Original Article

Efficacy and Safety of Quarter-Dose Blood Pressure–Lowering Agents

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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See Editorial Commentary, pp 32–34

Abstract—There is a critical need for blood pressure–lowering strategies that have greater efficacy and minimal side effects. Low-dose combinations hold promise in this regard, but there are few data on very-low-dose therapy. We, therefore, conducted a systematic review and meta-analysis of randomized controlled trials with at least one quarter-dose and one placebo and standard-dose monotherapy arm. A search was conducted of Medline, Embase, Cochrane Registry, Food and Drug Administration, and European Medicinal Agency websites. Data on blood pressure and adverse events were pooled using a fixed-effect model, and bias was assessed using Cochrane risk of bias. The review included 42 trials involving 20 284 participants. Thirty-six comparisons evaluated quarter-dose with placebo and indicated a blood pressure reduction of −4.7/−2.4 mm Hg (P<0.001). Six comparisons were of dual quarter-dose therapy versus placebo, observing a −6.7/ −4.4 mm Hg (P<0.001) blood pressure reduction. There were no trials of triple quarter-dose combination versus placebo, but one quadruple quarter-dose study observed a blood pressure reduction of −22.4/−13.1 mm Hg versus placebo (P<0.001). Compared with standard-dose monotherapy, the blood pressure differences achieved by single (37 comparisons), dual (7 comparisons), and quadruple (1 trial) quarter-dose combinations were +3.7/+2.6 (P<0.001), +1.3/−0.3 (NS), and −13.1/−7.9 (P<0.001) mm Hg, respectively. In terms of adverse events, single and dual quarter-dose therapy was not significantly different from placebo and had significantly fewer adverse events compared with standard-dose monotherapy. Quarter-dose combinations could provide improvements in efficacy and tolerability of blood pressure–lowering therapy. **(*Hypertension*. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.09202.) • Online Data Supplement**

Key Words: blood pressure ■ hypertension ■ meta-analysis ■ pharmacology ■ safety

High blood pressure is the leading cause of preventable morbidity and mortality globally.[1] Yet control of blood pressure is poor, with only 1 in 3 people on treatment achieving blood pressure targets.[2–5] The largest global survey of hypertension practice showed that while 88% of those aware of hypertension receive some pharmacological treatment, only 34% of those treated were controlled. Overall, 61% of those treated only received monotherapy[5] even though combination therapy is usually required to achieve acceptable levels of blood pressure control.[6] In the absence of more effective new blood pressure drug classes, better blood pressure control is likely to require more use of existing agents in combination.

Minimization of side effects is critical for long-term treatment of a largely asymptomatic condition such as high blood pressure. Several studies suggest that low-dose combinations may provide the best ratio of side effects to blood pressure reduction, because at low doses most side effects are avoided and most benefit is realized.[7] Given that blood pressure dose–response gradients are typically shallow above quarter standard dose,[7] combinations containing quarter doses of several antihypertensive agents may be of particular benefit. One small trial reported in 2007 a large blood pressure reduction from quadruple quarter-dose combination therapy compared with monotherapy,[8] and a small trial recently completed also showed large reductions compared with

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placebo.[9] We, therefore, conducted a systematic review of randomized trials of quarter-dose blood pressure–lowering agent(s) to place these trials in the context of all evidence concerning quarter-dose therapy and to assess the potential clinical role of quarter-dose monotherapy and combination therapy.

Methods

The review methods are detailed in the protocol (online-only Data Supplement) and were written in accordance with the preferred Cochrane Collaboration–reporting items for systematic reviews and meta-analyses.

Search Strategy and Selection Criteria

Electronic searches were conducted in EMBASE (inception to June 2016), MEDLINE (inception to June 2016), Cochrane Central Registry of Controlled Trials (inception to June 2016) and the Food and Drug Administration and European Medicines Agency websites. Searches of trial registers were performed for any ongoing trials including World Health Organization International Clinical Trials Registry Platform, Australia New Zealand Clinical Trial Register, and Clinical Trials Registry – India. Retrieval of studies from reference lists of key clinical trials, systematic reviews, and published articles was also undertaken. The Medline search has been included in the online-only Data Supplement).

During the initial phase of the search, 2 reviewers (A.B., M.C.) independently performed the searches assessing titles and abstracts, excluding any studies that did not qualify. Both the reviewers then inspected the full text of those selected articles identified in the initial phase. A third reviewer (A.R.) resolved any disagreement on the included articles.

Types of Studies

Randomized controlled trials (either parallel or crossover) with a treatment and follow-up of at least 2 weeks were sought. Uptitration studies must have had blood pressure or safety data for at least the first 2 weeks before titration occurred. Studies were included only if there were efficacy or safety data that were measured for at least 1 of the 5 major classes of blood pressure–lowering medications: calcium channel blockers, β-blockers, angiotensin receptor II antagonists, angiotensin-converting enzyme inhibitors, and thiazide diuretics (TZs). All included medications were registered for use by the Food and Drug Administration or European Medicines Advisory and indicated for the treatment of hypertension.

Studies were eligible for inclusion if participants were ≥18 years of age and written and published in English. No study was excluded on the basis of baseline blood pressure, presence or absence of disease, or year performed. Studies were only considered if at least one arm was allocated quarter-dose therapy (with one or multiple agents) and at least one arm allocated placebo or standard-dose monotherapy (to allow comparison with the 2007 trial[8]). In this review, the standard dose was defined as the most reported usual maintenance dose recorded by the British National Formulary, Martindale and Monthly Index of Medical Specialties, similar to the method of Law et al.[7] The World Health Organization Defined Daily Dose was used as a tiebreaker if no consensus was found. If there was still no consensus between the selected pharmacopoeias, the most reported dose was judged as the standard dose (Table 1). However, there were 2 exceptions. A quarter dose of hydrochlorothiazide of 6 and 5 mg were used for the studies by Jounela et al[10] and Pool et al[11] because there was no 6.25 mg arm.

Efficacy was assessed using the mean absolute difference between the intervention and control deltas (mean changes in systolic blood pressure [SBP] and diastolic blood pressure [DBP] from baseline to end of study). Safety was defined as adverse events (all and side effect related, as defined by each trial) at follow-up, and change in biochemical data (potassium and uric acid) from baseline to follow-up.

Data Extraction and Risk of Bias

Two reviewers (A.B. and M.C.) independently extracted data using a standard extraction form. The variables extracted included study design, sample size, mean age, percentage of female patients, randomization, blinding, intervention, dose(s), follow-up, percent lost to follow-up, and study outcomes. In studies where numeric blood pressure changes were not presented (n=5), a visual estimate was made based on the figures provided. Both reviewers independently estimated the difference, with the average of the 2 being used.

The 2 reviewers (A.B. and M.C.) also independently assessed the risk of bias in each trial based on the Cochrane Collaboration's risk of bias tool[12] (Figure S8 in the online-only Data Supplement). This estimates the risk based on sequence generation, allocation concealment, selective outcome reporting, potential threats to validity, blinding of participants, personnel and outcome assessors, and incomplete data. The risk of bias in each included trial was reported as low, unclear, or high. A third reviewer (A.R.) resolved any differences.

Data Analysis

One reviewer (A.B.) entered the data into Microsoft Excel and then into the Comprehensive Meta-analysis Software.[13] A second reviewer (H.-M.D.) checked the data for accuracy with a third reviewer (A.R.) resolving any disagreements. The data were analyzed according to intention to treat when possible. Binary outcomes were analyzed using the Mantel–Haenszel approach and summarized as risk ratios with 95% confidence intervals (CIs). Continuous outcomes were summarized as difference in means with 95% CIs. Individual trial results were pooled using fixed-effect meta-analysis with inverse variance weighting. Heterogeneity was quantified by Q test, I^2, and τ statistics[14,15] (Table S2). Publication bias was assessed and reported using a funnel plot (Figure S6).

Given the role of baseline blood pressure in determining the extent of blood pressure reduction from blood pressure–lowering drugs[16] and because there was heterogeneity across trials in mean baseline levels, blood pressure was standardized to that expected from a baseline of 150/95 mm Hg. This involved a 0.1 mm Hg reduction in a given study's SBP change score for each mm Hg baseline SBP over 150 mm Hg, and a 0.1 mm Hg increase for each mm Hg baseline SBP below 150 mm Hg. Similarly, 0.11 mm Hg was subtracted or added for each mm Hg DBP above or below 95 mm Hg.[16] If no baseline blood pressure was reported for a given trial, then for that comparison, the mean of the included trials was used.

To analyze all randomized comparisons of quarter-dose therapy versus placebo and versus standard-dose monotherapy, some participants contributed to more than one analysis, and not all comparisons within multiarm trials were included. For example, Frishman et al[17] conducted a 4×3 factorial dose–response trial of 2 agents, with 12 cells labeled A through L in Table 2.

These cells contributed to the different analyses as shown in Table 3.

Variability data were absent in 12 trials, in which cases the SD was imputed as a pooled SD derived from other trials with similar study arms.[18] Although not ideal, this approach has been used in such occasions as outlined by the Cochrane Handbook of Systematic Reviews of Interventions.[19] All biochemical data reported had missing variability data, and, thus, a common SD was used, derived for potassium from the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack)[20] and for uric acid from the review by Weidmann.[21] Meta-regression was used to undertake subgroup analysis of the effect that age and treatment period (>6 weeks) had on efficacy. Also, 3 sensitivity analyses were undertaken, to compare fixed-effect versus random-effects models, standardized versus nonstandardized blood pressure differences, and the impact of imputation for studies with missing variability data.

Results

Search Results

The initial search identified 1730 studies, with 1554 screened after exclusion of duplicate citations (Figure 1). Fifty-eight studies with extractable data met the inclusion criteria, and 16 studies were excluded after full-text evaluation. A total of 42 studies were included in the meta-analysis (online-only Data Supplement).

