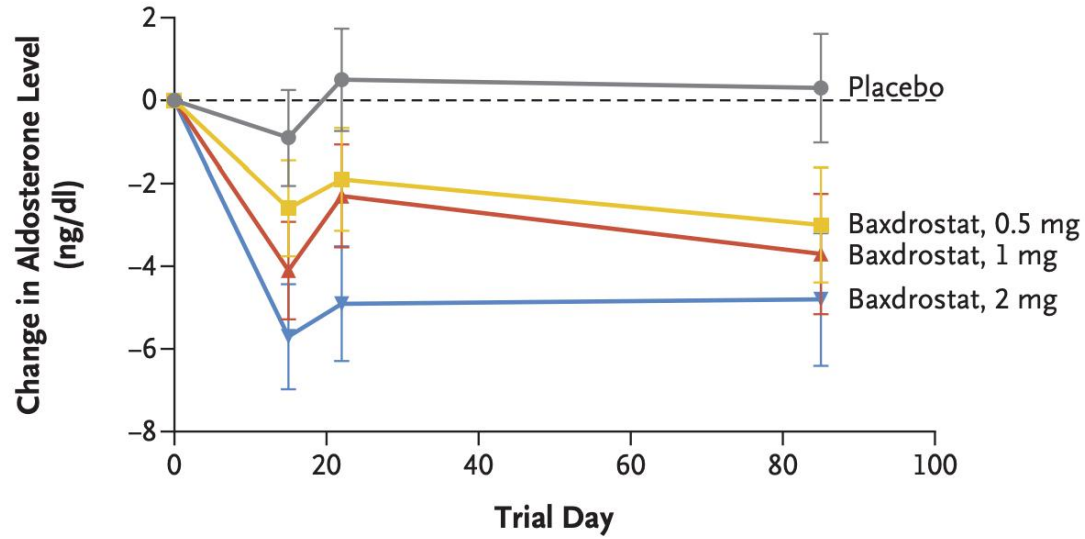

A Change from Baseline in Systolic Blood Pressure
LSM Change (mm Hg)
0
−5
−10
−15
−20
−25
−30
−9.4
−12.1
−17.5
P=0.003
−20.3
P<0.001
Placebo
0.5 mg
1 mg
2 mg
Baxdrostat
B Change from Baseline in Diastolic Blood Pressure
LSM Change (mm Hg)
0
−5
−10
−15
−20
−9.2
−8.6
−11.8
−14.3
Placebo
0.5 mg
1 mg
2 mg
Baxdrostat

A 24-Hr Urinary Aldosterone Normalized for Creatinine



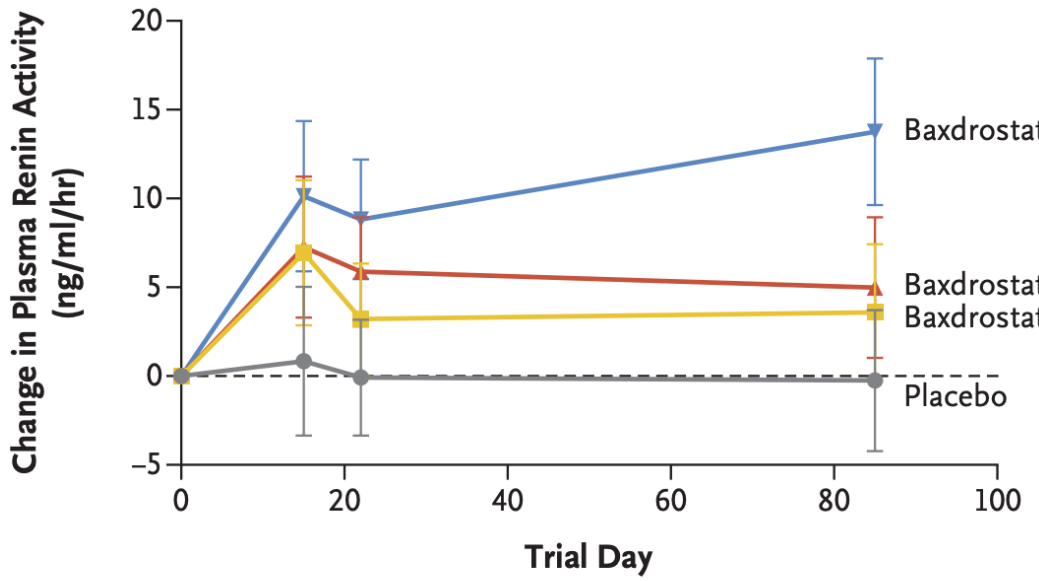
	Mean (±SD) Baseline 24-Hr Urinary Aldosterone Level
	ng/g
Placebo	364±228
Baxdrostat, 0.5 mg	437±264
Baxdrostat, 1 mg	398±233
Baxdrostat, 2 mg	431±399

