European Journal of Internal Medicine 113 (2023) 83–90

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

A systematic review and meta-analysis of all sham and placebo controlled trials for resistant hypertension

Mohammad Ahmed [a], Matthew Nudy [b], Rahul Bussa [a], Edward J. Filippone [c], Andrew J. Foy [b,*]

[a] Penn State Hershey Medical Center, Department of Internal Medicine, United States
[b] Penn State Hershey Medical Center, Heart and Vascular Institute, Division of Cardiology, United States
[c] Thomas Jefferson University Hospitals, Division of Nephrology, United States

ARTICLE INFO

Keywords:
Resistant hypertension
Beta-blocker
Mineral corticoid receptor antagonist
Renal denervation

ABSTRACT

Introduction: There is a lack of consensus regarding the best add on therapy for treatment of resistant hypertension (RH). This is likely secondary to a paucity of data on the comparative effectiveness of proposed therapies for RH.

Methods: Placebo-controlled and sham-controlled randomized clinical trials testing therapies for the treatment of RH were included in this meta-analysis. Therapies with two or more studies were included as subgroups in this meta-analysis. The primary outcomes being tested were 24-hr systolic blood pressure (SBP) and office SBP.

Results: Eight studies were identified that tested mineralocorticoid receptor antagonist (MRA) including 1,414 participants. The raw mean difference (RMD) between MRA and placebo control was statistically significant for 24-hour SBP (-10.56 mmHg; 95% confidence interval (CI) -12.82 to -8.30), 24-hour diastolic (DBP) (-5.48 mmHg; 95% CI -8.48 to -2.58), office SBP (-11.97 mmHg; 95% CI -16.41 to -7.54), and office DBP (-4.14 mmHg; 95% CI -5.62 to -2.65). Six studies were identified that tested renal denervation (RD) including 989 participants. The RMD between RD and sham control was not statistically significant for 24-hour SBP (-1.84 mmHg; 95% CI -3.92 to 0.24), 24-hour DBP (-0.66 mmHg; 95% CI -1.85 to 0.54), office SBP (-1.57 mmHg; 95% CI -6.04 to 2.89), and office DBP (-1.49 mmHg; 95% CI -3.52 to 0.55). Four studies were identified that tested endothelin receptor antagonists (ERA) including 1,193 participants. The raw mean difference (RMD) between ERA and placebo control was statistically significant for 24-hr systolic (SBP) (-7.02 mmHg; 95% CI -9.15 to -4.90, 24-hr diastolic (DBP) (-6.22 mmHg; 95% CI -7.61 to -4.82), office SBP (-5.84 mmHg; 95% CI -10.08 to -1.60), and office DBP (-3.73 mmHg; 95% CI -5.87 to -1.59).

Discussion: MRA lowers BP in patients with RH more than RD, which seems to have little to no effect in RH. ERAs lead to a statistically significant reduction in BP but the confidence in efficacy is limited due to the low number of studies and differences in trial population. Individual factors and their impact on treatment response in RH should be investigated in future research.

Abbreviations

α1	alpha-1
α1	alpha −2
βB	beta-blocker
BP	blood pressure
BRA	baroreflex activation
CI	confidence interval
DBP	diastolic blood pressure
ERA	endothelin receptor antagonist
MRA	mineralocorticoid receptor antagonist
RD	renal denervation
RH	resistant hypertension
SBP	systolic blood pressure

1. Introduction

Patients who have uncontrolled blood pressure (BP) despite being on maximally tolerated doses of 3 antihypertensive medications of different classes (one of which must be a diuretic) or who are controlled on 4 or more antihypertensive medications are defined as having resistant hypertension (RH). [1–3] An estimated 10–14% of hypertensive patients

* Corresponding author at: 500 University Drive, PO Box 850 H047, Hershey, PA 17033-0850.
E-mail address: afoy@pennstatehealth.psu.edu (A.J. Foy).

https://doi.org/10.1016/j.ejim.2023.04.021
Received 3 March 2023; Received in revised form 12 April 2023; Accepted 26 April 2023
Available online 5 May 2023

have treatment-resistant hypertension with the burden of RH being highest for patients with chronic kidney disease (CKD). [4] The most common fourth-line treatment is the addition of a mineralocorticoid receptor antagonist (MRA) to the treatment regimen. [5] In recent years, other pharmacological interventions as well as various device-based strategies have been tested for treatment of RH. The main objective of this study was to assess efficacy of therapies for RH. For the purposes of minimizing bias, we only selected studies with either placebo or sham control.

2. Methods

Electronic databases PubMed and Cochrane Register of Clinical Trials were searched by two independent investigators (M.A. and R.B.) from database inception to March 18th, 2022. Placebo-controlled and sham-controlled randomized clinical trials testing different interventions for RH in adult patients (≥18 years of age) were selected. We used search terms: "resistant hypertension" AND "sham-controlled trial" OR "placebo-controlled trial" AND "randomized-controlled trial (Supplement Table 1). Trials were categorized based on the intervention being tested versus control. Each included study was independently assessed for internal validity using the Cochrane bias assessment. [6] The biases assessed included selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selection reporting), and other bias (industry sponsored trials, handling of control subjects, choice of comparator, etc.).

Two investigators (M.A. and R.B.) independently reviewed all studies meeting the inclusion criteria and performed standardized data extraction. Trials not including a sham-control or placebo-control were not included in this analysis. The prespecified primary efficacy outcomes were the cumulative raw mean differences and 95% confidence interval (CI) in 24-hour ambulatory systolic BP (SBP) and diastolic BP (DBP), and office SBP and DBP. Cumulative raw mean differences and 95% CI for each subgroup were calculated. Results from the intention-to-treat analysis in trials were used to calculate raw mean difference. A sensitivity analysis for outcome effect estimate was performed for each endpoint by systematically excluding each study. We prespecified an I^2 value ≥ 30% as the cutoff for moderate heterogeneity. If heterogeneity

Table 1
Lists all the studies included in this meta-analysis, intervention tested in each study, mean age of trial participants, percent of female participants, and baseline blood pressures for each study.