Study Characteristics

Table S1 details the characteristics of included studies. On average, the trials were published 17 years ago, and 85% of

Table 1. Standard Dosing Table for Included Trial Medications

Medication	WHO Defined Daily Dose*	BNF Dose Range	Martindale Dose Range	MIMS Dose Range	Standard-Dose Selected for This Review
β-Blocker, mg					
Atenolol	75	25–50	50–100	50–100	50
Metoprolol	150	100–200	100–200	100–200	100
Bisoprolol	10	10	10	10	10
Carvedilol	37.5	25	25	25–50	25
Nebivolol	5	5	5- 40	5	5
Penbutolol	40	…	20–40	…	40
CCB, mg					
Amlodipine	5	5–10	5–10	2.5–10	5
Lercanidipine	10	10–20	10–20	10	10
Nitrendipine	20	…	20	…	20
Verapamil	240	240–480	240	240	240
ACE inhibitor, mg					
Captopril	50	25–150	100–150	50–100	100
Benazepril	7.5	…	20–40	…	20
Fosinopril	15	10–40	10–40	10–40	10
Lisinopril	10	20	20	10–20	20
Quinapril	15	20–40	20–40	10–40	20
Trandolapril	2	1–2	1–2	1–2	2
Enalapril	10	20	10–20	10–40	20
ARB, mg					
Valsartan	80	80	80–160	80	80
Irbesartan	150	150–300	150	150	150
Candesartan	8	8	8	8–16	8
Telmisartan	40	40	20–80	40	40
Olmesartan	20	10–20	20	20	20
Azilsartan	…	40	40	…	40
TZ, mg					
Hydrochlorothiazide	25	…	25–50	…	25
Bendroflumethiazide	2.5	2.5	2.5	…	2.5

Standard dose was defined as the most reported usual maintenance dose recorded by the BNF, Martindale, and MIMS. If no consensus was found, the World Health Organization–defined daily dose was used as a tiebreaker. If there was still no consensus between the selected pharmacopoeias, the lowest, most reported, dose was judged as the standard dose. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNS, British National Formulary; CCB, calcium channel blocker; MIMS, monthly index of medical specialties; and TZ, thiazide.

trials had eligibility criteria based solely on DBP. Of the 42 studies, 38 reported quarter-dose monotherapy, 7 reported dual quarter-dose combination therapy, and 2 reported quadruple quarter-dose therapy compared with either placebo or each component at a standard dose. Follow-up ranged from 4 to 12 weeks, averaging 7 weeks. Most studies were dose–response trials testing 3 to 4 doses of one agent versus placebo. Fourteen trials (included trials 8, 10, 12, 13, 15, 17, 18, 20, 21, 22, 24, 34, 35, and 37, for more details, please see online-only Data Supplement) were factorial dose–response trials, testing several doses of 2 agents. Only 1 out of the 42 studies did not have at least one arm containing standard-dose monotherapy, and all but 2 included a placebo control arm. Overall, there were 20 284 participants with a mean age of 54 years, 61% were men, and mean baseline blood pressure was 154/101 mm Hg.

Efficacy

Quarter-Dose Therapy Versus Placebo

The efficacy in blood pressure lowering of single quarter-dose therapy versus placebo was assessed in 4721 participants in 36 trials (Figure 2). Overall, placebo-corrected single quarter-dose therapy reduced blood pressure by −4.7 (95% CI, −5.4

Table 2. Factorial Dose–Response of 2 Agents

		Thiazide Dose		
		0	Quarter	1
β-Blocker dose	0	A	B	C
	Quarter	D	E	F
	1	G	H	I
	4×	J	K	L

to −3.9)/−2.4 (−2.8 to −1.9) mm Hg. There was broad consistency in treatment effect across the 5 major treatment classes (I^2 SBP: 3, DBP: 0), and each was separately significant except for calcium channel blockers.

Six trials measured the efficacy of dual quarter-dose therapy compared with placebo (Figure 2). All but one trial used a TZ diuretic in the dual quarter-dose combination. In the 312 participants assessed, the effect of the dual quarter-dose combination was an overall blood pressure drop of −6.7 (−8.6 to −4.8)/−4.4 (−5.5 to −3.3) mm Hg. There was some evidence of heterogeneity present across the different dual combinations (I^2 SBP: 18, DBP: 37). No studies measured triple quarter-dose therapy versus placebo. One study (included trial 40, for more details, please see online-only Data Supplement) measured efficacy of quadruple quarter-dose therapy versus placebo and showed an office blood pressure reduction of −22.4 (−28.3 to −16.5)/−13.1 (−17.3 to −8.8; Figure 2). This was the only trial to report effects on 24-hour blood pressure profile, with reductions in 24 hour, day-time, and night-time BP of −18.7/−14.2, −22.3/−15.3, and −10.4/−12.5 mm Hg, respectively.

Quarter-Dose Therapy Versus Standard-Dose Monotherapy

Figure 3 illustrates the comparisons of single, dual, and quadruple quarter-dose therapy compared with standard-dose monotherapy on blood pressure reductions. Single quarter-dose therapy was less efficacious than standard-dose monotherapy by 3.7 (3.0–4.5)/2.6 (2.2–3.1) mm Hg (I^2 SBP: 24.3; DBP: 10.2). Dual quarter-dose therapy showed an equivalent blood pressure–lowering effect compared with standard-dose monotherapy. Only one study[8] assessed blood pressure lowering with quadruple quarter-dose therapy versus standard-dose monotherapy and showed a substantially greater blood pressure reduction in the quarter-dose group of −13.1 (−20.1 to −6.1)/−7.9 (−12.1 to −3.7) mm Hg.

Safety and Tolerability

Adverse Events

Fifteen studies provided data on adverse events. Overall, compared with placebo, no significant difference in the risk of adverse events in the 14 single quarter-dose comparisons (relative risk, 1.0 [0.91–1.2], I^2: 20.8). This was also observed in 6 dual quarter-dose comparisons (0.93 [0.29–2.9]) and in a solitary quadruple (2.0 [0.2–20.2]) quarter-dose placebo comparison (Figure 4). Moreover, no individual medication class was associated with a greater risk of adverse events compared with placebo. Both single and dual quarter-dose therapy produced significantly fewer adverse events than standard-dose monotherapy (Figure 4). In terms of tolerability of quadruple quarter-dose therapy, in the 2007 trial compared with standard-dose therapy, the only information available was that therapy was well tolerated by all of the participants, and, in particular, there was no case of hypotension.(J. Feely, personal communication). In the 2017 trial, no patient withdrew because of side effects.[9] However, in each trial, treatment was for only 4 weeks and a total of 40 patients received quadruple quarter-dose therapy.

Table 3. Factorial Dose–Response Comparisons

Comparison	Cells Included in Comparison(s)
Quarter vs placebo	D vs A, B vs A
Quarter vs standard dose	B vs half (C+G), D vs half (C+G)
Dual quarter vs placebo	E vs A
Dual quarter vs standard dose	E vs C, E vs G

Biochemical Adverse Effects

Table 4 compares the mean difference from baseline to follow-up in biochemical measures, for placebo, single quarter-dose, dual quarter-dose, and standard-dose therapy. Overall, data on potassium concentrations were reported in 10 studies; of these, 8 were amenable to pooling. Compared with placebo, none of the single (n=5), dual (n=3), or quadruple (n=1) quarter-dose therapy comparisons showed a significant difference in potassium concentration. Treatment with TZ standard-dose monotherapy (n=4) resulted in a significantly greater reduction in potassium concentration compared with single quarter-dose TZ, dual quarter β-blockers+quarter TZ and dual quarter angiotensin-converting enzyme inhibitor+quarter TZ. Similar trends were seen in 2 trials reporting the proportion of patients below a certain potassium level (<3.5 mmol/L)[22] or the number of participants who developed a >0.05 mmol change in potassium concentration.[23]

Three studies reported data on uric acid concentrations in a format that allowed the data to be pooled. Compared with placebo, no significant differences were observed for single or dual quarter-dose treatment arms; however, quadruple quarter-dose therapy did result in a small increase compared with placebo (0.03, 95% CI, 0.001–0.04 mmol/L; P=0.003). Standard-dose TZ resulted in greater uric acid concentration versus single quarter-dose TZ, versus dual quarter angiotensin receptor II antagonists+quarter TZ and versus dual quarter β-blockers+quarter TZ. These findings are comparable to one trial that only reported percentage change from baseline.[24] There was a also a small difference in creatinine compared with quadruple quarter-dose therapy compared with placebo (4.4, 95% CI, 0.9–7.8 mmol/L; P=0.02), but no patient had more than a 12% increase.[9]

Effects on heart rate were generally not reported but were available for both quadruple quarter-dose combinations: Chow et al,[9] reported a reduction of 6.5 bpm (95% CI, 2.3–10.6) compared with placebo and Mahmud and Feely[8] reported a reduction from baseline of 6 SD 3 bpm.

