Renal Denervation

Magnitude of Blood Pressure Reduction in the Placebo Arms of Modern Hypertension Trials

Implications for Trials of Renal Denervation

Hitesh C. Patel,* Carl Hayward,* Baris Ata Ozdemir, Stuart D. Rosen, Henry Krum, Alexander R. Lyon, Darrel P. Francis, Carlo di Mario

Abstract—Early phase studies of novel interventions for hypertension, such as renal sympathetic denervation, are sometimes single-armed (uncontrolled). We explored the wisdom of this by quantifying the blood pressure fall in the placebo arms of contemporary trials of hypertension. We searched Medline up to June 2014 and identified blinded, randomized trials of hypertension therapy in which the control arm received placebo medication or a sham (placebo) procedure. For nonresistant hypertension, we have identified all such trials of drugs licensed by the US Food and Drug Administration since 2000 (5 drugs). This US Food and Drug Administration–related restriction was not applied to resistant hypertension trials. This produced 7451 patients, who were allocated to a blinded control from 32 trials of nonresistant hypertension and 694 patients from 8 trials of resistant hypertension (3 drugs and 2 interventions). Systolic blood pressure fell by 5.92 mm Hg (95% confidence interval, 5.14–6.71; P<0.0001) in the nonresistant cohort and by 8.76 mm Hg (95% confidence interval, 4.83–12.70; P<0.0001) in the resistant cohort. Using metaregression, the falls were larger in trials that did not use ambulatory blood pressure monitoring as an inclusion criterion (z=2.84; P=0.0045), in those with higher baseline blood pressures (z=−0.3; P=0.0001), and in those where the patients were prescribed a continuous background of antihypertensives (z=−2.72; P=0.0065). The nontrivial magnitude of these apparent blood pressure reductions with perfectly ineffective intervention (placebo) illustrates that efficacy explorations of novel therapies for hypertension, once safety is established, should be performed with a randomized, appropriately controlled, and blinded design. (Hypertension. 2015;65:401-406. DOI: 10.1161/HYPERTENSIONAHA.114.04640.) ● Online Data Supplement

Key Words: hypertension □ meta-analysis □ placebos □ randomized controlled trial

The sham arm of the SYMPLICITY HTN-3 trial reported a reduction in systolic blood pressure of 11.8 mm Hg, which was not significantly different from the active arm.1 This led to a widespread moratorium on renal sympathetic denervation as a treatment for resistant hypertension. The placebo arm results of SYMPLICITY HTN-3 were a surprise to those expecting to replicate SYMPLICITY HTN-2 in which the open-control arm had a 1 mm Hg increase in systolic blood pressure.2 In this article, we analyze whether the results from the placebo arm of SYMPLICITY HTN-3 are out of keeping with findings from the placebo arms of other hypertension trials.

Methods

Resistant hypertension is a term applied to a cohort of patients in whom a combination of ≥3 antihypertensives (1 of which is a diuretic) has failed to control their blood pressure.4 Although commonly overlooked, white coat hypertension5 and noncompliance need to be excluded to confirm the diagnosis.5 Important differences exist between resistant and nonresistant hypertensives, with the former associated with a higher prevalence of obesity, longer duration of hypertension, and more end-organ damage.6 As such, we performed a meta-analysis of a series of hypertension trials, considering the resistant and nonresistant subjects separately. To minimize the bias, we included only those trials that have a randomized, placebo/sham-controlled, and blinded design.

Search Strategy, Eligibility Criteria, and Data Extraction

The US Food and Drug Administration has approved 5 drugs for hypertension since 2000 (azilsartan, aliskiren, nebivolol, eplerenone, and olmesartan). We restricted our analysis of trials of nonresistant hypertension to those involving these licensed drugs. We searched PubMed for trials using the following criteria: (((((Drug name)) AND Random*) AND Control*) AND Blind*)). We also searched the Food and Drug Administration medical reviews for each of the drugs (listed on the Drugs@FDA database). To identify trials of resistant...
hypertension, the following search fields were used: (((Resistant AND Hypertension) AND Control) AND Random). Searches were limited to humans in English language and with date ranging from the start of PubMed to June 2014. We also performed a manual search of citation lists, review articles, and PubMed links to related citations.

