Effects of Blood Pressure Lowering Drugs in Heart Failure: a systematic review and meta-analysis of randomised controlled trials

Effects of Blood Pressure Lowering Drugs in Heart Failure

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Abstract

We aimed to combine evidence from all heart failure trials that have investigated the effects of drugs with blood pressure lowering properties to assess (1) the extent to which such drugs reduce blood pressure in heart failure, (2) the association between the net change in blood pressure between treatment arms and cause-specific outcomes, and (3) whether treatment effects (efficacy and safety) vary according to baseline blood pressure. We conducted a systematic review and meta-analysis including randomised clinical trials of drugs with blood pressure-lowering properties in patients with chronic heart failure with at least 300 patient-years follow-up. We included a total of 37 trials (91,950 patients) and showed that treatment with drugs with blood pressure-lowering properties resulted in a small but significant decrease in systolic blood pressure in patients with heart failure with no evidence that the efficacy and safety of those drugs varied according to baseline blood pressure.

Condensed abstract

The relationship between blood pressure and clinical outcomes remains poorly understood. This systematic review and meta-analysis combined evidence from randomised clinical trials of drugs with blood pressure lowering properties in patients with chronic heart failure. It showed that treatment with those drugs achieved a small but significant reduction in systolic blood pressure with no evidence that the efficacy and safety of those drugs varied according to baseline blood pressure.

Key words

Blood pressure; Hypertension; Antihypertensive agent; Heart Failure; Systematic review; Meta-analysis
Introduction

Elevated blood pressure (BP) is one of the major preventable causes of premature morbidity and mortality worldwide, second only to smoking as leading risk factor for the global burden of disease in 2016.[1] It is estimated that antecedent elevated BP (above 140/90 mmHg) is present in 75% of patients with chronic heart failure (HF),[2] which itself is an increasing burden in the UK, now similar to the four most common causes of cancer combined.[3]

In populations without known cardiovascular (CV) disease, epidemiological studies have shown a continuous log-linear positive association between BP and future CV events with no evidence of a BP threshold below which the relationship changes.[4] By contrast, in patients with pre-existing CV disease including those with HF, studies have typically shown a J-shaped relationship between systolic BP (SBP) and all-cause and CV mortality. However, because of the inability of such observational studies to draw causal conclusions, it remains uncertain whether the observed higher risk of death associated with hypotension is just a marker of disease severity,[5-7] in particular for patients with HF and reduced ejection fraction (HFrEF),[8] and whether lowering BP further might cause more harm than benefit.

Randomised controlled trials and subsequent meta-analysis are not prone to issues of reverse causality or uncontrolled confounding and are, therefore, ideally suited to investigate causal effects of BP lowering. Previous large-scale meta-analyses[9,10] of BP lowering trials in patients without HF showed that decreasing BP significantly reduced fatal and non-fatal CV outcomes, and this protective effect was proportional to the magnitude of BP reduction, thus suggesting that BP-dependent mechanisms partially underpinned the observed benefits of BP-lowering drugs. However, to what extent those findings are applicable to HF patients remains unclear. To date there have been no trials of BP lowering per se in patients with HF and reports from individual trials of drugs with BP lowering effects have been insufficient and somewhat conflicting.[11-16] Thus, in the absence of any reliable information, clinical practice guidelines
have been making cautious recommendations about intensive BP reduction in HF. The 2018 ESC/ESH guidelines, for instance, state that “it might be wise to avoid actively lowering BP to below 120/70 mmHg” in patients with HF.[17]

We, therefore, sought to take advantage of the fact that several licenced heart failure drugs have known BP lowering properties, to combine evidence from all HF trials that have investigated the effects of such drugs to assess (1) the extent to which such drugs lower BP in HF patients, (2) the association between the net change in BP between treatment arms and cause-specific outcomes, and (3) whether treatment effects (including benefits and potential harms) vary according to baseline BP.

**Methods**

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of interventional studies[18] and The Cochrane Collaboration.[19] The protocol was registered with the PROSPERO database of systematic reviews (CRD42018095395).

**Literature Search**

Bibliographic databases MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to December 2018 using terms related to heart failure and all drugs with known BP lowering properties (details in Appendix). The search was restricted to clinical trials, controlled clinical trials, randomised controlled trials or meta-analyses. No language restrictions were applied. This search was complemented with hand-search of reference lists of eligible studies and related meta-analyses, and search of trials registries (https://clinicaltrials.gov/).