Quality of Evidence

The Trim and Fill approach did not suggest evidence of publication bias (Figure S6). The risk of bias was assessed in all 42 studies (Figure S8). Overall, 8 studies described the method of

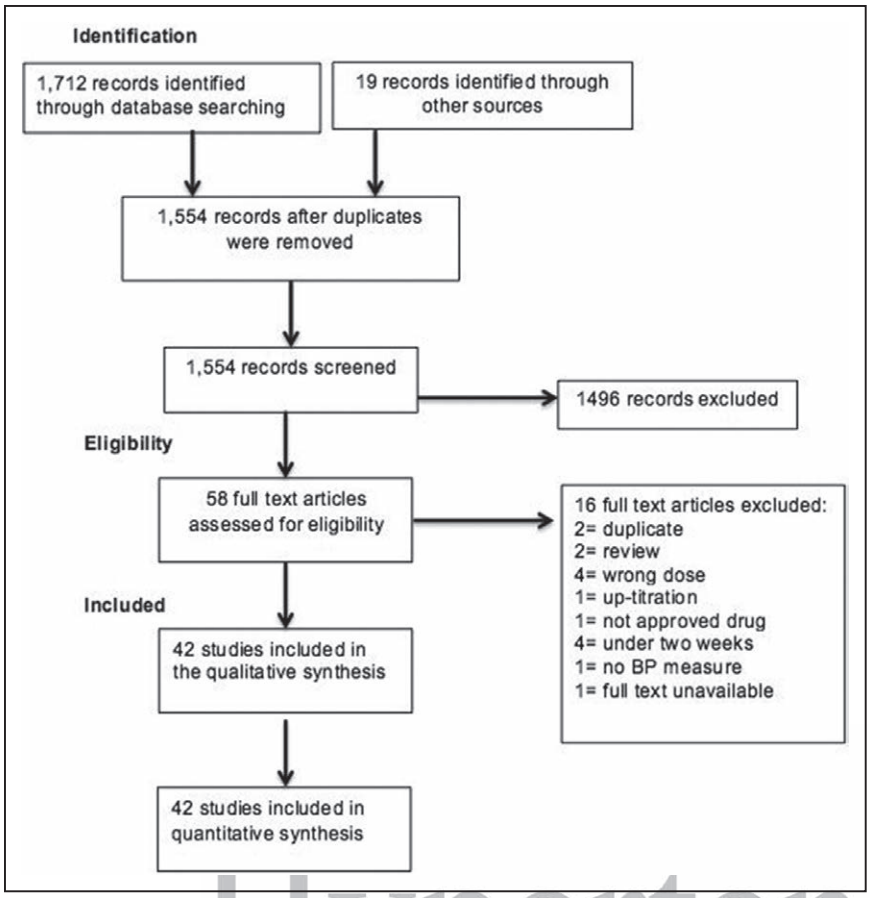

Figure 1. Study flow includes the number of articles identified, eligible, and included. BP indicates blood pressure.

sequence generation; 7 described the method of concealment and 28 described and dealt with missing data. In the absence of detailed study protocols, it was not possible to assess whether outcomes were selective. Likewise, other potential threats to validity could not be assessed. Blinding of participants and personnel was undertaken in some capacity for 41 trials (40 of which were double-blinded, 1 single blinded, and 1 open label).

Subgroup Analyses

Subgroup analyses undertaken using meta-regression did not suggest any significant correlation between DBP lowering and age (P=0.38) or >6 week treatment (P=0.18; Figure S7).

Sensitivity Analyses

The mean blood pressure reduction for a single quarter dose versus placebo was essentially the same using the random-effects model (−4.7 [−5.4 to −3.9]/−2.3 [−2.8 to −1.9] mm Hg), compared with the fixed-effect model (−4.7 [−5.4 to −3.9]/−2.4 [−2.8 to −1.9] mm Hg). Exclusion of studies with missing data on variability also did not substantially affect this estimate (−5.0 [−5.7 to −4.2]/−2.4 [−2.9 to −1.8] mm Hg). Finally, pooling of nonstandardized changes in blood pressure, rather than changes standardized to a baseline blood pressure of 150/95 mm Hg provided an overall estimate of −5.0 (−5.8 to −4.3)/−2.9 (−3.4 to −2.3) mm Hg for quarter-dose therapy versus placebo.

Discussion

This review is the first to compare quarter-dose therapy to both standard dose and placebo and indicates a potential clinical advantage in terms of reducing side effects and, with the use of quadruple combinations, increasing efficacy. Single quarter-dose therapy reduced blood pressure by ≈−4.7/−2.4 mm Hg compared with placebo (about half as much as standard-dose monotherapy), with no apparent side effects. Dual quarter-dose therapy had about the same efficacy as standard-dose monotherapy, with fewer side effects. The data on quadruple quarter-dose therapy was limited to 2 small trials that indicated that these combinations are significantly more efficacious than placebo and standard-dose monotherapy. A clear dose response in efficacy was seen between single, double, and quadruple quarter-dose therapy.

Strengths and Weaknesses of the Study

This review has several strengths. It was conducted in line with recommended systematic review methodology and included a relatively large number of studies, doubling the number of trials of quarter-dose therapy included in a previous systematic review.[9] Several studies were identified in regulatory submissions that had not been published in the medical literature. The large number of trials allowed precise estimates of treatment effects, at least for single and dual combinations, and assessment of consistency of results across major drug classes. The review also has some limitations. We did not review non–English language trials. No individual-patient data were used, and data were not checked with original trialists because most trials were completed more than 17 years ago. There were some missing data, particularly on variability, but sensitivity analyses did suggest the findings were reasonably robust.

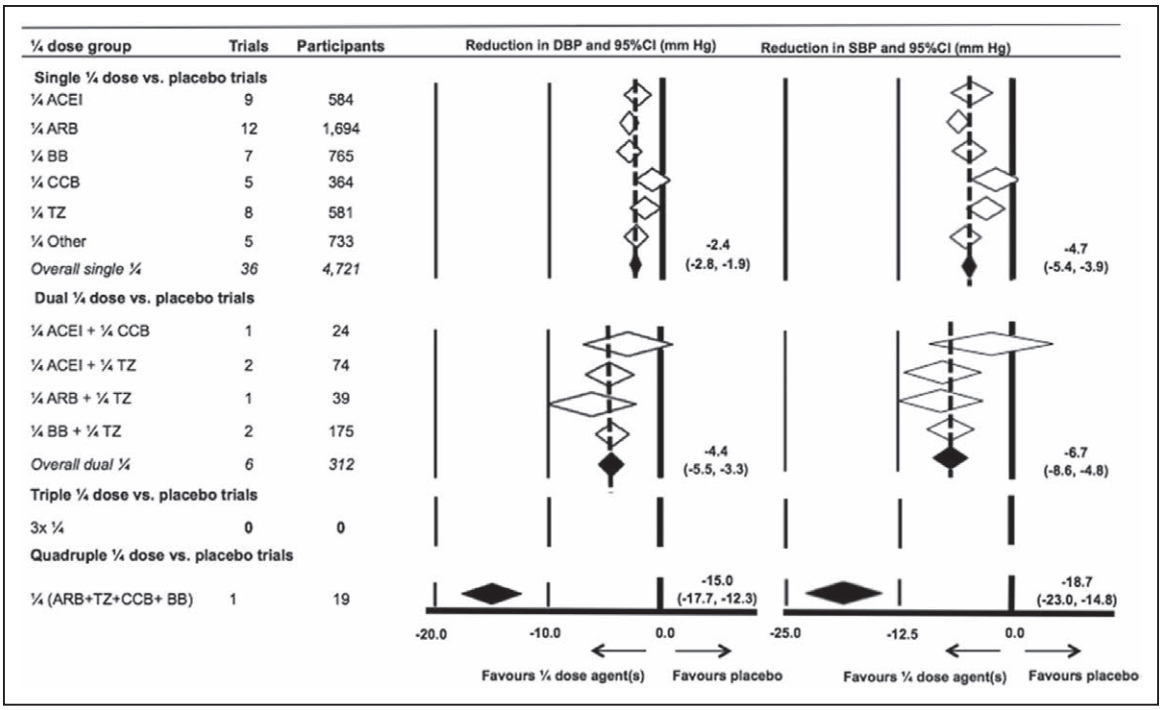

Figure 2. Data presented as difference in means (lower confidence limit, upper confidence limit). Heterogeneity (Q value, *P* value, and I^2 statistic) observed for single quarter vs placebo, DBP: 32, 0.75, 0. SBP: 39, 0.37, 3.0 and observed for dual quarter vs placebo, DBP: 8, 0.16, and 37. SBP: 3.7, 0.36, and 18.2. Trial and participant numbers represent single quarter dose vs placebo DBP analysis. Quarter dose vs placebo SBP analysis trials=34, participants=4573. Mean difference (mm Hg)=1/4 dose(s)–placebo. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; and TZ, thiazide diuretic.

Only one trial assessed effects on 24-hour BP profile, and it remains unknown whether better night-time BP reduction can be achieved with different components. Finally, defining standard-dose–involved some assumptions, but to minimize their impact, the authors used data from 4 pharmacopoeias.

Context of Other Evidence

Law et al undertook the most relevant previous review in 2003, which assessed placebo-controlled trials of blood pressure–lowering drugs available at that time.[7] The principal aim of that review was to quantify effects of standard doses of blood pressure–lowering agents and dose response. Analysis of low-dose therapy was largely restricted to half dosages, indicating that half-dose blood pressure treatment was ≈80% as efficacious as standard dose and that side effects generally rose steeply with dose. In terms of results for quarter-dose therapy, there were limited data on efficacy, and no analyses on side effects from the 19 studies quantifying single quarter-dose effects in the Law 2003 review. The present review included a further 23 trials of quarter-dose therapy. As with the current review, Law et al did not find any clear evidence that one drug class was more effective than any other. However, as with other systematic reviews of dose response within treatment classes,[25] Law et al also noted that there is considerable variability in potency per mg, and so the choice of standard dose is relevant to such comparisons. In the context of other low-dose combination therapy trials, the most relevant compared triple half-dose therapy (amlodipine 2.5 mg, losartan 25 mg,