Two reviewers independently scrutinized the search results (H.C.P. and C.H.). Trials were selected if their design was randomized, controlled (placebo or sham), parallel group, and blinded. Data on baseline demographics, blood pressure inclusion criteria, trial duration (time in weeks from randomization to planned final follow-up), and change in systolic and diastolic blood pressures in the placebo/sham arms were extracted. Where this was not possible, the trial was excluded from the pooled series. When blood pressure changes were reported at multiple time points, we used the time that was stated as the primary outcome. Discrepancies were resolved by discussion and consensus.

Statistics
To compare the baseline characteristics of the nonresistant and resistant hypertension trials, the independent sample t test was used to compare sample size–weighted continuous variables and the Fisher exact test was used to compare categorical data. SD and SE are quoted as appropriate. A meta-analysis was conducted for the selected trials, weighting the effect size estimates by the inverse variance. We pooled the data on office blood pressure effect size using a random effect model and presented them as weighted mean differences with 95% confidence intervals [CIs]. Trial heterogeneity is expressed using $\chi^2$ and $I^2$.

To explore any heterogeneity in the trials, a multivariable meta-regression analysis was applied to the nonresistant hypertension trials. The best model was described using $R^2$, the unstandardized $\beta$ coefficient, and the standardized coefficient to rank the relative contribution of each covariate to the model. Data analysis was performed with Review Manager (version 5.3; The Cochrane Collaboration) and the program R using the metator package. All analyses were performed independently by 2 authors (H.C.P. and B.A.O.) with discrepancies in findings resolved by discussion.

Results
Nonresistant Hypertension Trials
Fifty-two trials fulfilled our inclusion criteria, involving 7451 patients, who were allocated to blinded placebo (Figure S1 in the online-only Data Supplement). The key characteristics of each trial are summarized in S2. All but 8 of the trials recruited patients using only diastolic blood pressure cutoffs. Thirteen trials had more stringent inclusion criteria, which required not only elevated office blood pressure measurements but also elevated ambulatory measurements. Thirty-eight trials mandated that patients should be on no therapy for hypertension at the time of randomization (ie, patients underwent a complete drug washout phase).

There was a significant blood pressure reduction in the control arm, 5.92 mm Hg (95% CI, 5.14–6.71; P<0.0001) systolic blood pressure and 5.40 mm Hg (95% CI, 4.80–6.01; P<0.0001) diastolic blood pressure (Figure). The sample size–weighted baseline blood pressure for these trials was 155/98 mm Hg with a mean study period of 8.5 weeks (Table 1). There was significant heterogeneity in trial characteristics, with an $I^2$ value of 0.71 for the systolic blood pressure effect, suggesting that 71% of the observed variance could be explained by differences between the studies and, hence, it might be explained by study-level covariates. For diastolic blood pressure change, the $I^2$ value was 80%.

For systolic blood pressure, meta-regression analysis (Table 2) found that the predictors of the fall in the placebo arm were, in decreasing order of importance, baseline blood pressure, the use of ambulatory blood pressure monitor readings as an inclusion criterion, and the number of antihypertensive medications being taken at randomization. The reduction in blood pressure in the control arm was less in trials that used ambulatory monitoring. Trials of patients with higher baseline systolic blood pressures and those with patients on antihypertensives at randomization observed a greater fall in pressure in the control arm. The overall $R^2$ was 0.38 (ie, the model accounts for 38% of the heterogeneity). The unstandardized regression coefficient for baseline office systolic blood pressure was ~0.3, which equates to an additional blood pressure reduction of 0.3 mm Hg (in the placebo arm) for every higher baseline systolic blood pressure of 1 mm Hg. Similarly, for every additional blood pressure tablet taken at the baseline, there is an expected further 2.43 mm Hg decrease with placebo. The use of ambulatory monitoring as an inclusion criterion is a categorical variable (no/yes) as opposed to a continuous one, which changes the interpretation of its unstandardized regression coefficient. Where ambulatory monitoring is used, there is an associated 2.48 mm Hg reduction in the magnitude of systolic blood pressure reduction with placebo.