Study	Blinding	Follow up time (weeks)	Intervention	Dose	Age	Female percent	Baseline 24-hr SBP	Baseline 24-hr DBP	Baseline Office SBP	Baseline Office DBP
Abolghasmi et al. 2011	Double blind	12	Spironolactone	25 mg/day	49.54	19 (46.34%)			170.5	94
Ni et al. 2014	Double blind	12	Spironolactone	25–50 mg/day	55.32	31 (40.78%)	146.25	90.25		
Oxlund et al. 2013	Double blind	16	Spironolactone	50 mg/day	63.39	28 (23.53%)	143.5	78	141.5	77.5
Vaclavik et al. 2014	Double blind	8	Spironolactone	25 mg/day	60.05	42 (37.83%)	143.8	82.15	154.1	92.1
Williams et al. 2015	Double blind	12	Spironolactone	25–50 mg/day	61.4	105 (31.3%)			157	90
Rossignol et al. 2018	Double blind	32	Spironolactone	25 mg/day	72.42	244 (60.55%)			148	88
Karns et al. 2012	Double blind	8	Eplerenone	50 mg BID	58	25 (37.88%)	153.8	89.1	153.4	90.1
Schneider et al. 2017	Double blind	26	Eplerenone	50 mg BID	59.91	10 (19.10%)			162.5	92.5
Azizi et al. (TRIO) 2021	Single blind	8	Renal Denervation		52.55	27 (19.85%)	144.75	89.25	155.3	100.4
Desch et al. 2015	Double blind	24	Renal Denervation		60.9	19 (26.76%)	140.3	79.6		
Bhatt et al. (SIMPLICITY) 2014	Single blind	24	Renal Denervation		57.36	210 (39.25%)	159.3	89.45	179.95	97.7
Mathiassen et al. (RESET) 2016	Double blind	24	Renal Denervation		55.64	51 (73.91%)	152.5	90	163	92.5
Schmieder et al. (WAVE) 2018	Double blind	24	Renal Denervation		61.12	21 (25.93%)	155.6	86.85	182.9	99.85
Kario et al. (REQUIRE) 2021	Single blind	12	Renal Denervation		53.11	35 (35.7%)	161.7	93.8	159	96.5
Black et al. 2007	Double blind	10	Darusentan	300 mg/day	62.34	47 (40.87%)	134	78	149.4	81.5
Bakris et al. 2010	Double blind	14	Darusentan	179 mg/day	62.25	378 (45%)	135	78	152	88
Schailch et al. 2022		4	Aprocintental	25 mg/day	61.7	197 (40.5%)	137.3	82.5	153.3	87.4
Weber et al. 2009	Double blind	14	Darusentan	300 mg/day	62	191 (50%)	134	78	151	86
Bakris et al. 2010	Double blind	14	Guanfacine	1 mg daily	62.25	378 (45%)	135	78	152	88
Ranasinghe et al. 2020	Double blind	13	Propranolol	40–80 mg TID	56.63	24 (72.73%)	150.9	86.2	158.85	89.6
Williams et al. 2015	Double blind	12	Bisoprolol	5–10 mg	61.4	105 (31.3%)			157	90
Williams et al. 2015	Double blind	12	Doxazosin	4–8 mg	61.4	105 (31.3%)			157	90
Bisognano et al. (RHEOS) 2011	Double blind	24	Baroreflex activation		53.29	103 (38.87%)			168.5	100.5

was found, a sensitivity analysis was conducted to assess if exclusion of any one study significantly reduced or eliminated heterogeneity.

A two-sample, two-treatment model was used to perform the meta-analysis. Analysis was performed using Comprehensive Meta-Analysis Version 3, Biostat, Englewood, NJ, 2013. For endpoints with moderate heterogeneity, a random-effects model was used; and for those without heterogeneity, a fixed-effects model was used.

3. Results

Twenty studies were identified that included 4452 participants. [7–26] Thirteen trials compared medications to a placebo, with some testing multiple medications compared to placebo. [7-12,19-24,26] Of these, there were 8 trials testing MRA, 4 testing endothelin receptor antagonists (ERA), 2 testing beta blockers (βB), 1 testing an alpha-1 (α1) antagonist, and 1 testing an alpha-2A (α2A) agonist. Seven trials compared device-based invasive interventions to sham control. [13-18, 25] There were 6 trials testing RD and 1 trial testing baroreflex activation (BRA) (Fig. 1). The mean age (±SD) was 58.89 (±5.05) years. The lowest average age was 49 years, and the highest average age was 74 years at baseline. Forty-five percent of participants were women. The mean follow-up time was 16.14 weeks (Table 1). The two domains most likely to be judged at high risk of bias were selection bias and other bias (Supplement Fig. 2). Explanations for assessment of other bias are provided in detail in the supplement (Supplement Table 2).

3.1. 24-hour ambulatory BP

Fifteen trials reported 24-hour (hr) ambulatory BP, with some testing multiple medications compared to placebo. This included 6 trials for RD, 4 trials for MRA, 4 trials for ERA, and 1 trial each for βB and α2A agonist. [8-10,13-22,24,26] Meta-analyses were conducted for interventions tested in 2 or more trials.