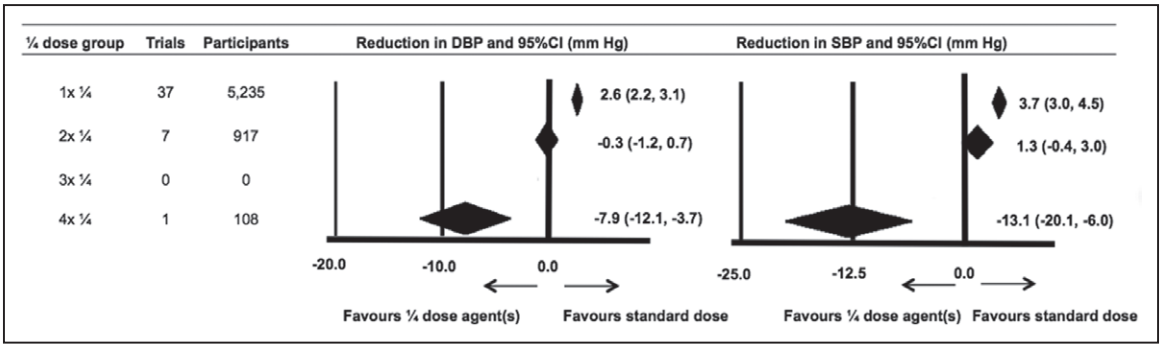

Figure 3. Data presented as difference in means (lower confidence limit, upper confidence limit). Heterogeneity (Q value, *P* value, and I^2 statistic) observed for single quarter dose vs standard dose, DBP: 37, 0.5, and 0. SBP: 46, 0.1, and 22. Observed for dual quarter dose vs standard dose, DBP: 13, 0.04, and 55. SBP: 4, 0.69, and 0. Trial and participant numbers represent single quarter-dose vs standard-dose DBP analysis. Quarter-dose vs standard-dose SBP analysis trials=35, participants=5146. Mean difference (mm Hg)=1/4 dose(s)–standard dose. CI indicates confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

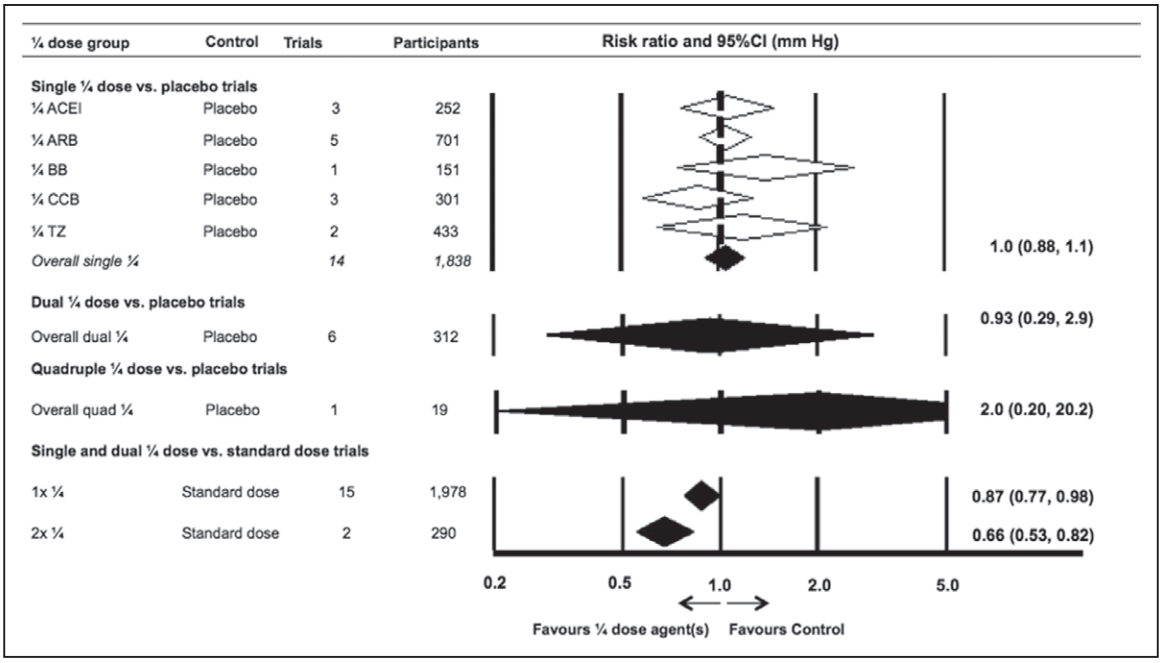

Figure 4. Risk ratio presented as risk ratio (lower CI, upper CI). Heterogeneity (Q value; *P* value, and I^2 statistic) observed for single quarter dose vs placebo: 6, 0.8, and 0 observed for single quarter vs standard dose: 17, 0.11, and 35 observed for dual quarter vs standard dose: 0.4, 0.52, and 0. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; and CI, confidence interval.

hydrochlorothiazide 12.5 mg) with placebo and also observed a large blood pressure reduction, of −17.9/−9.8 mm Hg.[26]

Perspectives

This review suggests a potentially broader clinical role for low-dose blood pressure–lowering drugs. Use of dual quarter-dose blood pressure–lowering therapy may be preferable to standard-dose monotherapy, given comparable blood pressure reduction with better tolerability. Alternatively, addition of a single quarter-dose agent to existing therapy is likely to confer an extra 3 to 4 mm Hg systolic blood pressure reduction without additional side effects and thus could be preferable to doubling the dose of the existing agent, which on average confers only about a 1–2 mm Hg extra systolic blood pressure reduction at the expense of increased side effects.[7,27] Currently, there are a few low-dose combinations available to clinicians: for example, a bisoprolol–hydrochlorothiazide combination is on the market in the United States (Ziac), with a dual quarter-dose version indicated for initial treatment of hypertension; a perindopril–indapamide combination is available that includes half dose and quarter dose, supported by clinical trial data showing improved rates of adverse event-free blood pressure control compared with sequential monotherapy or stepped care.[28] Quarter doses are available for many β-blockers and are obtainable for other classes from halving existing half-doses. However, for many patients, more blood pressure reduction than that given by standard-dose monotherapy or dual quarter-dose therapy is needed.[29] This review suggests considerably more research is required, to examine the potential of triple or quadruple quarter-dose combinations to determine whether they could provide substantial blood pressure–lowering with little or no drug-specific side effects, that is, more or less pure blood pressure lowering. Future trials should explore this hypothesis, testing quarter-dose combinations as initial therapy and also for those uncontrolled on monotherapy who need additional blood pressure reduction and for particular patient groups of interest, such as the elderly or those with impaired renal function. Further information on tolerability of such combinations is critical, given the near absence of data in this regard. Relevant clinical trials should also assess patient acceptability and the potential for low-dose combination pills to improve long-term adherence.

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Table 4. Change in Biochemical Measures From Baseline to Follow-Up With Single and Dual Quarter-Dose Therapy, Compared With Placebo and Standard-Dose Monotherapy

Quarter Dose(s)	Comparison Group	Trials	Patients	Mean Difference (95% CI)	*P* Value
Potassium, mmol/L					
Quarter ACEI	Placebo	1	88	0.14 (–0.15 to 0.43)	0.35
	Standard-dose ACEI		85	0.01 (–0.29 to 0.31)	0.95
Quarter BB	Placebo	1	115	0.21 (–0.05 to 0.47)	0.11
	Standard-dose BB		121	0.10 (–0.15 to 0.35)	0.43
Quarter TZ	Placebo	4	294	–0.02 (–0.19 to 0.16)	0.85
	Standard-dose TZ		227	0.27 (0.08 to 0.45)	0.01*
Quarter ACEI+quarter TZ	Placebo	1	83	0.03 (–0.27 to 0.33)	0.85
	Standard-dose ACEI		88	–0.22 (–0.51 to 0.07)	0.14
	Standard-dose TZ		85	0.36 (0.06 to 0.66)	0.02*
Quarter ARB+quarter TZ	Placebo	1	77	–0.05 (–0.36 to 0.26)	0.75
	Standard-dose TZ		75	0.22 (–0.1 to 0.54)	0.17
Quarter BB+quarter TZ	Placebo	1	84	0.07 (–0.25 to 0.39)	0.67
	Standard-dose BB		90	–0.04 (–0.35 to 0.27)	0.80
	Standard-dose TZ		67	0.39 (0.05 to 0.73)	0.02*
Quarter BB+quarter TZ†	Standard-dose CCB	1	160	0.2 (–0.02 to 0.42)	0.07
Quarter BB+quarter TZ+quarter ARB+quarter CCB	Placebo	1	19	0.1 (–0.1 to 0.2)	0.90
Uric acid, μmol/L					
Quarter BB	Placebo	1	115	1.0 (–24.7 to 26.7)	0.94
	Standard-dose BB		121	–12.0 (–37.1 to 13.1)	0.35
Quarter TZ	Placebo	3	200	9.4 (–10.8 to 29.6)	0.36
	Standard-dose TZ		182	–35.9 (–56.5 to –15.2)	0.001*
Quarter ARB+quarter TZ	Placebo	1	77	11.7 (–19.7 to 43.1)	0.47
	Standard-dose TZ		75	–39.8 (–71.5 to –8.1)	0.01*
Quarter BB+quarter TZ	Placebo	1	84	–2.0 (–33.9 to 29.9)	0.90
	Standard-dose BB		90	–15.0 (–46.2 to 16.2)	0.35
	Standard-dose TZ		67	–48.0 (–82.0 to –14.0)	0.01*
Quarter BB+quarter TZ†	Standard-dose CCB	1	160	29.0 (7.3 to 50.7)	0.01*
Quarter ARB+quarter BB+quarter CCB+quarter TZ	Placebo	1	19	100.0 (5.0 to 195.0)	0.03*

Data are presented as mean difference (lower confidence interval–upper confidence interval). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CI, confidence interval; and TZ, thiazide diuretic.

*$P<0.05$.

†Signifies a trial that did not compare a dual combination with its component quarter doses. Mean difference=quarter dose(s)–(placebo or standard dose). Potassium: TZ vs placebo 0.522, 0.91, and 0. TZ vs standard dose 0.17, 0.98, and 0; uric acid: TZ vs placebo: 0.15, 0.93, and 0. TZ vs standard dose: 0.5, 0.80, and 0.