**Inclusion and Exclusion Criteria**
Trials conducted in patients with chronic ambulatory and symptomatic HF were included if they met one of the following criteria: (i) randomisation of patients to BP lowering drug(s) or placebo (or other inactive control comparator) or (ii) randomisation of patients to drugs with various intensity of BP lowering property. Although included in the search query, trials on cardiac devices were excluded from this systematic review because they were not relevant to the study aims.

No restriction on publication date, setting, drugs or devices investigated was applied. Exclusion criteria were the following: (i) trials without a clearly defined comparison arm; (ii) trials conducted in patients hospitalised for acute HF either as first event or as decompensated chronic HF; (iii) trials conducted in patients with acute HF or reduced ejection fraction in the context of myocardial infarction (MI) (iv) trials conducted in patients with asymptomatic reduced ejection fraction, that is, trials that focused on prevention of HF. To minimise the risk of small-study effects, all studies were required to have a minimum of 300 patient-years of follow-up.

**Outcomes**

Clinical outcomes were (1) HF requiring hospitalization; (2) CV death (as defined and reported in each primary trial); and (6) total mortality. Secondary outcomes were (1) serious adverse events (as defined in each primary trial); and (2) adverse events leading to treatment discontinuation. All outcomes were extracted from data reported by primary trials at the end of follow-up.

**Screening and Selection of studies**

Two investigators independently screened titles and abstracts of all identified studies according to inclusion and exclusion criteria. Full-text articles were retrieved and reviewed in duplicate, with disagreements resolved by consensus. EndNote X8 software was used to manage references and organise screening.
Data Extraction

An electronic data abstraction form was used to record patient and study characteristics, including sample size, treatment comparisons, baseline BP, achieved BP, and mean BP reduction. Data was also collected for all the available pre-defined outcomes.

Risk of Bias Assessment

The methodological quality of eligible studies was assessed using the Cochrane risk of bias tool for interventional studies.[19] Trials were classified as having a low, moderate, high or unclear risk of the following: selection bias (randomisation and allocation concealment), performance bias (blinding of participants and investigators), detection bias (blinding of outcome adjudicators), attrition bias (differential loss to follow-up), and reporting bias (selective outcome reporting). Each trial was finally ascribed an overall risk of bias based on whether the risk of bias in each of the aforementioned domains could have led to material biases in the risk estimates.

Data analysis

A two-step approach was used to compare BP reduction between study arms for all trials that reported BP values at baseline and at a second time point, either at the end of follow-up or at the end of drug up-titration depending on what was available in trial reports. When multiple time points were available, achieved BP at the end of drug up-titration (usually 6 to 8 weeks) was used, because this was the most commonly reported value when only a single time point was available. Firstly, mean BP reduction was calculated as the difference between mean achieved BP and mean baseline BP. Secondly, the difference in BP reduction was computed as the BP reduction in intervention group minus the BP reduction in the control group, so that a negative value represents a larger BP reduction in the intervention group. Some trials reported only the difference between those two groups and that value was used, because it was impossible to compute the mean BP reduction in each trial arm.
Four trials had three arms, including three active treatment groups, and adequate strategies were used to avoid double-counting of participants in each trial. For the ATMOSPHERE trial,[20] enalapril was compared with the combination of enalapril and aliskiren, and the aliskiren only group was excluded. For the J-CHF trial,[21] which compared three different doses of carvedilol were compared against each other, low dose was compared with high dose and medium dose was excluded. For the RESOLVD trial[22], which compared enalapril and candesartan isolated and combined, each drug was compared with the combination of both, with the participants in the latter arm split in equal parts. A similar approach was used for the CARMEN trial,[23] which compared carvedilol and enalapril isolated and combined. For analysis stratified by study type, those two trials were included in the group of placebo-controlled trials, because the combined treatment was compared against each single drug plus placebo. The VACS trial[24] had three study arms including placebo, prazosin and isosorbide dinitrate-hydralazine and therefore each active treatment was compared with placebo, with the participants in the latter arm split in equal parts. For the remaining trials with two arms, the reference category was considered as: (1) placebo in placebo-controlled trials; (2) the standard of care in trials with two different drug classes; and (3) the low dose in trials with different doses of the same drug.