The 4 trials testing MRA had a total of 411 participants with a mean age of 59 years, and 35.0% of the participants were female. Trial participants were on an average of 3.8 medications and had a mean baseline BP of 147/85 mmHg with a mean follow up time of 11.0 weeks (Fig. 2). [8-10,22] Ni et al. and Karns et al. were judged to be at moderate to high risk of bias (Supplement Fig. 2). [8,22] Oxlund et al., and Vaclavik et al. were judged to be at low risk of bias (Supplement Fig. 2). [9,10] Raw mean difference for SBP reduction between the MRA arm and placebo control arm was −10.56 mmHg and was statistically significant (95% CI −12.82 to −8.30). There was no interstudy heterogeneity ($I^2 = 0.00\%$) (Fig. 2). The effect estimate was not sensitive to the exclusion of any trials. Raw mean difference for DBP reduction between the MRA arm and placebo control arm was −5.48 mmHg and was statistically significant (95% CI −8.39 to −2.58). There was a moderate level of interstudy heterogeneity ($I^2 = 59.00\%$) (Fig. 3). The heterogeneity was sensitive to the exclusion of Karns et al. ($I^2 = 0.00\%$). The effect estimate was also sensitive to the exclusion of Karns et al. (−3.90; 95% CI −5.81, −1.99) by reducing the treatment effect by approximately 1.6 mmHg; however, it remained statistically significant.

The 6 trials testing RD had a total of 989 participants with a mean age of 57 years, and 35.2% of the participants were female. Trial participants were on an average of 4.4 medications and had a mean baseline BP of 152/88 mmHg with a mean follow up time of 19.3 weeks (Fig. 2). [13–18] Schmieder et al. was judged to be at moderate risk of bias and all other trials were low risk of bias (Supplement Fig. 2). [17] Raw mean difference for SBP reduction between the RD arm and sham control arm was −1.84 mmHg and was not statistically significant (95% CI −3.92 to 0.24) (Fig. 2). Raw mean difference for DBP reduction between the RD arm and sham control arm was −0.66 mmHg and was not statistically significant (95% CI −1.85 to 0.54) (Fig. 3). There was no interstudy heterogeneity for either SBP or DBP outcomes ($I^2 = 0.00\%$). The effect estimates were not sensitive to the exclusion of any trials.

The 4 trials testing ERA had a total of 1193 participants with a mean age of 62 years, and 44.1% of the participants were female. Trial participants had a mean baseline BP of 135/79 mmHg and a mean follow up time of 10.5 weeks. Total baseline medications were not provided in any of the trials. [19-21,26] Black et al. was judged to be at high risk of bias.

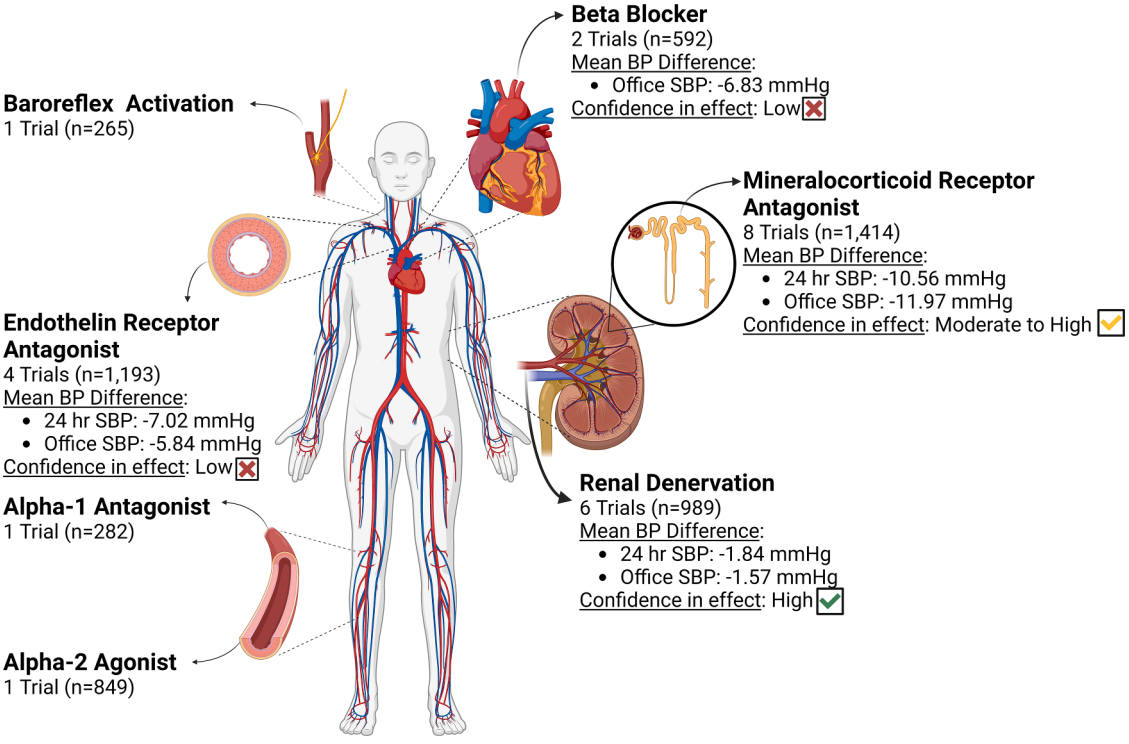

Fig. 1. Illustrated image depicting the site of action in the human body for each intervention tested. The figure provides the number of trials for each intervention, number of participants in each trial, the systolic blood pressure outcomes, and the level of confidence the investigators have in the effect estimate.