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George Health Enterprises has also received investment to develop fixed-dose combinations containing aspirin, statins, and blood pressure–lowering drugs. The other authors report no conflicts.

References

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2224–2260. doi: 10.1016/S0140-6736(12)61766-8.
2. Webster RJ, Heeley EL, Peiris DP, Bayram C, Cass A, Patel AA. Gaps in cardiovascular disease risk management in Australian general practice. *Med J Aust*. 2009;191:324–329.
3. Peiris DP, Patel AA, Cass A, Howard MP, Tchan ML, Brady JP, De Vries J, Rickards BA, Yarnold DJ, Hayman NE, Brown AD. Cardiovascular disease risk management for Aboriginal and Torres Strait Islander peoples in primary health care settings: findings from the Kanyini Audit. *Med J Aust*. 2009;191:304–309.
4. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U; EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet*. 2009;373:929–940. doi: 10.1016/S0140-6736(09)60330-5.
5. Chow CK, Teo KK, Rangarajan S, et al; PURE (Prospective Urban Rural Epidemiology) Study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310:959–968. doi: 10.1001/jama.2013.184182.
6. Gradman AH. Rationale for triple-combination therapy for management of high blood pressure. *J Clin Hypertens (Greenwich)*. 2010;12:869–878. doi: 10.1111/j.1751-7176.2010.00360.x.
7. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003;326:1427. doi: 10.1136/bmj.326.7404.1427.
8. Mahmud A, Feely J. Low-dose quadruple antihypertensive combination: more efficacious than individual agents–a preliminary report. *Hypertension*. 2007;49:272–275. doi: 10.1161/01.HYP.0000254479.66645.a3.
9. Chow CK, Thakkar J, Bennett A, et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review. *Lancet*. 2017;389:1035–1042. doi: 10.1016/S0140-6736(17)30260-X.
10. Jounela AJ, Lilja M, Lumme J, Mörlin C, Hoyem A, Wessel-Aas T, Borrild NJ. Relation between low dose of hydrochlorothiazide, antihypertensive effect and adverse effects. *Blood Press*. 1994;3:231–235. doi: 10.3109/08037059409102262.
11. Pool JL, Cushman WC, Saini RK, Nwachuku CE, Battikha JP. Use of the factorial design and quadratic response surface models to evaluate the fosinopril and hydrochlorothiazide combination therapy in hypertension. *Am J Hypertens*. 1997;10:117–123.
12. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
13. Comprehensive Meta-Analysis Version 2 [computer program]. Englewood NJ: Biostat; 2005.
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558. doi: 10.1002/sim.1186.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
16. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
17. Frishman WH, Bryzinski BS, Coulson LR, DeQuattro VL, Vlachakis ND, Mroczek WJ, Dukart G, Goldberg JD, Alemayehu D, Koury K. A multifactorial trial design to assess combination therapy in hypertension. Treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med*. 1994;154:1461–1468.
18. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol*. 2006;59:7–10. doi: 10.1016/j.jclinepi.2005.06.006.
19. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration 2011; updated 2011:http://handbook.cochrane.org/chapter_16/16_1_3_1imputing_standard_deviations.htm.
20. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme Inhibitor or calcium channel blocker vs diuretic The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
21. Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies. *Drug Saf*. 2001;24:1155–1165.
22. Villamil A, Chrysant SG, Calhoun D, Schober B, Hsu H, Matrisciano-Dimichino L, Zhang J. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens*. 2007;25:217–226. doi: 10.1097/HJH.0b013e3280103a6b.
23. Canter D, Frank GJ, Knapp LE, Phelps M, Quade M, Texter M. Quinapril and hydrochlorothiazide combination for control of hypertension: assessment by factorial design. Quinapril Investigator Group. *J Hum Hypertens*. 1994;8:155–162.
24. EC403 Drug approval package: Candesartan (Atacand) Medical Review: Drugs@FDA: FDA Approved Drug Products; 1996:210–222.
25. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension*. 2012;59:1104–1109. doi: 10.1161/HYPERTENSIONAHA.111.190637.
26. Wald DS, Morris JK, Wald NJ. Randomized Polypill crossover trial in people aged 50 and over. *PLoS One*. 2012;7:e41297. doi: 10.1371/journal.pone.0041297.
27. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300. doi: 10.1016/j.amjmed.2008.09.038.
28. Mourad JJ, Waeber B, Zannad F, Laville M, Duru G, Andréjak M; investigators of the STRATHE trial. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. *J Hypertens*. 2004;22:2379–2386.
29. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016;387:435–443. doi: 10.1016/S0140-6736(15)00805-3.

Novelty and Significance

What Is New?

- There are few data on the efficacy or tolerability of ultralow-dose blood pressure combinations.
- Quadruple quarter-dose therapy seems to be around twice as efficacious as standard-dose monotherapy, but there are few data on side effects.

What Is Relevant?

- Dual quarter-dose therapy is as effective as standard-dose monotherapy, with fewer side effects.

Summary

Quarter-dose combinations could provide improvements in efficacy and tolerability of blood pressure–lowering therapy.

Hypertension
Journal of the American Heart Association

Efficacy and Safety of Quarter-Dose Blood Pressure–Lowering Agents: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Efficacy and safety of quarter dose blood pressure lowering agents: a systematic review and meta-analysis of randomised controlled trials

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3. Subgroup analysis (Figure S7)
4. Risk of Bias tool (Figure S8)

Medline search

1. Hypertension/ or hypertension.mp.
2. high blood pressure.mp. or Hypertension/
3. resistant hypertension.mp.
4. severe hypertension.mp.
5. persistent high blood pressure.mp.
6. persistent hypertension.mp.
7. sustained high blood pressure.mp.
8. sustained hypertension.mp.
9. raised blood pressure.mp.
10. elevated blood pressure.mp.
11. hypertensive.mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. very low dos$.mp.
14. ultra low dose$.mp.
15. quarter dose$.mp.
16. one quarter dose$.mp.
17. very low fixed dose$.mp.
18. very low dose combination$.mp.
19. very low fixed dose combination$.mp.
20. Dose-Response Relationship, Drug/ or dose response relationship$.mp.
21. dose finding.mp.
22. factorial$.mp.
23. factorial design.mp.
24. Antihypertensive agent$.mp. or Antihypertensive Agents/
25. angiotensin converting enzyme inhibitor$.mp. or Angiotensin-Converting Enzyme Inhibitors/
26. Angiotensin Receptor Antagonists/ or angiotensin II receptor 1 antagonist$.mp.
27. dose rang$.mp.
28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 27
29. angiotensin receptor blocker$.mp.
30. calcium channel blocker$.mp. or Calcium Channel Blockers/
31. Adrenergic beta-Antagonists/ or beta-blocker$.mp.
32. ACEI.mp.
33. ACE inhibitor.mp.
34. diuretic$.mp. or Diuretics/
35. ARB.mp.
36. 24 or 25 or 26 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. drug therapy.fs.
41. randomly.ab.
42. trial.ab.
43. groups.ab.
44. exp animals/ not humans.sh.
45. Randomized controlled trial.pt.
46. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 45

47. 46 not 44
48. Pediatrics/
49. Adult/
50. 49 not 48
51. 12 and 28 and 36 and 47 and 50

List of included trials in meta-analysis

1. #866-09 (2001), Drugs@FDA: FDA Approved Drug Products, Drug approval package: Olmesartan (Benicar), Medical Review, Part 5 pages 174-183. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21286_Benicar_medr_P5.pdf

2. #866-10 (1999), Drugs@FDA: FDA Approved Drug Products, Drug approval package: Olmesartan (Benicar), Medical Review, Part 3-4 pages 108-129. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21286_Benicar_medr_P3.pdf

3. #866-204, Drugs@FDA: FDA Approved Drug Products, Drug approval package: Olmesartan (Benicar), Medical Review, Part 2-3 pages 51-69. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21286_Benicar_medr_P2.pdf

4. #866-305 (1999), Drugs@FDA: FDA Approved Drug Products, Drug approval package: Olmesartan (Benicar), Medical Review, Part 3 pages 70-83. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21286_Benicar_medr_P2.pdf

5. Benetos A, Consoli S, Safavian A, Dubanchet A, Safar M. Efficacy, safety, and effects on quality of life of bisoprolol/hydrochlorothiazide versus amlodipine in elderly patients with systolic hypertension. *Am Heart J*. 2000; 140: E11.

6. Bergstrand R, Herlitz H, Johansson S, Berglund G, Vedin A, Wilhelmsson C, Gomez HJ, Cirillo VJ, Bolognese JA. Effective dose range of enalapril in mild to moderate essential hypertension. *British Journal of Clinical Pharmacology.* 1985; 19: 605-611.

7. Canter D, Frank GJ, Knapp LE, Phelps M, Quade M, Texter M. Quinapril and hydrochlorothiazide combination for control of hypertension: assessment by factorial design. Quinapril Investigator Group. *Journal of Human Hypertension.* 1994*;* 8: 155-162.

8. Casadei B, Conway J, Coats AJ, Bird R. Antihypertensive effect of carvedilol: a preliminary dose-response study. *Clinical investigator.* 1992; 70: 1.

9. Chrysant SG, Fagan T, Glazer R, Kriegman A. Effects of benazepril and hydrochlorothiazide, given alone and in low- and high-dose combinations, on blood pressure in patients with hypertension. *Archives of Family Medicine.* 1996*;* 5: 17-24; discussion 25.

10. De Bruijn JH, Orofiamma BA, Pauly NC. Efficacy and tolerance of trandolapril (0.5-2 mg) administered for 4 weeks in patients with mild-to-moderate hypertension. Investigator Study Group. *Journal of Cardiovascular Pharmacology.* 1994; 23 Suppl 4: S60-64.