For the analysis of SBP as outcome, mean difference (MD) with 95%CI between SBP in intervention arm and SBP in control arm was computed for each trial. To investigate whether the effect of BP-lowering drugs on SBP varied depending on the type of study, stratified analysis was performed considering placebo-controlled trials and trials comparing two active treatments. For clinical outcomes, relative risks (RRs) with 95% confidence intervals (CI) were computed from the number of events and total number of patients in each trial arm. To investigate whether the effect of BP-lowering drugs on SBP and clinical outcomes varied depending on baseline SBP, trials were divided into five strata of mean baseline SBP.
aggregated at trial level (<120, 120–124, 125–129, 130–135, and ≥135 mm Hg). Subgroup analysis was also performed for type of drug, categorised as beta-blocker (BB), renin-angiotensin-aldosterone system (RAAS) inhibitor, and any other type of drug. Only placebo-controlled trials were included in the latter analysis because trials comparing two active treatments would not fit into this categorisation. Further sub-group analyses were performed for hypertension at baseline, NYHA class at baseline, age and duration of follow-up as requested during the peer-review process. For hypertension, trials were split into two categories using a threshold of 50% for prevalence of baseline hypertension; for NYHA class, trials were divided into two categories according to the class in which most of the patients were at baseline (class 1/2 versus class 3/4); for follow-up duration, trials were split into two categories using a threshold of 18 months, which was the median of the mean follow-up duration of the included trials; and for age, trials were split into two categories using a threshold of 65 years-old, as this was the median of the mean age of included trials. These additional analyses were reported in Supplemental Data.

Random-effect meta-analyses with inverse variance weighing were used to calculate summary estimates with 95% CI for all outcomes, and Restricted Maximum Likelihood (REML) estimators were chosen as they strike a good balance between unbiasedness and efficiency.[25] Heterogeneity between individual studies was quantified using Cochran’s Q test for the estimate (QE) and $I^2$ statistic with respective p-values. For subgroup analyses, heterogeneity between sub-groups was quantified using Q test for the model (QM) with respective p-value.

Meta-regression using REML estimators was performed to investigate whether there was a correlation between the relative risk (RR) for each clinical outcome and the change in SBP between study groups. The RR for primary and secondary outcomes was regressed against the difference between the change in SBP in the intervention and control groups. All p-values were
calculated from two-tailed tests, with values below 5% considered statistically significant. All analyses were performed using the ‘metafor’ package for R version 3.2.0.

**Ethics and Confidentiality**

This study involved secondary analysis of existing and anonymised data and it did not involve recruitment of patients or access to patient identifiable information.

**Results**

A total of 37 trials (91,950 patients) of BP-lowering drugs were identified as potentially eligible for investigation of at least one of the three study aims (eTable 1 and eTable 2 in Supplemental Data). The trials covered a time span from 1986 to 2017 and overall included participants from all five continents. The follow-up duration ranged between 10 and 56 months, with a mean of 29 months. Five trials included three study arms whilst the remaining had two-study arms: 8 trials tested beta-blocker against placebo; 6 tested angiotensin-converting enzyme inhibitor/angiotensin receptor blocker against placebo; 3 trials tested mineralocorticoid receptor antagonist against placebo; 3 trials tested calcium-channel blocker against placebo; 2 trials compared beta-blocker with angiotensin-converting enzyme inhibitor; 7 compared different doses or drugs within the same class of beta-blocker or angiotensin-converting enzyme inhibitor; 3 trials compared isosorbide dinitrate-hydralazine with placebo or alternative treatment; 1 trial tested angiotensin receptor blocker against standard treatment; and the remaining 4 trials studied aliskiren, omapatrilat, sacubitril-valsartan and bosentan.