Trials that used ambulatory blood pressure monitor measurements and office blood pressure recordings (on separate days) as an inclusion criterion (Figure S2) had smaller reductions in blood pressure in the placebo arm than those in studies based solely on measurement of office blood pressure (systolic blood pressure effect, 3.37 mm Hg [SE=0.93] versus 6.76 mm Hg [SE=0.39]; P<0.0001) for the difference between groups.

For diastolic blood pressure, the use of ambulatory blood pressure monitors for recruitment and baseline diastolic blood pressure associated significantly with the magnitude of blood pressure reduction in the placebo arm ($R^2=0.50$; Table 2). The direction of change was as described for systolic blood pressure responses earlier.

Age, trial duration, washout/run-in period duration, and dropout rate (which includes protocol violations, unsatisfactory therapeutic effects, adverse events, withdrawal of patient consent, and loss to follow-up) were not significantly associated with either systolic or diastolic placebo responses, and were consequently removed from the models.

Resistant Hypertension Trials
The literature search algorithm yielded 236 potential studies of resistant hypertension (Figure S1). After applying our inclusion criteria, all but 8 trials were excluded, and these studies randomized a total of 694 subjects to the control arm (Figure S2). The average number of antihypertensives consumed at the baseline was 4.1 (Table 1). Diuretics were taken by 98% of patients, inhibitors of the renin–angiotensin system by 97%, calcium channel blockers by 72%, and $\beta$-blockers by 68%. Two of the trials were nonpharmacological, investigating renal sympathetic denervation and baroreceptor activation as therapies.

There was a significant blood pressure reduction in the control arms; 8.76 mm Hg (95% CI, 4.83 and 12.70; $P<0.0001$) systolic blood pressure and 3.56 mm Hg (95% CI, 1.45 and 5.95; $P=0.001$) diastolic blood pressure (Figure). The sample size–weighted baseline blood pressure for these trials was...
There was significant heterogeneity between the trials. The $I^2$ value was 77% with respect to systolic blood pressure response and 79% with diastolic blood pressure.

Invasive placebo procedures showed a nonsignificant trend toward a greater placebo response on systolic blood pressure than medication in the treatment of resistant hypertension ($-13.2\pm2.4$ mmHg [SE] versus $-7.24\pm2.4$ mmHg [SE]; $P=0.102$).

**Discussion**

On average, systolic blood pressure falls by $6$ mmHg in the placebo/sham arms in trials of nonresistant hypertension and $9$ mmHg in the trials of resistant hypertension. Blood pressure reductions of this size are not trivial and, if genuine, would deliver a 14% decrease in stroke and 7% reduction in mortality. It seems unlikely that there is a genuine biological effect of the placebo on blood pressure. More likely, there are 3 broad contributors to the reduction in blood pressure seen in the placebo arm of hypertension trials.

**Figure.** Forest plots for systolic blood pressure (SBP) effects (left) and diastolic blood pressure (DBP) effects (right) for nonresistant hypertension trials (white background) and resistant hypertension trials (gray background). CI indicates confidence interval; and FDA, Food and Drug Administration.
in the placebo group. Measures to reduce regression to the mean include taking multiple blood pressure measurements across several weeks before randomizing patients. Our data support this notion because the studies that used ambulatory monitoring to determine eligibility displayed smaller placebo responses.