B **Serum Aldosterone**



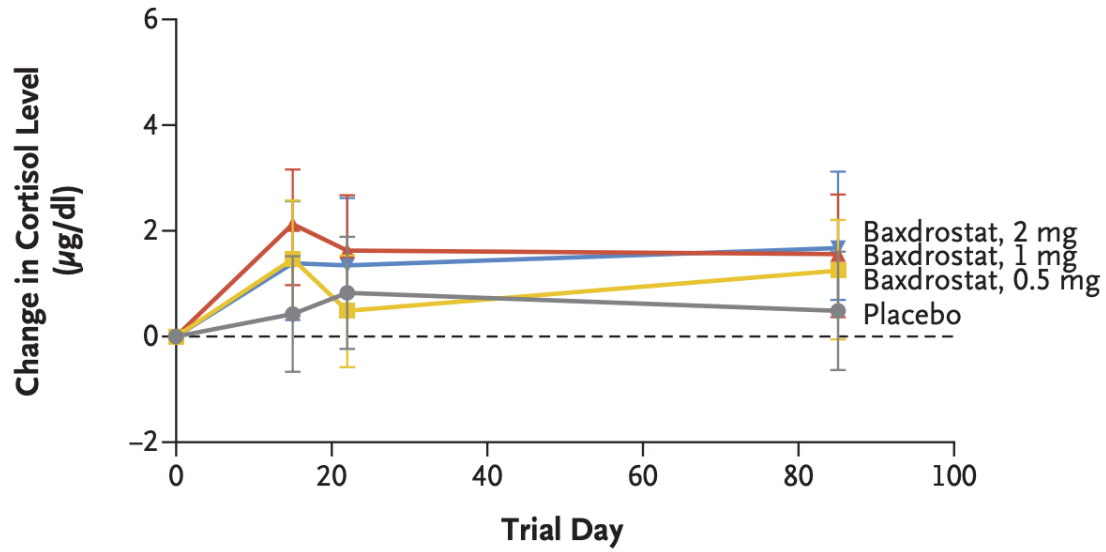
	Mean (±SD) Baseline Serum Aldosterone Level
	ng/dl
Placebo	6.7±4.8
Baxdrostat, 0.5 mg	6.9±4.2
Baxdrostat, 1 mg	7.9±5.8
Baxdrostat, 2 mg	8.4±5.5

C **Plasma Renin Activity**



	Mean (±SD) Baseline Plasma Renin Activity
	ng/ml/hr
Placebo	4.5±6.7
Baxdrostat, 0.5 mg	3.1±5.2
Baxdrostat, 1 mg	5.2±10.8
Baxdrostat, 2 mg	6.7±10.4

D **Serum Total Cortisol**



	Mean (±SD) Baseline Serum Total Cortisol Level
	μg/dl
Placebo	8.9±3.6
Baxdrostat, 0.5 mg	9.6±4.0
Baxdrostat, 1 mg	9.7±4.1
Baxdrostat, 2 mg	10.3±4.0

to enter clinical development, LCI-699 (osilodrostat), was associated with off-target inhibition of cortisol synthesis and was ultimately repurposed to treat excess cortisol states rather than hypertension.[25] The selective action of baxdrostat may

Thank You For Your Attention