11. DeQuattro V, Lee D. Fixed-dose combination therapy with trandolapril and verapamil SR is effective in primary hypertension. Trandolapril Study Group. *American Journal of Hypertension.* 1997; 10: 138S-145S.

12. Devi P, Xavier D, A Sigamani, et al. Effect of fixed dose combinations of metoprolol and amlodipine in essential hypertension: MARS--a randomized controlled trial. *Blood Press Suppl.* 2011*;* 2: 5-12.

13. EC009 (1994), Drugs@FDA: FDA Approved Drug Products, Drug approval package: Candesartan (Atacand), Medical Review, Part 2 pages 84-88.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20838_ATACAND_medr_P2.pdf

14. EC403 (1996), Drugs@FDA: FDA Approved Drug Products, Drug approval package: Candesartan (Atacand), Medical Review, Part 4-5 pages 210-222.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20838_ATACAND_medr_P4.pdf

15. Frick MH, McGibney D, Tyler HM. A dose-response study of amlodipine in mild to moderate hypertension. *Journal of Internal Medicine. 1989;* 225: 101-105.

16. Frishman WH, Bryzinski BS, Coulson LR, DeQuattro VL, Vlachakis ND, Mroczek WJ, Dukart G, Goldberg JD, Alemayehu D, Koury K. A multifactorial trial design to assess combination therapy in hypertension. Treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med.* 1994*;* 154: 1461-1468.

17. Frishman WH, Hainer JW, Sugg J and MFS Group. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). *American Journal of Hypertension.* 2006*;* 19: 388-395.

18. Gomez, HJ, Cirillo VJ, Sromovsky JA, Otterbein ES, Shaw WC, Rush JE, Chrysant SG, Gradman AH, Leon AS, MacCarthy EP. Lisinopril dose-response relationship in essential hypertension. *British Journal of Clinical Pharmacology.* 1989*;* 28: 415-420.

19. Gradman AH, Cutler NR, Davis PJ, Robbins JA, Weiss RJ, Wood BC, Michelson EL. Long-term efficacy, tolerability, and safety of the combination of enalapril and felodipine ER in the treatment of hypertension. Enalapril-Felodipine ER Factorial Study Group. *Clinical Therapeutics.* 1998*;* 20: 527-538.

20. Jounela AJ, Lilja M, Lumme J, Morlin C, Hoyem A, Wessel-Aas T, Borrild NJ. Relation between low dose of hydrochlorothiazide, antihypertensive effect and adverse effects. *Blood Pressure.* 1994*;* 3: 231-235.

21. Kochar M, Guthrie R, Triscari J, Kassler-Taub K, Reeves RA. Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens.* 1999*;* 12: 797-805.

22. Mahmud A, Feely J. Low-dose quadruple antihypertensive combination: more efficacious than individual agents-a preliminary report. *Hypertension.* 2007*;* 49: 272-275.

23. McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *Clinical Therapeutics.* 2001*;* 23: 833-850.

24. McMaho FG, Reder RF. The relationship of dose to the antihypertensive response of verapamil-sustained release in patients with mild to moderate essential hypertension. The Verapamil-SR Study Group. *J Clin Pharmacol.*1989*;* 29: 1003-1007.

25. Mehta JL, Lopez LM, Vlachakis ND, Gradman AH, Nash DT, O'Connell MT, Garland WT, Pickering BI. Double-blind evaluation of the dose-response relationship of amlodipine in essential hypertension. *American Heart Journal.*1993*;* 125: 1704-1710.

26. Meinek I, Feltkamp H, Hogeman A, Gundert-Remy U. Pharmacokinetics and pharmacodynamics of candesartan after administration of its pro-drug candesartan cilexetil in patients with mild to moderate essential hypertension--a population analysis. *European Journal of Clinical Pharmacology.* 1997*;* 53: 221-228.

27. Mitrovic V, Willenbrock R, Miric M, Seferovic P, Spinar J, Dabrowski M, Kiowski W, Marks DS, Alegria E, Dukat A, Lenz K, Arens HA. Acute and 3-month treatment effects of candesartan cilexetil on hemodynamics, neurohormones, and clinical symptoms in patients with congestive heart failure. *Am Heart J.*2003*;* 145: E14.

28. Moser M, Abraham PA, Bennett WM, Brachfeld N, Goodman RP, McKenney JM, Hollifield JW, Kirkendall WM, Lasseter KC, Leonv AS. The effects of benazepril, a new angiotensin-converting enzyme inhibitor, in mild to moderate essential hypertension: a multicenter study. *Clinical Pharmacology and Therapeutics.* 1991*;* 49: 322-329.

29. NEB-302 (2003), FDA Approved Drug Products, Drug approval package: Nebivolol (Bystolic), Medical Review, Part 11 pages 112-136. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021742s000_MedR_P11.pdf

30. Neutel J, Weber M, Pool J, Smith D, Fitzsimmons S, Chiang YT, Gatlin M. Valsartan, a new angiotensin II antagonist: antihypertensive effects over 24 hours. *Clin Ther.* 1997*;* 19: 447-458; discussion 367-448.

31. Omboni S, Zanchetti A. Antihypertensive efficacy of lercanidipine at 2.5, 5 and 10 mg in mild to moderate essential hypertensives assessed by clinic and ambulatory blood pressure measurements. Multicenter Study Investigators. *J Hypertens.* 1998*;* 16: 1831-1838.

32. Oparil S, Dyke S, Harris F, Kief J,James D,Hester A, Fitzsimmons S. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clinical Therapeutics.* 1996*;* 18: 797-810.

33. Papademetriou V, Hainer JW, Sugg J, Munzer D, AS Group. Factorial antihypertensive study of an extended-release metoprolol and hydrochlorothiazide combination. *American Journal of Hypertension*. 2006; 19: 1217-1225.

34. Pool JL, Cushman WC, Saini RK, Nwachuku CE, Battikha JP. Use of the factorial design and quadratic response surface models to evaluate the fosinopril and hydrochlorothiazide combination therapy in hypertension. *American Journal of Hypertension.* 1997*;* 10: 117-123.

35. Reif M, White WB, Fagan TC, Oparil S, Flanagan TL, Edwards DT, Cushing DJ, Michelson EL. Effects of candesartan cilexetil in patients with systemic hypertension. Candesartan Cilexetil Study Investigators. *American Journal of Cardiology.* 1998*;* 82: 961-965.

36. Roca-Cusachs A, Torres F, Horas M, Rios J, Calvo G, Delgadillo J, Teran M, Spanish G and Nitrendipine/Enalapril Collaborative Study. Nitrendipine and enalapril combination therapy in mild to moderate hypertension: assessment of dose-response relationship by a clinical trial of factorial design. *Journal of Cardiovascular Pharmacology.*2001*;* 38: 840-849.

37. Schoenberger JA. Usefulness of penbutolol for systemic hypertension. Penbutolol Research Group. *Am J Cardiol.*1989*;* 63: 1339-1342.

38. Sedman AJ, Posvar E. Clinical pharmacology of quinapril in healthy volunteers and in patients with hypertension and congestive heart failure. *Angiology* .1989;40: 360-369.

39. Study 01-05 (2006), FDA Approved Drug Products, Drug approval package: Azilsartan (Edarbi), Medical Review, pages http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200796Orig1s000MedR.pdf

40. Chow C, Thakkar J, Bennett A et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension – placebo-controlled crossover randomised trial and systematic review. *The Lancet.* 2017*;* 389: 1035–1042.

41. Villamil A, Chrysant SG, Calhoun D, Schober B, Hsu H, Matrisciano-Dimichino L, Zhang J. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* .2007; 25: 217-226.

42. Williams RL, Goyle KK, Herman TS, Rofman BA, Ruoff GE, Hogan LB. Dose-dependent effects of betaxolol in hypertension: a double-blind, multicenter study. *J Clin Pharmacol* .1992; 32: 360-367.

Supplementary references

Nil

Table S1. Baseline characteristics of included trials

Trial	Origin	Design	Study treatments	Sample size [n, ITT]	Mean age (yrs)	% female	Disease criteria	BP measure	BP eligibility (mmHg)	Mean baseline SBP/DBP (mmHg)	Relevant reported outcomes	Intervention (weeks)	% lost to follow-up
#866-09, 2001	EU	double blind, 6 groups, parallel	Olmesartan (¼ ½, 1, 2, 4) vs. placebo	790	56	-	Mild-moderate essential hypertension	in office, sitting	100<DBP <115	164/NA	DBP, SBP, treatment discontinuation	12	7%
#866-10, 1999	EU	double blind, 4 groups, parallel	Olmesartan (¼ ½, 1) vs. placebo	600	59	-	-	in office, sitting	95<DBP< 110	164/105	DBP, SBP	12	-
#866-204	USA	double blind, 7 groups, parallel	Olmesartan (od & bid: ¼, 1, 4) vs. placebo	299	-	-	Essential hypertension	in office, supine	100<DBP <115	155/104	DBP, SBP, treatment discontinuation	8	-
#866-305, 1999	USA	double blind, 6 groups, parallel	Olmesartan (¼, ½, 1, 2, 4) vs. placebo	517	55	-	Essential hypertension	in office, sitting	100<DBP <115	154/103	DBP, SBP	8	-
Benetos, 2000	France	double blind, 2 groups, parallel	[Bisoprolol, HCTZ (¼+¼)] amlodipine (1)	160	72	63%	Isolated systolic hypertension	in office, supine	160<SBP <210	172/84	DBP, SBP, adverse events, uric acid, potassium	12	11%