### Unintentional Bias by Clinical Observers

The second source may be related to clinicians and their training to use all clinical information in making decisions. There may, therefore, be a temptation (check-once-more bias) to remeasure values that seem superficially inconsistent with what the clinician knows. For example, imagine a patient enrolled in a double-blind trial having a follow-up blood pressure measurement. Suppose the patient is receiving placebo, although of course the clinician is unaware of the study arm allocation. If the pressure is, by chance, an unusually low value, the clinician might accept this (recognizing that some patients are having efficacious therapy). If, in contrast, the pressure is an unusually high value, the clinician (knowing that neither arm is receiving a blood-pressure raising therapy) might be more likely to consider the value erroneous and in need of repeating. The net effect would be to trend blood pressure measurements downwards.\(^{13}\)

A previous comparison of office and ambulatory blood pressure reduction in randomized placebo-controlled blinded drug trials may be instructive.\(^{14}\) Although the effects beyond placebo were identical regardless of whether documented by staff (office blood pressure) or documented by machine (ambulatory blood pressure), the effects within the placebo arm were significantly larger, when documented by staff than by machine. This suggested \(\approx 2.9\) mm Hg artificial appearance of pressure drop with staff-documented blood pressures. Ambulatory monitoring should be considered not only to reduce bias in patient selection for a trial but also to monitor their response to therapy. This approach has been shown to be useful in recent head-to-head trials\(^{15}\) and in placebo-controlled ones.\(^{16}\)

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### Table 1. Sample Size–Weighted Summaries of Key Characteristics of the Trials of Nonresistant and Resistant HTN

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonresistant HTN, 52 Trials</th>
<th>Resistant HTN, 8 Trials</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.2 (3.8)</td>
<td>59.6 (3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>55.9 (6.8)</td>
<td>59.2 (6.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black, %</td>
<td>17.9 (19.5)</td>
<td>21.1 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>11.2 (3.1)</td>
<td>45.1 (18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>154.5 (5.2)</td>
<td>159.7 (13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline DBP, mm Hg</td>
<td>98.2 (3.3)</td>
<td>90.8 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trial length, wk</td>
<td>8.5 (2.2)</td>
<td>17.6 (5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of antihypertensives</td>
<td>0.4 (0.5)</td>
<td>4.1 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drop-out rate, %</td>
<td>0.13 (0.08)</td>
<td>0.05 (0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Run-in/washout period, wk</td>
<td>4.3 (1.3)</td>
<td>2.3 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP as inclusion criterion</td>
<td>7 (13.7)</td>
<td>8 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM as inclusion criterion</td>
<td>13 (25.5)</td>
<td>3 (37.5)</td>
<td>0.429</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean (SD) and count data as number (%). ABPM indicates ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HTN, hypertension; and SBP, systolic blood pressure.

### Regression to the Mean

Registries have repeatedly demonstrated that the higher the baseline blood pressure, the bigger the fall after intervention.\(^{10,11}\) This effect occurs whenever a variable has inherent biological variability, and patients are selected on the basis of recording a high-value. Statistically, it is known as regression to the mean. We have previously suggested an informal term, predestined to be lower. The larger the spontaneous temporal baseline blood pressure, the bigger the fall after intervention.\(^{10,11}\) This effect occurs whenever a variable has inherent biological variability and the more intense the selection, the larger the statistical expectation of fall in the variable, without any intervention.

Indeed, our pooled data showed evidence of regression to the mean at the study level; the studies with higher starting baseline blood pressures demonstrated greater responses.

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### Table 2. Summary of the Metaregression Model for Blood Pressure Effects

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta)</td>
<td>SE</td>
<td>(z) Value</td>
</tr>
<tr>
<td><strong>SBP effect</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intercept</td>
<td>40.41</td>
<td>12.16</td>
<td>3.32</td>
</tr>
<tr>
<td>No. of blood pressure tablets</td>
<td>-2.43</td>
<td>0.89</td>
<td>-2.72</td>
</tr>
<tr>
<td>ABPM as inclusion criteria</td>
<td>2.48</td>
<td>0.87</td>
<td>2.84</td>
</tr>
<tr>
<td>Baseline office SBP</td>
<td>-0.3</td>
<td>0.08</td>
<td>-3.83</td>
</tr>
<tr>
<td><strong>DBP effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>12.52</td>
<td>8.13</td>
<td>1.54</td>
</tr>
<tr>
<td>No. of blood pressure tablets</td>
<td>-1.09</td>
<td>0.63</td>
<td>-1.73</td>
</tr>
<tr>
<td>ABPM as inclusion criteria</td>
<td>2.63</td>
<td>0.63</td>
<td>4.41</td>
</tr>
<tr>
<td>Baseline office DBP</td>
<td>-0.18</td>
<td>0.08</td>
<td>-2.29</td>
</tr>
</tbody>
</table>