Four trials were conducted in patients with HFpEF, 30 trials the remaining were conducted in patients with HFrEF and 3 trials included a mix of both. J-CHF[21] did not report any of the primary or secondary outcomes considered in this meta-analysis and was therefore not included in any of the quantitative analyses. CIBIS II[26] did not report baseline or achieved BP and hence it was also not included in the quantitative analysis.
Thirty-three studies had a low risk of bias (eTable 3 in Supplemental Data). Two studies were considered to have an unclear risk of bias, because they did not detail randomisation method and allocation concealment,[27,28] and a further two were considered to have moderate risk of bias because they were open-label.[29,30]

**Aim 1: Effect on BP**

Although baseline BP was reported in 35 trials, only 20 trials reported achieved BP in enough detail to be included in the meta-analysis, two of which contributed with two study arms.[23,31] Treatment with BP-lowering drugs resulted in a significant 2.0 mmHg (95% CI [−2.9, −1.1]) reduction in SBP when all trials where considered and 2.4 mmHg (95% CI [−3.2, −1.5]) reduction in SBP when only placebo-controlled trials where included but with significant heterogeneity between trials which was largely driven by a single trial – MERIT-HF (Figure 2). There was no significant change in SBP amongst trials comparing two active treatments. The heterogeneity on average SBP reduction amongst placebo-controlled trials was not explained by baseline SBP (QM= 0.42, p=0.518) (Figure 3 and eFigure 1) but, there was suggestive evidence for differential effects by drug classes, with RAAS inhibitors reducing SBP by 3.2 mmHg (95% CI [−4.0, −2.4]), whilst BB appeared to have a neutral effect on SBP. However, there was no heterogeneity in sensitivity analysis excluding the outlier trial MERIT-HF (eFigure 2 in Supplemental Data). Other drug classes were grouped together and achieved a SBP reduction of 2.4 mmHg (95% CI [−3.8, −1.3]) (Figure 4 with more details in eFigure 3 in Supplemental Data).

**Aim 2: Effect on clinical outcomes according to BP change**

Clinical outcomes were variably reported, with 35 trials reporting all-cause mortality, 27 trials reporting CV mortality, 26 trials reporting HF hospitalisation, and 20 reporting adverse events
leading to treatment discontinuation. With the data available for each outcome, we performed meta-regression to investigate whether the magnitude of the BP change between treatment arms was associated with all-cause mortality, CV mortality, and HF hospitalisation. Total, specific and serious adverse events were inconsistently reported, and the only variable related to adverse events that was suitable for analysis and reported in a sufficient number of trials was adverse events leading to treatment discontinuation. Overall, there was no significant association between the trial-level magnitude of BP change and risk of all-cause mortality, CV mortality, HF hospitalisation or adverse events leading to treatment discontinuation, but there was substantial heterogeneity (Figure 5). To investigate whether this could be due differences in LVEF across trials, we performed stratified analysis by mean trial-level LVEF (below 30% and equal/above 30%) for all outcomes (eFigures 4 to 7 in Supplemental data) but there was no apparent difference between the subgroups of LVEF for all outcomes.

**Aim 3: Effect on clinical outcomes according to baseline BP**

Trial-level mean baseline SBP ranged from 116 to 139 mmHg and therefore, it was divided into 5-mmHg categories: less than 120 mmHg, 120-124 mmHg, 125-129 mmHg, 130-134 mmHg and 135 mmHg or more. There was no evidence of significant heterogeneity between categories of mean baseline SBP aggregated at trial level for the effect of treatment with drugs with BP-lowering properties on all-cause mortality, CV mortality and HF hospitalisation (Figure 6). There was significant heterogeneity between SBP strata for adverse events leading to treatment discontinuation driven by the significantly lower relative risk of events in the SBP <120 mmHg category, which only included a single small trial (Figure 6). Heterogeneity was no longer present when sensitivity analysis was performed excluding that category with only one relatively small trial (eFigure 12 in Supplemental Data). Although not the main focus of this analysis, treatment with drugs with BP-lowering properties significantly decreased the relative
risk of CV mortality and HF hospitalisation by about 10%, but they did not significantly influence all-cause mortality or adverse events leading to treatment discontinuation (Figure 6 and eFigures 8 to 11 in Supplemental Data).
Discussion

This systematic review and meta-analysis showed that treatment with drugs with BP-lowering properties results in a small decrease (about 2 mmHg) in SBP with no evidence of heterogeneity across strata of baseline SBP aggregated at trial-level. Furthermore, there was no evidence that the relative risk reduction afforded by treatment for all-cause mortality, CV mortality and HF hospitalisation was significantly different across categories of baseline SBP. There was also no strong evidence for heterogeneity of effects on adverse events leading to treatment discontinuation by baseline SBP strata. However, published information was insufficient to thoroughly investigate the effect of drugs on BP and its association with a wider range of clinical outcomes. Indeed, information on specific outcomes such as stroke and MI, which are more likely to show a relationship with BP changes, was reported only in a few trials and meta-regression performed for less specific outcomes, such as all-cause mortality, CV mortality and adverse events leading to treatment discontinuation did not show significant associations between the magnitude of BP reduction achieved in each trial and risk of such outcomes. There was substantial heterogeneity in all analyses, but data aggregated at trial-level did not allow adequately exploring sources of heterogeneity.