Bergstrand, 1985	Sweden	double blind, 6 group, incomplete-block	Enalapril (1/8, ¼ ½, 1, 2) vs. placebo	91	56	37%	Mild-moderate hypertension	in office, sitting	90<DBP<116	159/97	DBP, SBP	3	0%
Canter, 1994	USA	double blind, 4 x 4 factorial	HCTZ (¼, ½, 1) quinapril (1/8, ½, 2) vs. placebo	458	53	37%	Hypertension	in office, sitting	100<DBP<115	162/105	DBP, SBP, potassium	4	0%
Casadei, 1992	UK	double-blind, cross-over	Carvedilol (¼ ½, 1) vs. placebo	20	27	-	Untreated hypertension	ABP monitor	90<DBP	151/100	DBP, SBP	4	13%
Chrysant, 1996	USA	double blind, incomplete 4 x 4 factorial	Benazepril (¼, ½, 1) HCTZ (¼, ½, 1) vs. placebo	334	53	37%	Uncomplicated essential hypertension	in office, sitting	95<DBP<115	-	DBP, SBP, adverse events, treatment discontinuation, potassium	6	10%
De Bruijn, 1994	Netherlands	double blind, 4 groups, parallel	Trandolapril (¼ ½, 1) vs. placebo	170	-	-	Mild-moderate hypertension	in office, supine	95<DBP<115	161/100	DBP, SBP	4	-
DeQuattro, 1997	USA	double blind, 5 x 4 factorial	Trandolapril (¼, 1, 4) verapamil	726	55	37%	Stage I-III diastolic primary	in office, sitting, trough	95<DBP<114	153/101	DBP, SBP, adverse events	6	7%

			(½, 3/4, 1) vs. placebo				hypertension						
Devi, 2011	India	Open label, 2 x 2 factorial	Metoprolol (¼ ½), amlodipine (½, 1)	402	-	46%	Hypertension	in office, sitting	90<DBP<114 140<SBP<180	155/97	DBP, SBP, adverse events	8	-
EC009, 1994	Germany	double blind, 5 group, parallel	Candesartan (¼ ½, 1, 2) vs. placebo	232	-	-	Hypertension	-	95<DBP<114	-	DBP, SBP, adverse events	4	3%
EC403, 1996	Germany	double blind, 4 x 2 factorial	Candesartan (¼, ½, 1, 2) HCTZ (½, 1) vs. placebo	1,038	-	-	Mild-moderate hypertension	-	95<DBP<110	NA/101	DBP, SBP, treatment discontinuation, uric acid	6	-
Frick, 1988	Finland	single blind, parallel	Amlodipine (¼, ½, 1) vs. placebo	205	50	-	Mild-moderate hypertension	in office, supine	90<DBP<115	161/102	DBP, SBP, adverse events, treatment discontinuation	4	-
Frishman, 1994	USA	double blind, 4 x 3 factorial	Bisoprolol (¼, 1, 4) HCTZ (¼, 1) vs. placebo	465	53	29%	Mild-moderate essential hypertension	in office, sitting	95<DBP<114	151/101	DBP, SBP, uric acid, potassium	12	21%

Frishman, 2006	USA	double blind, unbalanced 4 x 4 factorial	Metoprolol (¼, 1, 4) felodipine (½, 2, 4) vs. placebo	1,087	54	43%	Essential hypertension	in office, sitting	95<DBP<114	153/100	DBP, SBP, treatment discontinuation	9	17%
Gomez, 1989	USA & Sweden	double blind, 4 groups, parallel	Lisinopril (¼, 1, 4) vs. placebo	216	-	10%	Mild-moderate, uncomplicated essential hypertension	in office, supine	95<DBP<115	159/101	DBP, SBP, adverse events, treatment discontinuation, potassium	6	11%
Gradman, 1998	USA	double blind, 3 x 4, factorial	Enalapril (¼, 1) felodipine (½, 1, 2) vs. placebo	705	53	35%	Essential hypertension	in office, sitting	95<DBP<115	155/102	DBP, SBP	8	9%
Jounela, 1994	Scandinavia	Double blind, 5 groups, parallel	HCTZ (1/8, ¼, ½, 1) vs. placebo	111	48	-	Mild-moderate essential hypertension	in office, supine	95<DBP<115	152/99	DBP, SBP, adverse events, mediation discontinuation	6	3%
Kochar, 1999	USA	double blind, 4 x 4 factorial	Irbesartan (¼, 2/3, 2) HCTZ (¼,	683	55	15%	Mild-moderate	in office, sitting	95<DBP	151/100	DBP, SBP, uric acid	8	8%

			½, 1) vs. placebo				hypertension						
Mahmud, 2006	Ireland	single-blind, parallel	Amlodipine (1) atenolol (1) BFMZ (1), captopril (1), combination (4x¼)	110	50	35%	Hypertension	in office, supine	90<DBP or 140<SBP	160/96	DBP, SBP, treatment discontinuation	4	2%
McGill, 2001	USA	double blind, 4 x 5 factorial	HCTZ (¼, ½, 1) telmisartan (½, 1, 2, 4) vs. placebo	749	53	40%	Mild-moderate hypertension	in office, supine	140<SBP <200	154/101	DBP, SBP, Potassium	8	7%
McMahon, 1989	USA	double blind, 5 groups, parallel	Verapamil (¼, ½, 1, 2) vs. placebo	213	55	43%	Mild-moderate essential hypertension	in office, supine	95<DBP< 115	156/101	DBP, SBP, adverse events, treatment discontinuation	6	9%
Mehta, 1993	USA	double blind, 5 groups, parallel	Amlodipine (¼, ½, 1, 2) vs. placebo	203	53	46%	Mild-moderate essential hypertension	in office, supine	95<DBP< 115	152100	DBP, SBP, treatment discontinuation	4	3%

Meineke, 1997	Germany	double blind, 6 groups, parallel	Candesartan (¼, ½, 1, 2, 4) vs. placebo)	232	53	56%	Mild-moderate arterial hypertension	in office, sitting	95<DBP<115	150/98	DBP, SBP	4	-
Mitrovic, 2003	EU and RSA	double blind, 5 groups, parallel	Candesartan (¼, ½, 1, 2) vs. placebo	218	54	15%	Heart failure (NYHA class II or III)	right heart catheter	-	-	adverse events, treatment discontinuation, uric acid, potassium	12	-
Moser, 1991	USA	double blind, 7 groups, parallel	Benazepril (1/10, ¼, ½, 1) HCTZ (1) vs. placebo	206	50	34%	Mild-moderate hypertension	in office, supine	95<DBP<115	153/102	DBP, adverse events, treatment discontinuation	4	14%
NEB-302, 2003	USA	double blind, 6 groups, parallel	Nebivolol (¼, ½, 1, 2, 4) vs. placebo	909	55	43%	Mild-moderate, uncomplicated hypertension	in office, sitting, trough	95<DBP<110	153/100	SBP, DBP, treatment discontinuation	-	-
Neutel, 1997	USA	double blind, 6 groups, parallel	Valsartan (¼, 1, 2, 4) vs. placebo	216	-	25%	Uncomplicated essential	in office, supine	95<DBP<115	148/91	DBP, SBP	8	0%

Omboni, 1989	Italy	double blind, 4 groups, parallel	Lercanidipine (¼, ½, 1) vs. placebo	243	51	34%	hypertension Mild-moderate essential hypertension	in office, sitting	90<DBP< 110	155/99	DBP, SBP, adverse events, treatment discontinuation	4	5%
Oparil, 1996	USA	double blind, 5 groups, parallel	Valsartan (¼, 1, 2, 4) vs. placebo	729	53	34%	Uncomplicated essential hypertension	in office, supine	95<DBP< 115	151/101	DBP, SBP, adverse events, treatment discontinuation	8	8%
Papademetriou, 2006	USA	double blind, 5 x 4 factorial	Metoprolol (¼, ½, 1, 2) HCTZ (¼, ½, 1) vs. placebo	1559	53	50%	Hypertension	in office, sitting	95<DBP< 115 SBP<180	151/100	DBP, SBP	10	11%
Pool, 1997	USA	double blind, 4 x 4 factorial	Fosinopril (¼, 1, 2, 4) HCTZ ((¼	548	52	39%	Mild-moderate	in office, sitting	95<DBP< 110	150/100	DBP, SBP	8	-
Reif, 1996	USA	double blind, 6 groups,	Candesartan (¼, ½, 1,	360	55	34%	Systemic	in office, sitting,	95<DBP< 115	153/100	DBP, SBP, adverse	8	9%
Roca-Cusachs, 2001	Spain	double blind, 4 x 4 factorial	Enalapril (¼, ½, 1) nitrendipine (¼, ½, 1) vs. placebo	378	56	60%	Mild-moderate essential	in office, sitting	90<DBP< 110	158/99	DBP, SBP	6	9%

							hypertension						
Schoenberger, 1989	USA	double blind, 4 groups, parallel	Penbutolol (¼, ½, 1) vs. placebo	302	51	47%	Systemic hypertension	in office, supine	95<DBP<115	152/100	DBP, SBP, adverse events	6	12%
Sedman, 1989	USA	double blind, 4 groups, parallel	Quinapril (¼, ½, 1) vs. placebo	247	-	-	Uncomplicated mild hypertension	in office, sitting, trough	95<DBP<115	156/103	DBP, SBP	6	8%
Study 01-05, 2006	USA, SA	double blind, 5 groups, parallel	Azilsartan (¼, ½, 1, 2) olmesartan (1) vs. placebo	404	-	-	Mild-moderate, uncomplicated hypertension	in office, sitting	95<DBP<115	151/100	DBP, SBP, adverse events	8	10%
Thakkar, 2016	AUS	Double blind, 2 groups, crossover	Amlodipine (¼), atenolol (¼), HCTZ (¼), irbesartan (¼) vs. placebo	20	58	52%	Hypertension	In office, sitting	90<DBP or 140<SBP	148/87	DBP, SBP, adverse events, treatment discontinuation, potassium, uric acid	4	10%

Villamil, 2007	USA	Double blind, factorial 4 x 4 factorial	Aliskiren (½,1, 2) HCTZ (¼, ½, 1) vs. placebo	2,752	55	45%	Mild-moderate hypertension	in office, sitting, trough	95<DBP< 110	153/99	DBP, SBP, Adverse events, treatment discontinuation	8	-
Williams, 1992	USA	double blind, 4 groups, parallel	Betaxolol (¼, ½, 1) vs. placebo	317	-	38%	Mild-moderate hypertension	in office, supine	95<DBP	150/100	DBP, SBP, treatment discontinuation	4	9%
Overall	**-**	**-**	**-**	**20,284**	**54**	**39%**	**-**	**-**	**-**	**154/101**	**-**	**7**	**8%**

ITT- Intention-to-treat, BP- Blood pressure, SBP-Systolic Blood Pressure, DBP, Diastolic Blood Pressure, HCTZ- Hydrochlorothiazide, USA- United States of America, EU- European Union, RSA- Republic of South Africa, SA- South America, AUS – Australia. Trials listed in supplemental material.