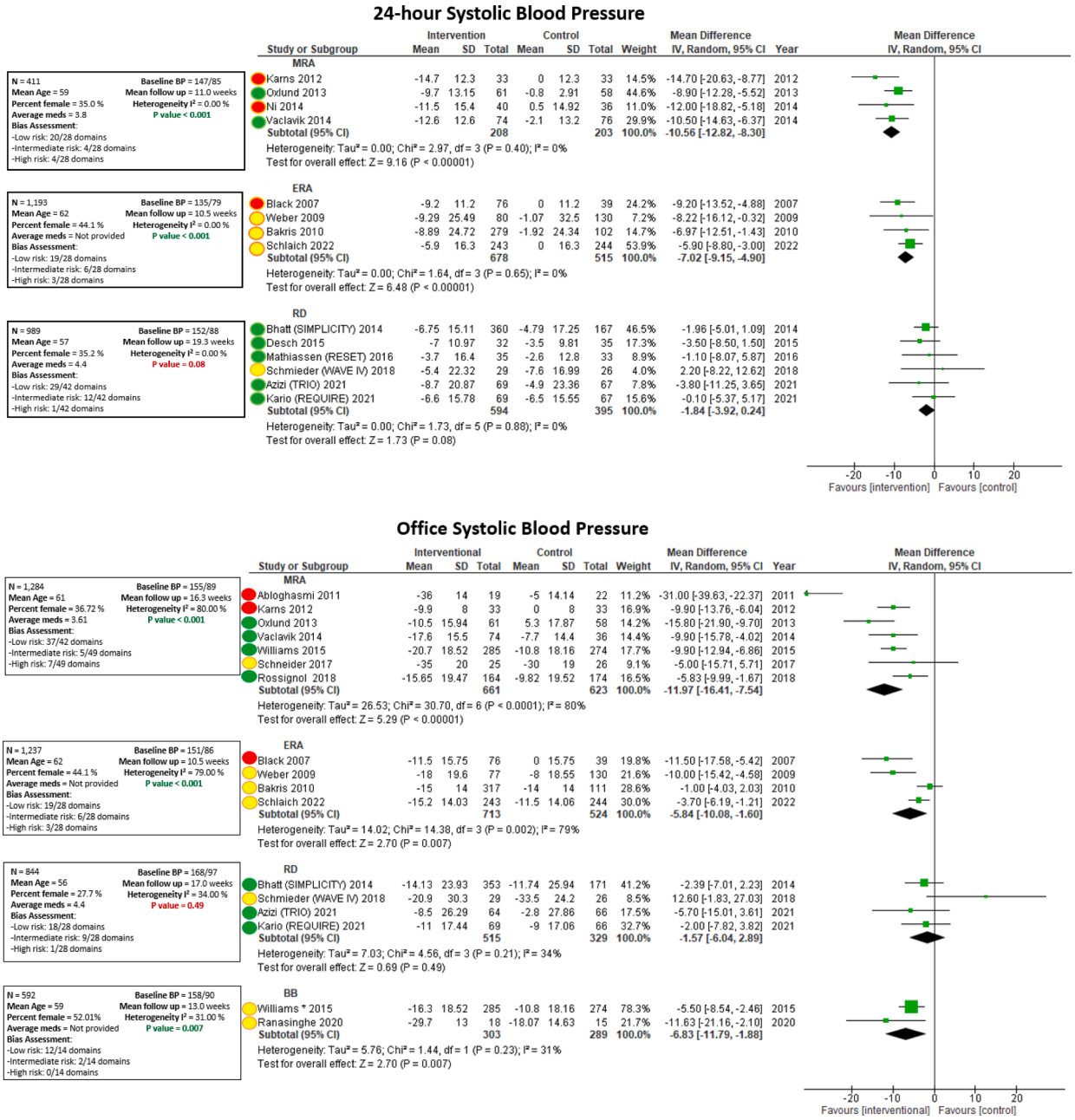

Fig. 2. Individual trial level data showing baseline characteristics and raw mean difference between control arm and intervention arm for systolic blood pressure outcomes for each intervention tested.

[20] All other trials were judged to be at moderate risk of bias (Supplement Fig. 2). [19,21,26] Raw mean difference for SBP reduction between the ERA arm and placebo control arm was −7.02 mmHg and was statistically significant (95% CI −9.15 to −4.90) (Fig. 2). Raw mean difference for DBP reduction between the ERA arm and placebo control arm was −6.22 mmHg and was statistically significant (95% CI −7.61 to −4.82) (Fig. 3). There was no interstudy heterogeneity for either SBP or DBP outcomes ($I^2 = 0.00\%$). The effect estimates for either outcome was not sensitive to the exclusion of any trials.

3.2. Office BP

Seventeen trials reported office BP, with some testing multiple medications compared to placebo. [7,9-13,15,17-26] This included 4 trials for RD, 7 trials for MRA, 3 trials for ERA, 2 trial for BB, and 1 trial each for α2A agonist, α1 antagonist, and baroreflex activation. Meta-analyses were conducted for interventions tested in 2 or more trials.

The 7 trials testing MRA had a total of 1284 participants with a mean age of 61 years, and 36.7% of the participants were female. Trial participants were on an average of 3.6 medications and had a mean baseline BP of 155/89 mmHg with a mean follow up time of 16.3 weeks. [7,9-12, 22,23] Abolghasmi et al., and Karns et al. were judged to be at high risk of bias. [7,22] Schneider et al. was evaluated to be at moderate to high risk of bias (Supplement Fig. 2). [23] The raw mean difference for SBP reduction between the MRA arm and placebo control arm was −11.97 mmHg and was statistically significant (95% CI −16.41 to −7.54) (Fig. 2). There was substantial interstudy heterogeneity ($I^2 = 80.00\%$) and it was sensitive to the exclusion of Abolghasmi et al. ($I^2 = 0.00\%$). The clinical effect declined by approximately 2.4 mmHg but remained statistically significant (−9.56; 95% CI −12.05, −7.08). Raw mean difference for DBP reduction between the MRA arm and placebo control