The longstanding controversy on whether drugs with BP-lowering properties actually reduce SBP in patients with HF remains far from being resolved. Our meta-analysis suggested that there was a small decrease in SBP (around 2.5 mmHg in placebo-controlled trials), which is consistent with findings in the general population for a similar range of baseline SBP. Indeed, a landmark meta-analysis[32] that included 354 trials of anti-hypertensive drugs reported a reduction in 2 to 5 mmHg in SBP in patients with baseline SBP below 120 mmHg. Although our estimate is at the lower end of that range, this does not appear to be due to drug dosing because the doses used in HF RCTs were at least as high as the standard doses considered in the aforementioned meta-analysis. A possible explanation is the fact that trials of drugs with
BP-lowering properties in HF patients allow concomitant treatment with other drugs that also have BP-lowering properties, contrary to what happens in trials of anti-hypertensive medications.

Further analyses by type of drug suggested that RAAS inhibitors achieved the greatest SBP reduction, whilst BB had no significant impact on SBP. However, there were only 4 trials including BB and our sensitivity analysis suggested that the overall SBP change across BB trials was skewed by the heavy weight of the MERIT-HF trial, in which the SBP increased in the metoprolol arm compared to placebo arm.[33] Putting this outlier trial aside, our findings are in keeping with evidence in the general population, where BB tend to be on average less effective in lowering BP.[17]

Our findings suggesting that the relative effect of drugs with BP-lowering properties on outcomes investigated were broadly consistent across the spectrum of baseline SBP are in keeping with previous studies that reported similar relative risk reductions across strata of baseline BP in non-HF trials.[15,34] This together with previous evidence that patients in the lowest baseline BP stratum experienced a greater absolute risk of CV events and HF hospitalisation[15,34-36] provides reassurance to clinicians and argues against overzealous treatment in that group of patients. Furthermore, our finding that the relative risk of adverse events leading to treatment discontinuation was similar across the range of baseline SBP was also in line with previous studies, which showed that BP-lowering treatment did not increase the risk of adverse events in comparison to placebo in patients with the lowest baseline BP (SBP below 120 mmHg).[37] Therefore, treatment discontinuation in those patients might be related to the severity of the underlying illness rather than to the extent of BP reduction and treatment with the study drug.

Our findings lend further support to the safety of drugs with BP-lowering properties in patients with HF regardless of baseline SBP, the clinical implications of which cannot be
overlooked. Indeed, concerns about potentially harmful consequences of further BP reduction in patients with HF who already have low baseline BP seem common causes of noncompliance with therapeutic recommendations.[38,39] Paradoxically, patients with the lowest BP, who tend to have the highest absolute risk of CV events and thus experience a greater absolute risk reduction, are the least likely to be titrated to target doses.[40-42] Furthermore, the absence of an association between treatment effects and magnitude of BP reduction observed in our meta-regression is in keeping with evidence suggesting that the main mechanisms of action of guideline-recommended drugs in HF are related to neurohumoral modulation and thus independent of their BP-lowering properties.[43] This underpins why despite considerable uncertainty regarding BP management in HF, guidelines recommend titrating HF drugs, including new agents (e.g. combined neprilysin-angiotensin receptor antagonist),[44] according to tolerance irrespective of achieved BP.[45]

Despite these reassuring findings, the question of the appropriate intensity or threshold of BP lowering in those with chronic HF, in particular when baseline BP is low, could not be answered in this study, largely because of missing information from several trials. In the absence of such direct evidence, we are left with contradictory evidence provided by individual studies or need to extrapolate findings from non-HF populations. Neither of these options seems adequate to fully understand how agents with BP-reducing properties influence BP in patients with HF and whether this has positive and/or negative consequences on clinical outcomes. HF patients have several features that render extrapolation from the general population unreliable. For instance, their average BP tends to be substantially lower[15,16] and outcomes that are strongly associated with high BP such as stroke and MI tend to be less common in such patients who tend to suffer from several CV and other types of comorbidities.[46-50]
In addition, observational studies in patients with HF have shown a strong interaction between BP and left ventricular function.[51] How such differences might impact on outcomes when BP is intentionally or unintentionally reduced to very low levels remains unclear. Although stratified analyses have been attempted in individual trials, these are typically limited by lack of power to detect small but clinically important differences, particularly in subgroup analyses including more than one variable to test potential interactions.[34,52-54]