\(\chi^2\) value, the greater the influence of the covariate on the dependent variable. ABPM indicates ambulatory blood pressure monitor; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
Improvement in Compliance
The third source is the potential for patients to increase compliance to antihypertensive medications when participating in a trial because of observation and education of patients. Poor compliance with medications has long been shown to contribute to uncontrolled hypertension. Studies using high-performance liquid chromatography-tandem mass spectrometry urine analysis have demonstrated full or partial drug noncompliance in up to 53% of resistant hypertensives and 25% of all patients in a specialist hypertension clinic. Longitudinal studies to ascertain changes objectively in compliance with hypertension medications over time are lacking, but there is evidence linking poor adherence to increased risk of stroke in both the short- and long-term.

Our study found that the greater the number of antihypertensive medications prescribed at the baseline, the greater the drop in blood pressure in the control group. This would be expected if trial participation resulted in increased compliance. One approach to minimizing this in trials is to replace the prior medications with a single-blind inert tablet in a phase known as run-in before randomization. Some nonresistant hypertension trials have chosen to give an active drug during the single-blind run-in period. In contrast, all the trials of resistant hypertension continued prior medications, which may have contributed to the larger reductions in blood pressure observed in the placebo arm of these trials. In addition to improved compliance, education and observation of patients can reduce their level of anxiety, which might contribute to a reduction in blood pressure.

Procedural Versus Medical Placebo
There has been a suggestion that trials that involve an elaborate or invasive sham procedure are prone to larger placebo effects. Our pooling of data from resistant hypertension trials was underpowered, but it did show a trend that might support this notion. This phenomenon was particularly visible in the Rheos Pivotal Trial, in which 265 patients with resistant hypertension were implanted with baroreceptor stimulators. The patients were monitored for a month with the device in place and then randomized 2:1 in a blinded fashion to device on or off. An 8 mmHg drop in blood pressure was seen after implantation, before the device was even turned on.

A contributor to the greater effect seen in the trials of invasive sham might be that they had greater scope for regression to the mean bias because they had a higher enrolment threshold systolic blood pressure at 160 mmHg versus 140 mmHg of other resistant hypertension trials.

Limitations
We have restricted our analysis to contemporary data. Global awareness of hypertension has improved during the past 20 years, not only for physicians but also for patients. Using historic trials would, therefore, not be representative. For the second analysis, we identified all trials that treated patients with resistant hypertension using placebo/sham control and blinding. This excluded several trials including SYMPLECTICITY HTN-2, reducing further the number of trials in the resistant hypertension group. However, inclusion of these unblinded studies would not have answered our study question of the size of the fall in pressure in an appropriately blinded placebo arm.

The majority of the trials did not clearly state the proportion of patients in the placebo group who may have received additional antihypertensive drugs during follow-up as a result of protocol violation. However, 50 of 52 nonresistant hypertension trials did report the study withdrawal rate, which we used as a surrogate. This was not found to be an important modifier of fall in blood pressure in the control group.

We performed meta-regression analysis as a hypothesis-generating exercise to try and understand the factors (at the trial level) that affect the placebo response. We cannot imply causality in any of our assertions. We did not perform meta-regression on the resistant hypertension trials because the number of available trials is small. This paucity of robust clinical trials on resistant hypertension also has implications in clinical practice, with little guidance on how to manage this challenging medical condition. Statistically, our findings from the nonresistant hypertension meta-analysis should not be extrapolated to the resistant hypertension trials because of the large differences between the populations.