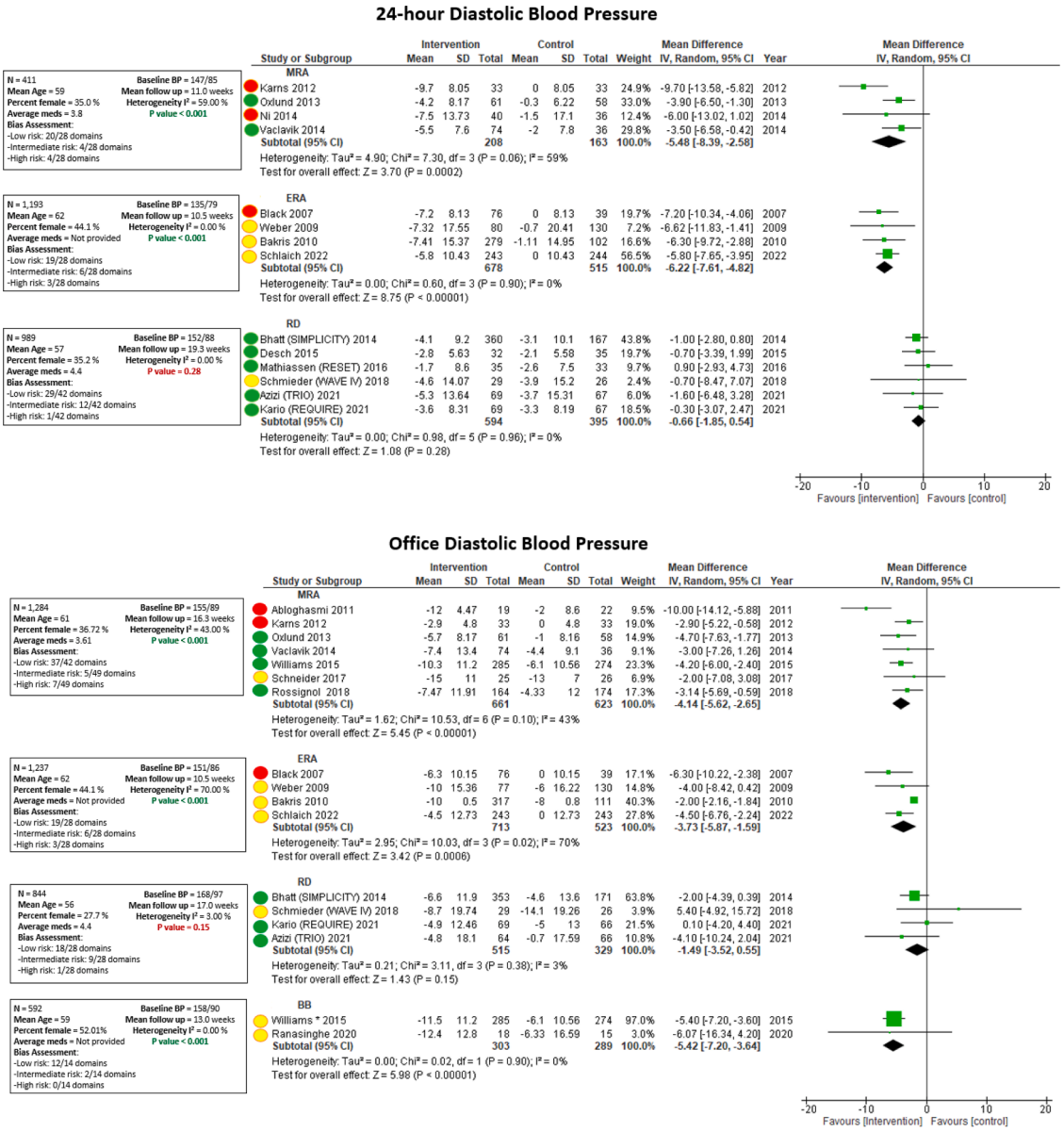

Fig. 3. Individual trial level data showing baseline characteristics and raw mean difference between control arm and intervention arm for diastolic blood pressure outcomes for each intervention tested.
Abbreviations: Mineralocorticoid receptor antagonist (MRA), Endothelin receptor antagonist (ERA), Beta-blocker (βB), Renal Denervation (RD).

arm was −4.14 mmHg and was statistically significant (95% CI −5.62 to −2.65) (Fig. 3). There was a moderate level of interstudy heterogeneity (I^2= 43.00%), which was also sensitive to the exclusion of Abolghasmi et al. (I^2 = 0.00%). The clinical effect declined by about 0.5 mmHg but remained statistically significant (−3.63; 95% CI −4.71, −2.54).

The 4 trials testing RD had a total of 844 participants with a mean age of 56 years, and 27.7% of the participants were female. Trial participants were on an average of 4.4 medications and had a mean baseline BP of 168/97 mmHg with a mean follow up time of 17.0 weeks. [13,15, 17,18] Schmieder et al. was evaluated to be at moderate risk of bias (Supplement Fig. 2). [17] Raw mean difference for SBP reduction between the RD arm and sham control arm was −1.57 mmHg and was not statistically significant (95% CI −6.04 to 2.89). There was a moderate level of interstudy heterogeneity (I^2 = 34.00%) and it was sensitive to the exclusion of Schmieder et al. (I^2 = 0.00%) (Fig. 2). The clinical effect increased by about 1 mmHg with the exclusion of Schmieder et al. but remained not statistically significant (−2.63; 95% CI −6.01, 0.64). Raw mean difference for DBP reduction between the RD arm and sham control arm was −1.49 mmHg and was not statistically significant (95% CI −3.52 to 0.55) (Fig. 3). The effect estimate was not sensitive to the exclusive of any trial. There was no significant interstudy heterogeneity (I^2 = 3.00%).

The 4 trials testing ERA had a total of 1237 participants with a mean age of 62 years, and 44.1% of the participants were female. Trial participants had a mean baseline BP of 151/86 mmHg and a mean follow up time of 10.5 weeks. Total baseline medications were not provided. [19-21,26] Black et al. was evaluated to be at high risk of bias. [20] All other trials were evaluated to be at moderate risk of bias (Supplement Fig. 2). [19,21,26] Raw mean difference for SBP reduction between the ERA arm and placebo control arm was −5.84 mmHg and was statistically significant (95% CI −10.02 to-1.60). There was substantial interstudy heterogeneity (I^2= 79.00%) and this was not sensitive to the exclusion of any individual trials (Fig. 2). The effect estimate was sensitive to the exclusion of Schlaich et al. (−7.15; 95% CI −14.48, 0.17). Raw mean difference for DBP reduction between the ERA arm and placebo control arm was −3.73 mmHg and was statistically significant

(95% CI −5.87 to −1.59) (Fig. 3). There was a substantial level of interstudy heterogeneity (I^2 =70.00%) and it was sensitive to the exclusion of Bakris et al. (I^2 = 0.00%). The clinical effect increased by about 1.0 mmHg with the exclusion of Black et al. and remained statistically significant (−4.79; 95% CI −6.59, −3.00).