The main limitations of this aggregate-data meta-analysis are related to the lack of data on baseline and achieved BP in published trial reports. At a minimum this is likely to have reduced study power to detect important associations.[55] The lack of relevant information from several trials could also affect the validity of our overall conclusions. A related limitation is that aggregate-data meta-analyses have limited ability in adjusting for multiple variables to explore potential sources of heterogeneity. Inconsistency in reporting clinical outcomes and adverse events also prevented analysing the impact of BP reduction on other clinical outcomes that could be potentially relevant, including MI, stroke, and renal impairment. Several of these limitations can be addressed in future collaborative work that seeks individual participant data (IPD) from all relevant trials with collection of information on a range of baseline and follow-up information. Such a collaboration could also indirectly help answers questions relevant to blood pressure control in other populations, when combined with IPD from hypertension trials that is coordinated by the Blood Pressure Lowering Treatment Trialists’ Collaboration.[56]

**Conclusion**

This systematic review and meta-analysis suggested that treatment with drugs with BP-lowering properties, particularly with RAAS inhibitors, resulted in a small but significant decrease in SBP in patients with HF irrespective of baseline SBP. In addition, there was no evidence that the effects of drugs with BP-lowering properties in patients with chronic HF
differed across the range of baseline SBP, which supports the efficacy and safety of those drugs in patients with low baseline BP. However, information from published trials was insufficient to adequately investigate the potential mediating role of BP on outcomes in patients with HF.
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on major cardiovascular events according to baseline blood pressure: meta-analysis of
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trials of blood-pressure-lowering treatments. World Health Organization-International
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Figure legends

Figure 1: PRISMA Flow Diagram, explaining in detail the process of study screening and selection.

Figure 2: Meta-analysis of the effect of blood pressure-lowering treatment in HF on systolic blood pressure stratified by study type. Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each trial and subgroup. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. Studies were separated into those that compared two active treatments and those that compared one active treatment with placebo. BP diff, difference between achieved and baseline systolic blood pressure

Figure 3: Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by baseline systolic blood pressure. Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. Only studies that compared active treatment with placebo were included. Further details for each trial provided in eFigure 1 in Supplemental Data. SBP, systolic blood pressure

Figure 4: Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by drug class. Mean differences between the change in systolic blood
pressure in the intervention group versus the control group are displayed for each drug class. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. Other drugs include calcium-channel blockers, alpha-blockers, and hydralazine-isosorbide dinitrate. Only studies that compared active treatment with placebo were included. Further details for each trial provided in eFigure 3 in Supplemental Data. SBP, systolic blood pressure; RAAS, renin-angiotensin-aldosterone system

**Figure 5:** Meta-regression of risk ratio for all-cause mortality, cardiovascular mortality, HF hospitalisation and adverse events leading to treatment discontinuation according to the difference in systolic blood pressure between study groups. Risk ratios for each clinical outcome (all-cause mortality, cardiovascular mortality, heart failure hospitalisation and adverse events leading to treatment discontinuation) were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. SBP, systolic blood pressure

**Figure 6:** Meta-analysis of the effect of blood pressure-lowering treatment on clinical outcomes stratified by baseline systolic blood pressure. Risk ratios and 95% confidence intervals are displayed for each clinical outcome (all-cause mortality, CV mortality, HF hospitalisation and adverse events leading to treatment discontinuation) for each strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. Further details including absolute number of events provided in eFigures 7 to 11 in Supplemental Data. SBP, systolic blood pressure
Figures

Figure 1: PRISMA Flow Diagram

Records identified through database searching (n = 30,212)
Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 20,142)

Records screened (title and abstract) (n = 20,142)

Records excluded (n = 19,223)

Full-text articles assessed for eligibility (n = 919)

Studies included in qualitative synthesis (n = 37)