Perspectives
The 11.7 mmHg reduction in systolic blood pressure in SYMPLECTICITY HTN-3 should not be considered surprisingly large. The only other antihypertensive sham-controlled device trial observed a systolic blood pressure drop of 17 mmHg. Placebo arms in drug trials also demonstrate a nontrivial reduction in blood pressure of the order of 6 mmHg. When the genuine effect of an interventional therapy may be similar in magnitude to this, we suggest that in future, it is unwise to design a trial that is unable to distinguish the genuine effect of the intervention from the placebo response. When novel therapies for hypertension undergo exploration for efficacy, we recommend from the outset a study design with appropriate randomization and blinding.

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H. Patel and C. Hayward were supported by the National Institute of Health Research Cardiovascular Biomedical Research Unit at the Royal Brompton Hospital, London. D.P. Francis was supported by a British Heart Foundation Senior Research Fellowship (FS/10/038).

Disclosures
H. Krum, D.P. Francis, and C.D. Mario have received honoraria and travel support from Medtronic Inc. H. Krum has additionally consulted for Merck, Pfizer, Mesoblast, Novartis, Roche, Schering Plough, Servier, and Gilead Sciences. The other authors report no conflicts.

References


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Magnitude of blood pressure reduction in the placebo arms of modern hypertension trials: Implications for trials of renal denervation

Hitesh C Patel,1,2,* Carl Hayward,1,2,* Baris Ata Ozdemir,3 Stuart D Rosen,2,4 Henry Krum,5 Alexander R Lyon,1,2 Darrel P Francis,2 Carlo di Mario1,2

1 NIHR Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, London, UK
2 National Heart and Lung Institute, Imperial College, London, UK
3 Department of Outcomes Research, St. George's Vascular Institute, St George's University, London, UK
4 Department of Cardiology, Ealing Hospital NHS Trust, Southall, London, UK
5 Monash Centre of Cardiovascular Research and Education in Therapeutics, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, VIC, Australia

*HP and CH contributed equally to the manuscript

Corresponding Author:
Dr Hitesh Patel, Cardiology Research Fellow
Cardiovascular BRU, Royal Brompton Hospital
London UK, SW3 6NP
Tel: +44 207 352 8121 x2920
Fax: +44 207 351 8184
Email: h.patel3@rbht.nhs.uk
Records identified after duplicates removed

Non-resistant Hypertension

- Aliskiren  n=94
- Azilsartan  n=12
- Nebivolol  n=56
- Eplerenone  n=96
- Olmesartan  n=132

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<td>Eplerenone</td>
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<td>Azilsartan</td>
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Records screened  n=400
Records excluded after abstract review  n=333

Full-text articles assessed for eligibility  n=87
Studies included  n=52

15 full-text articles were excluded:
- Insufficient BP outcome data=12
- No placebo/sham=1
- Cross-over study=1
- Substudy=1

Resistant Hypertension

- Studies included  n=52

Records screened  n=311
Records excluded after abstract review  n=301

Full-text articles assessed for eligibility  n=10
Studies included  n=8

2 full-text articles were excluded:
- Insufficient BP outcome data=2

S1: Flow chart for study selection. BP= blood pressure
### Baseline Inclusion/Exclusion Blood Pressure Criteria

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<tr>
<th>Study ID</th>
<th>Min SBP (mmHg)</th>
<th>Min DBP (mmHg)</th>
<th>Max SBP (mmHg)</th>
<th>Max DBP (mmHg)</th>
<th>Duration (weeks)</th>
<th>Washout (weeks)</th>
<th>Trial Duration (weeks)</th>
<th>N (placebo arm)</th>
<th>N (active arm)</th>
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<td>S2: Individual characteristics of the 52 non-resistant hypertension and 8 resistant hypertension trials included in the meta-analysis. SBP=systolic blood pressure; DBP=diastolic blood pressure; ABPM=ambulatory blood pressure monitoring; NR=no record.</td>
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Supplementary references