The 2 trials testing BB had a total of 592 participants with a mean age of 59 years, and 52.01% of the participants were female. Trial participants had a mean baseline BP of 158/90 mmHg and a mean follow up time of 13 weeks. Total baseline medications were not provided. [11,24] Both studies were evaluated to be at moderate risk of bias (Supplement Fig. 2). Raw mean difference for SBP reduction between the BB arm and placebo control arm was −6.83 mmHg and was statistically significant (95% CI −11.79 to −1.88) The effect estimate was not sensitive to the exclusion of either trial. There was moderate interstudy heterogeneity (I^2 = 32.00%). Since there were only two trials sensitivity analyses for heterogeneity were not performed. Raw mean difference for DBP reduction between the BB arm and placebo control arm was −5.42 mmHg and was statistically significant (95% CI −7.20 to −3.64). The effect estimate was not sensitive to the exclusion of either trial and there was no interstudy heterogeneity (I^2 = 0.00%).

4. Discussion

In this meta-analysis of sham and placebo-controlled trials for resistant hypertension MRAs were found to have a statistically significant effect on all 4 outcomes tested and had the largest clinical effect on 2 of 4 outcomes (24 hr SBP and office SBP). Significant interstudy heterogeneity was found for 2 outcomes and when it was resolved with removal of key trial(s), the effect was reduced; however, remained statistically significant. ERAs were also found to have a statistically significant effect on all 4 outcomes, but these results should be viewed cautiously because significant interstudy heterogeneity was found for 2 out of 4 outcomes and information on baseline medications were not provided. Furthermore, the average patients in ERA trials had the lowest baseline BP. RD consistently had the smallest clinical effects for each outcome that was tested and none reached statistical significance. Compared to the other treatments tested, RD trials enrolled the most patients who on average had higher baseline BP and were on the most medicines. Given the significant differences in baseline characteristics and study design we opted not to conduct subgroup interaction testing.

To the best of our knowledge, this is the largest meta-analysis testing efficacy of treatments verses placebo or sham-control for resistant hypertension. We preferred this approach over a network approach because we wished to exclude trials that had active control arms or no control arms in an effort to minimize the impact of trial design features and bias susceptibility on results. Drastic differences in efficacy of interventions have been seen demonstrated previously when comparing data from open-label non-controlled pilot studies versus sham-controlled trials. Data from initial pilot studies for RD showed as much as 22/11 mmHg of BP reduction. [27] However, subsequent meta-analyses of sham-controlled trials have shown this reduction to be on the order of 4/2 mmHg. [28]

The administration of MRA as a fourth-line agent significantly reduced 24-hour ambulatory BP and office BP compared with placebo in this meta-analysis. Although the underlying mechanism of RH is unclear, there is some evidence that RH is generally volume-dependent, attributable to differing levels of aldosterone excess. [29,30] There is evidence that patients with RH have higher plasma aldosterone levels compared with nonresistant hypertension. [31] A previous meta-analysis has shown that spironolactone increased the concentration of serum potassium compared to placebo. However, when compared with other interventions such as angiotensin-converting-enzyme inhibitors (ACE-I), beta blockers, and alpha antagonists there was no significant difference in the serum potassium concentration with the use of spironolactone. [32]

The administration of ERAs as a fourth-line agent significantly reduced 24-hr ambulatory BP and office BP compared with placebo based on the results of our meta-analysis. Endothelin-1 (ET-1) is a 21 amino acid vasoconstrictor peptide that activates calcium flux in smooth muscle cells causing vasoconstriction. ET-1 levels have been shown to positively correlate with blood pressure, and ERAs have been shown to lower blood pressure in animal models. [33,34] However, the antihypertensive effectiveness of ERAs have remained controversial in human studies. A previous meta-analysis testing use of ERA for the treatment of hypertension reported side effects of edema, headaches, dizziness, anemia, fatigue, and hypotension; however, mortality was not significantly different between the ERA group and placebo. Of the 3406 patients included in this meta-analysis, 506 patients had at least one severe adverse event defined as cardiovascular events, acute pulmonary edema, dyspnea, severe allergies, or severe liver dysfunction. The majority of these adverse events were considered unrelated to treatment as 15.7% of patients in the ERA group and 12.8% in the placebo group experienced these side effects. [35] However, due to a statistically significant difference in side effects from Darusentan use as compared to placebo, the drug was no longer developed for use in RH. Despite side effects reported in hypertension trials, ERAs continue to be used safely and efficaciously for pulmonary hypertension. [36] Given the efficacy of ERAs seen in our analysis, further investigation for treatment of RH would be warranted.

The administration of beta-blockers (βB) as a fourth-line agent significantly reduced office BP compared with placebo based on the results of the 2 trials included in our meta-analysis. Use of BBs to treat hypertension started in 1960s due to the markedly lower side effect profile when compared to other drugs available at that time. [37] Since then, agents like ACE-Is, ARBs, and CCBs have been shown to be superior to BBs in reducing BP. [38,39] There has been very little investigation into the role of BBs in treating RH. Mechanistically, beta-blockers could be an appropriate treatment for RH, as they have been shown to be accompanied by deactivation of the sympathetic nervous system. [40] More research and higher quality studies, that provide information on background medication use, are needed to better understand the role of beta blockers in RH.