Studies included in quantitative synthesis (meta-analysis) (n = 35)

Full-text articles excluded, with reasons:
(n = 284 papers had less than 300 patient-years follow-up;
n = 223 papers had less than 600 pts;
n = 111 tested different interventions or were not in HF pts;
n = 60 papers were reviews or observational studies;
n = 204 papers were sub-studies or ad-hoc analysis of included trials)
Figure 2: Meta-analysis of the effect of blood pressure-lowering treatment in HF on systolic blood pressure stratified by study type

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<tr>
<td>SENIORS, 2005</td>
</tr>
<tr>
<td>PEP-CHF, 2006</td>
</tr>
<tr>
<td>COPERNICUS, 2001</td>
</tr>
<tr>
<td>Subgroup total (Q = 91.38, p = 0.000; I² = 74.8%)</td>
</tr>
</tbody>
</table>

All studies (Q = 254.33, p = 0.000; I² = 88.7%)
Between studies (Q = 2.40, p = 0.121)

Mean Difference

-10  -5  0  5
**Figure 3:** Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by baseline systolic blood pressure

<table>
<thead>
<tr>
<th>Baseline SBP</th>
<th>N trials</th>
<th>MD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;120 mmHg</td>
<td>4</td>
<td>-2.63 [-4.25, -1.00]</td>
</tr>
<tr>
<td>SBP 120–124 mmHg</td>
<td>6</td>
<td>-2.82 [-3.83, -1.80]</td>
</tr>
<tr>
<td>SBP 125–129 mmHg</td>
<td>2</td>
<td>-0.77 [-5.18, 3.64]</td>
</tr>
<tr>
<td>SBP 130–134 mmHg</td>
<td>2</td>
<td>-2.66 [-5.68, 0.37]</td>
</tr>
<tr>
<td>SBP &gt;135 mmHg</td>
<td>3</td>
<td>-2.64 [-3.90, -1.37]</td>
</tr>
</tbody>
</table>

All studies (Q = 91.38, p = 0.000; $I^2 = 74.8\%$)
Between studies (Q = 0.11, p = 0.735)

Mean Difference (MD)
Figure 4: Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by drug class

**Systolic Blood Pressure by drug class**

<table>
<thead>
<tr>
<th>Baseline SBP</th>
<th>N trials</th>
<th>MD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>4</td>
<td>−1.04 [−3.04, 0.97]</td>
</tr>
<tr>
<td>RAAS inhibitors</td>
<td>7</td>
<td>−3.23 [−4.01, −2.44]</td>
</tr>
<tr>
<td>Other drugs</td>
<td>6</td>
<td>−2.55 [−3.76, −1.33]</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td>−2.39 [−3.24, −1.54]</td>
</tr>
</tbody>
</table>

All studies (Q = 91.38, p = 0.000; $I^2 = 74.8\%$)

Between studies (Q = 5.66, p = 0.059)
Figure 5: Meta-regression of risk ratio for all-cause mortality, cardiovascular mortality, HF hospitalisation and adverse events leading to treatment discontinuation according to the difference in systolic blood pressure between study groups.

**All-cause mortality**

RR = 0.99; 95%CI [0.96 - 1.02]; p = 0.593; I² = 78.92%

**Cardiovascular mortality**

RR = 1.01; 95%CI [0.97 - 1.04]; p = 0.750; I² = 72.20%

**Heart failure hospitalisation**

RR = 1.01; 95%CI [0.97 - 1.06]; p = 0.602; I² = 76.68%

**Adverse events**

RR = 1.00; 95%CI [0.92 - 1.07]; p = 0.922; I² = 86.65%
**Figure 6:** Meta-analysis of the effect of blood pressure-lowering treatment on clinical outcomes stratified by baseline systolic blood pressure

### All-cause mortality

<table>
<thead>
<tr>
<th>Baseline SBP</th>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;120 mmHg</td>
<td>6</td>
<td>1.20 [0.91, 1.57]</td>
</tr>
<tr>
<td>SBP 120–124 mmHg</td>
<td>9</td>
<td>0.92 [0.81, 1.05]</td>
</tr>
<tr>
<td>SBP 125–129 mmHg</td>
<td>6</td>
<td>0.84 [0.72, 0.98]</td>
</tr>
<tr>
<td>SBP 130–134 mmHg</td>
<td>4</td>
<td>1.10 [0.76, 1.64]</td>
</tr>
<tr>
<td>SBP &gt;135 mmHg</td>
<td>4</td>
<td>0.90 [0.71, 1.17]</td>
</tr>
</tbody>
</table>