Renal denervation did not significantly reduce 24-hour ambulatory BP and office BP compared with placebo based on the results of our meta-analysis. There are potential mechanisms to explain this observation. RD aims to reduce BP by reducing a patient's sympathetic output via a variety of mechanisms including lowering plasma renin activity and ultimately, angiotension-II. [3] RH has been shown to develop from an aldosterone-induced volume excess, and such hyperaldosteronism most commonly is not affected by angiotensin-II. [30] Despite the large number of studies evaluating use of RD in treating hypertensive patients over the past years, the complex pathophysiology underlying RD is only partly understood. Sympathetic activity has known vasoconstrictive effects, but RD does not seem to significantly alter renal blood flow. [41,42] How other components of the sympathetic nervous system compensate for the effects of RD remains unknown and could possibly help explain this phenomenon. RD's effects on sodium excretion are unknown, and none of the studies included in our analysis evaluated sodium excretion. The only human trial investigating this endpoint showed mixed results. While RD led to higher sodium excretion, patients with a stronger BP response after RD showed a diminished effect on sodium excretion compared to those with less BP changes. Further investigation into RD's effects on sodium excretion could help explain its reduced efficacy for treating RH. [43]

There are important limitations to this meta-analysis. Many of our efficacy outcomes have significant heterogeneity, which is likely related to the complexity of patients being studied. Factors including age, BMI, diet, baseline BP level, baseline medication burden and kidney function, among other things, are likely to be related to variation in response to RH treatments. Future studies should attempt patient-level meta-analyses that focus on the role of these individual features in relation to treatment response. When comparing the clinical effects of these

treatments to each other we cannot exclude that differences in trial populations account for the differences in treatment response that we observed. In general, we believe the MRA and RD populations were similar enough to conclude with low to moderate confidence that MRA lowers BP more effectively than RD in RH patients. (Table 1) Chen et al. conducted a meta-analysis looking at all trials testing use of spironolactone for the treatment of RH. Part of their analysis included a subgroup analysis of two trials directly comparing spironolactone and RD showing a 9/3 mmHg greater reduction in 24-hr BP for spironolactone versus RD. [32,44,45] However, the difference in the ERA population compared to others was so striking that it renders us unable to reach any general conclusions about ERA compared to MRA or RD. Besides MRA, ERA and RD, the other treatments had too few studies with too many limitations to make any generalizable statements about efficacy. Additionally, we pooled primary and secondary endpoints in this present meta-analysis as not all studies reported office BP or 24-hr ambulatory BP as the primary outcome. Finally, we were unable to meta-analyze safety outcomes due to lack of standardized reporting of safety outcomes.

5. Conclusion

In conclusion, we have low to moderate confidence that MRA lowers BP in patients with RH more than RD, which seems to have little to no effect. Due to either the low number of trials or major differences in the patient population being tested, we do not have sufficient confidence to render a judgment on the efficacy of the other treatments for RH. Future work should focus on the role of individual factors in moderating treatment response and the conduct of high quality RCTs comparing interventions.

Funding

None

Disclosures

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.04.021.

References

[1] Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 2018;72(5):e53–90. https://doi.org/10.1161/HYP.0000000000000084.
[2] Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2018;138(17):e426–83. https://doi.org/10.1161/CIR.0000000000000597.
[3] Witkowski A, Prejbisz A, Florczak E, et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension 2011;58(4):559–65. https://doi.org/10.1161/HYPERTENSIONAHA.111.173799.
[4] Nazarzadeh M, Pinho-Gomes AC, Rahimi K. Resistant hypertension in times of changing definitions and treatment recommendations. Heart 2019;105(2):96–7. https://doi.org/10.1136/heartjnl-2018-313786.
[5] Vongpatanasin W. Resistant hypertension: a review of diagnosis and management. JAMA 2014;311(21):2216–24. https://doi.org/10.1001/jama.2014.5180.
[6] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343(d5928). https://doi.org/10.1136/bmj.d5928.
[7] Abolghasmi R, Taziki O. Efficacy of low dose spironolactone in chronic kidney disease with resistant hypertension. Saud J Kidney Dis Transpl 2011;22(1):75–8.
[8] Ni X, Zhang J, Zhang P, et al. Effects of spironolactone on dialysis patients with refractory hypertension: a randomized controlled study. J Clin Hypertens (Greenwich) 2014;16(9):658–63. https://doi.org/10.1111/jch.12374.
[9] Oxlund CS, Henriksen JE, Tarnow L, et al. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. J Hypertens 2013;31(10):2094–102. https://doi.org/10.1097/HJH.0b013e3283638b1a.
[10] Václavík J, Sedlák R, Jarkovský J, et al. Effect of spironolactone in resistant arterial hypertension: a randomized, double-blind, placebo-controlled trial (ASPIRANT-EXT). Medicine (Baltimore) 2014;93(27):e162. https://doi.org/10.1097/MD.0000000000000162.
[11] Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386(10008):2059–68. https://doi.org/10.1016/S0140-6736(15)00257-3.
[12] Rossignol P, Claggett BL, Liu J, et al. Spironolactone and resistant hypertension in heart failure with preserved ejection fraction. Am J Hypertens 2018;31(4):407–14. https://doi.org/10.1093/ajh/hpx210.
[13] Azizi M, Sanghvi K, Saxena M, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet 2021;397(10293):2476–86. https://doi.org/10.1016/S0140-6736(21)00788-1.
[14] Desch S, Okon T, Heinemann D, et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. Hypertension 2015;65(6):1202–8. https://doi.org/10.1161/HYPERTENSIONAHA.115.05283.
[15] Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014;370(15):1393–401. https://doi.org/10.1056/NEJMoa1402670.
[16] Mathiassen ON, Vase H, Bech JN, et al. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. J Hypertens 2016;34(8):1639–47. https://doi.org/10.1097/HJH.0000000000000977.
[17] Schmieder RE, Ott C, Toennes SW, et al. Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension - WAVE IV. J Hypertens 2018;36(3):680–9. https://doi.org/10.1097/HJH.0000000000001584.
[18] Kario K, Yokoi Y, Okamura K, et al. Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial. Hypertens Res 2022;45(2):221–31. https://doi.org/10.1038/s41440-021-00754-7.
[19] Bakris GL, Lindholm LH, Black HR, et al. Divergent results using clinic and ambulatory blood pressures: report of a darusentan-resistant hypertension trial. Hypertension 2010;56(5):824–30. https://doi.org/10.1161/HYPERTENSIONAHA.110.156976.
[20] Black HR, Bakris GL, Weber MA, et al. Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study. J Clin Hypertens (Greenwich) 2007;9(10):760–9. https://doi.org/10.1111/j.1524-6175.2007.07244.x.
[21] Weber MA, Black H, Bakris G, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. Lancet 2009;374(9699):1423–31. https://doi.org/10.1016/S0140-6736(09)61500-2.
[22] Karns AD, Bral JM, Hartman D, et al. Study of aldosterone synthase inhibition as an add-on therapy in resistant hypertension. J Clin Hypertens (Greenwich) 2013;15(3):186–92. https://doi.org/10.1111/jch.12051.
[23] Schneider A, Schwab J, Karg MV, et al. Low-dose eplerenone decreases left ventricular mass in treatment-resistant hypertension. J Hypertens 2017;35(5):1086–92. https://doi.org/10.1097/HJH.0000000000001264.
[24] Ranasinghe HN, Fernando N, Handunnetti S, et al. The impact of propranolol on nitric oxide and total antioxidant capacity in patients with resistant hypertension-evidence from the APPROPRIATE trial. BMC Res Notes 2020;13(1):228. https://doi.org/10.1186/s13104-020-05067-5.
[25] Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol 2011;58(7):765–73. https://doi.org/10.1016/j.jacc.2011.06.008.
[26] Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet 2022;400(10367):1927–37. https://doi.org/10.1016/S0140-6736(22)02034-7.
[27] Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373(9671):1275–81. https://doi.org/10.1016/S0140-6736(09)60566-3.
[28] Ahmed M, Nudy M, Bussa R, et al. A systematic review, meta-analysis, and meta regression of the sham controlled renal denervation randomized controlled trials. Trends Cardiovasc Med 2022. https://doi.org/10.1016/j.tcm.2022.05.009.
[29] Manolis AA, Manolis TA, Melita H, et al. Eplerenone Versus Spironolactone in Resistant Hypertension: an Efficacy and/or Cost or Just a Men's Issue? Curr Hypertens Rep 2019;21(3):22. https://doi.org/10.1007/s11906-019-0924-0.
[30] Egan BM, Li J. Role of aldosterone blockade in resistant hypertension. Semin Nephrol 2014;34(3):273–84. https://doi.org/10.1016/j.semnephrol.2014.04.004.
[31] Sartori M, Calò LA, Mascagna V, et al. Aldosterone and refractory hypertension: a prospective cohort study. Am J Hypertens 2006;19(4):373–9. https://doi.org/10.1016/j.amjhyper.2005.06.031.
[32] Chen C, Zhu XY, Li D, et al. Clinical efficacy and safety of spironolactone in patients with resistant hypertension: a systematic review and meta-analysis. Medicine