*Between studies (X² = 31.67, p = 0.029; I² = 64.7%) Between studies (X² = 5.05, p = 0.26) * 

<table>
<thead>
<tr>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.07</td>
<td>1.00</td>
</tr>
<tr>
<td>1.00</td>
<td>1.22</td>
</tr>
<tr>
<td>1.62</td>
<td>1.82</td>
</tr>
</tbody>
</table>

### Cardiovascular mortality

<table>
<thead>
<tr>
<th>Baseline SBP</th>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;120 mmHg</td>
<td>2</td>
<td>0.89 [0.76, 1.06]</td>
</tr>
<tr>
<td>SBP 120–124 mmHg</td>
<td>5</td>
<td>0.82 [0.69, 0.96]</td>
</tr>
<tr>
<td>SBP 125–129 mmHg</td>
<td>5</td>
<td>0.82 [0.69, 0.96]</td>
</tr>
<tr>
<td>SBP 130–134 mmHg</td>
<td>4</td>
<td>0.80 [0.68, 1.02]</td>
</tr>
<tr>
<td>SBP &gt;135 mmHg</td>
<td>4</td>
<td>0.86 [0.68, 1.11]</td>
</tr>
</tbody>
</table>

*Between studies (X² = 3.80, p = 0.434) Between studies (X² = 5.85, p = 0.019) * 

<table>
<thead>
<tr>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>1.00</td>
</tr>
<tr>
<td>0.07</td>
<td>1.22</td>
</tr>
<tr>
<td>0.84</td>
<td>1.48</td>
</tr>
</tbody>
</table>

### Heart failure hospitalisation

<table>
<thead>
<tr>
<th>Baseline SBP</th>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;120 mmHg</td>
<td>2</td>
<td>1.00 [0.81, 1.24]</td>
</tr>
<tr>
<td>SBP 120–124 mmHg</td>
<td>8</td>
<td>0.80 [0.64, 1.01]</td>
</tr>
<tr>
<td>SBP 125–129 mmHg</td>
<td>4</td>
<td>0.80 [0.64, 1.01]</td>
</tr>
<tr>
<td>SBP 130–134 mmHg</td>
<td>4</td>
<td>0.80 [0.64, 1.01]</td>
</tr>
<tr>
<td>SBP &gt;135 mmHg</td>
<td>4</td>
<td>0.80 [0.64, 1.01]</td>
</tr>
</tbody>
</table>

*Between studies (X² = 50.22, p = 0.000; I² = 82.2%) Between studies (X² = 5.85, p = 0.176) * 

<table>
<thead>
<tr>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35</td>
<td>1.00</td>
</tr>
<tr>
<td>0.86</td>
<td>1.22</td>
</tr>
<tr>
<td>1.00</td>
<td>1.82</td>
</tr>
</tbody>
</table>

### Adverse events

<table>
<thead>
<tr>
<th>Baseline SBP</th>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;120 mmHg</td>
<td>1</td>
<td>1.00 [0.71, 1.40]</td>
</tr>
<tr>
<td>SBP 120–124 mmHg</td>
<td>6</td>
<td>1.29 [0.96, 1.79]</td>
</tr>
<tr>
<td>SBP 125–129 mmHg</td>
<td>1</td>
<td>1.32 [1.14, 1.53]</td>
</tr>
<tr>
<td>SBP 130–134 mmHg</td>
<td>3</td>
<td>1.58 [1.26, 1.96]</td>
</tr>
<tr>
<td>SBP &gt;135 mmHg</td>
<td>3</td>
<td>1.30 [1.05, 1.61]</td>
</tr>
</tbody>
</table>

*Between studies (X² = 7.37, p = 0.118) Between studies (X² = 7.37, p = 0.118) * 

<table>
<thead>
<tr>
<th>N trials</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35</td>
<td>1.00</td>
</tr>
<tr>
<td>0.86</td>
<td>1.22</td>
</tr>
<tr>
<td>1.00</td>
<td>1.82</td>
</tr>
<tr>
<td>1.82</td>
<td>2.72</td>
</tr>
</tbody>
</table>