(Baltimore) 2020;99(34):e21694. https://doi.org/10.1097/MD.0000000000021694.
[33] da Silva AA, Kuo JJ, Tallam LS, et al. Role of endothelin-1 in blood pressure regulation in a rat model of visceral obesity and hypertension. Hypertension 2004;43(2):383–7. https://doi.org/10.1161/01.HYP.0000111139.94378.74.
[34] Donato AJ, Lesniewski LA, Stuart D, et al. Smooth muscle specific disruption of the endothelin-A receptor in mice reduces arterial pressure, and vascular reactivity and affects vascular development. Life Sci 2014;118(2):238–43. https://doi.org/10.1016/j.lfs.2013.12.209.
[35] Yuan W, Cheng G, Li B, et al. Endothelin-receptor antagonist can reduce blood pressure in patients with hypertension: a meta-analysis. Blood Press 2017;26(3):139–49. https://doi.org/10.1080/08037051.2016.1208730.
[36] Correale M, Ferraretti A, Monaco I, et al. Endothelin-receptor antagonists in the management of pulmonary arterial hypertension: where do we stand? Vasc Health Risk Manag 2018;14:253–64. https://doi.org/10.2147/VHRM.S133921.
[37] Prichard BN, Gillam PM. Use of propranolol (inderal) in treatment of hypertension. Br Med J 1964;2(5411):725–7. https://doi.org/10.1136/bmj.2.5411.725.
[38] Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005;366(9496):1545–53. https://doi.org/10.1016/S0140-6736(05)67573-3.
[39] Bradley HA, Wiysonge CS, Volmink JA, et al. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. J Hypertens 2006;24(11):2131–41. https://doi.org/10.1097/01.hjh.0000249685.58370.28.
[40] Tsioufis C, Kordalis A, Flessas D, et al. Pathophysiology of resistant hypertension: the role of sympathetic nervous system. Int J Hypertens 2011. https://doi.org/10.4061/2011/642416.
[41] DiBona GF. Physiology in perspective: the Wisdom of the Body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol 2005;289(3):R633–41. https://doi.org/10.1152/ajpregu.00258.2005.
[42] Ott C, Janka R, Schmid A, et al. Vascular and renal hemodynamic changes after renal denervation. Clin J Am Soc Nephrol 2013;8(7):1195–201. https://doi.org/10.2215/CJN.08500812.
[43] Pöss J, Ewen S, Schmieder RE, et al. Effects of renal sympathetic denervation on urinary sodium excretion in patients with resistant hypertension. Clin Res Cardiol 2015;104(8):672–8. https://doi.org/10.1007/s00392-015-0832-5.
[44] Oliveras A, Armario P, Clarà A, et al. Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: results from the DENERVHTA study - a randomized controlled trial. J Hypertens 2016;34(9):1863–71. https://doi.org/10.1097/HJH.0000000000001025.
[45] Rosa J, Widimský P, Waldauf P, et al. Role of adding spironolactone and renal denervation in true resistant hypertension: one-year outcomes of randomized PRAGUE-15 study. Hypertension 2016;67(2):397–403. https://doi.org/10.1161/HYPERTENSIONAHA.115.06526.