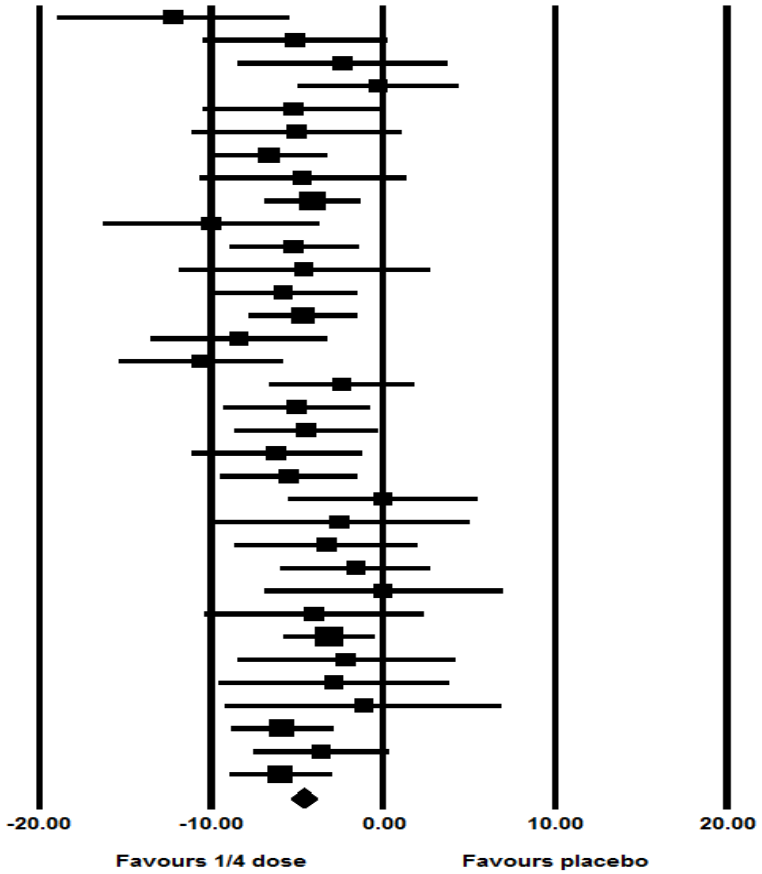
Table S2. Heterogeneity across all meta-analyses

Comparison (dosage)	Heterogeneity			
	Number of comparisons	I^2	Q value (df)	Tau^2
DBP reduction				
¼ vs. placebo	41	0	32.3 (40)	0.0
2x ¼ vs. placebo	6	36.9	7.9 (5)	1.2
¼ vs. standard	39	10.2	45.6 (38)	0.25
2x ¼ vs. standard	7	54.0	13.3 (6)	2.0
SBP reduction				
¼ vs. placebo	39	3.0	39.2 (38)	0.16
2x ¼ vs. placebo	4	18.2	3.7 (3)	1.1
¼ vs. standard	36	24.3	51.5 (35)	1.9
2x ¼ vs. standard	7	0	3.9 (6)	0
Adverse events				
¼ vs. placebo	14	20.8	16.4 (13)	0.02
2x ¼ vs. placebo	1	0	0	0
¼ vs. standard	15	47.4	26.6 (14)	0.05
2x ¼ vs. standard	2	0.50	0 (1)	0
Potassium				
¼ HCTZ vs. placebo	4	0	0.52 (3)	0
¼ HCTZ vs. standard HCTZ	4	0	0.173 (3)	0
Uric acid				
¼ HCTZ vs. placebo	3	0	0.15 (2)	0

DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Figure S1. Systolic blood pressure lowering of single quarter dose compared to placebo, of all comparisons

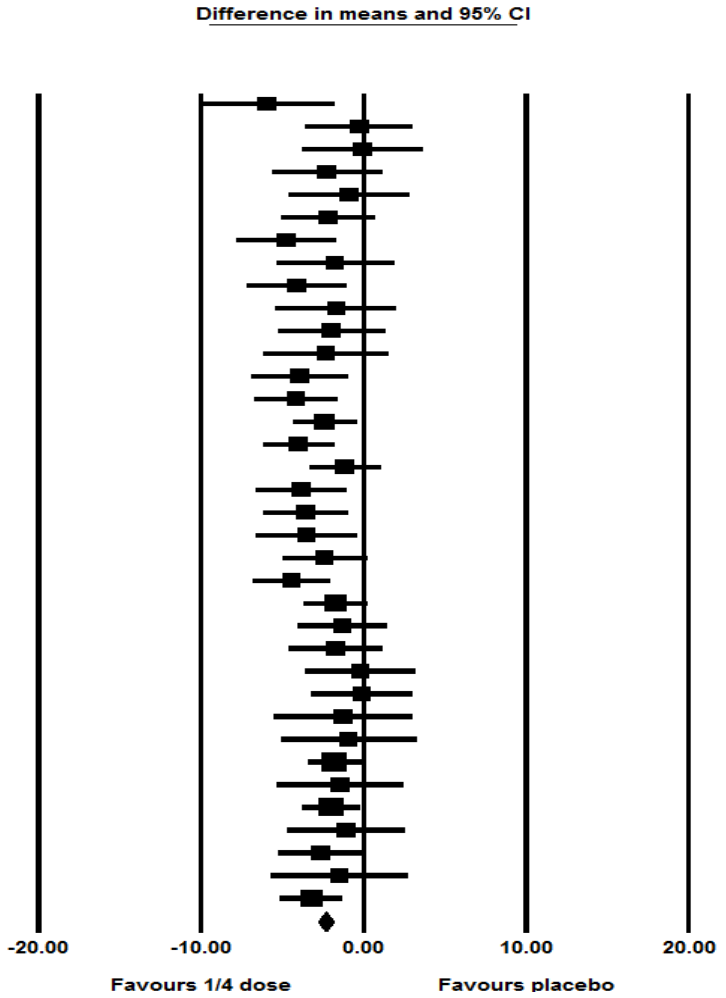
Study name	Comparison	Difference in means	Standard error	Lower limit	Upper limit
Bergstrand, 1984	ACEI	-12.2	3.4	-18.9	-5.5
DeQuattro, 1997	ACEI	-5.1	2.7	-10.5	0.2
Gradman, 1997	ACEI	-2.4	3.1	-8.4	3.7
Sedman, 1989	ACEI	-0.3	2.4	-5.0	4.4
De Brujin, 1994	ACEI	-5.2	2.7	-10.5	0.1
Gomez, 1989	ACEI	-5.0	3.1	-11.1	1.1
866-10, 1999	ARB	-6.7	1.7	-10.1	-3.3
Meineke, 1997	ARB	-4.7	3.1	-10.7	1.3
866-09, 2001	ARB	-4.1	1.4	-6.8	-1.4
866-204	ARB	-10.0	3.2	-16.3	-3.7
866-305, 1999	ARB	-5.2	1.9	-8.9	-1.5
EC403, 1996	ARB	-4.6	3.7	-11.9	2.7
Neutel, 1997	ARB	-5.8	2.2	-10.1	-1.5
Oparil, 1996	ARB	-4.7	1.6	-7.8	-1.6
Reif, 1996	ARB	-8.4	2.6	-13.5	-3.3
Study 01-05, 2006	ARB	-10.6	2.4	-15.3	-5.9
Schoenberger, 1989	BB	-2.4	2.1	-6.6	1.8
Williams, 1992	BB	-5.0	2.2	-9.2	-0.8
Casadei, 1992	BB	-4.5	2.1	-8.6	-0.4
Frishman, 2006	BB	-6.2	2.5	-11.1	-1.3
NEB - 302, 2003	BB	-5.5	2.0	-9.4	-1.6
Frick, 1988	CCB	0.0	2.8	-5.5	5.5
Mcmahon, 1989	CCB	-2.5	3.8	-10.1	5.0
Mehta, 1993	CCB	-3.3	2.7	-8.6	2.0
Omboni, 1998	CCB	-1.6	2.2	-5.9	2.7
Canter, 1994	DIURETIC	0.0	3.5	-6.9	6.9
Jounela, 1994	DIURETIC	-4.0	3.2	-10.4	2.3
Villamil, 2007	DIURETIC	-3.2	1.3	-5.8	-0.6
McGill, 2001	DIURETIC	-2.2	3.2	-8.5	4.1
Pool, 1997	OTHER	-2.9	3.4	-9.5	3.8
Roca-Cusachs, 2001	OTHER	-1.1	4.1	-9.1	6.9
Frishman, 1994	OTHER	-5.9	1.5	-8.8	-3.0
Kochar, 1999	OTHER	-3.6	2.0	-7.5	0.3
Papademetriou, 2006	OTHER	-6.0	1.5	-8.9	-3.1
		-4.7	0.4	-5.4	-3.9



DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Figure S2. Diastolic blood pressure lowering of single quarter dose compared to placebo, of all comparisons

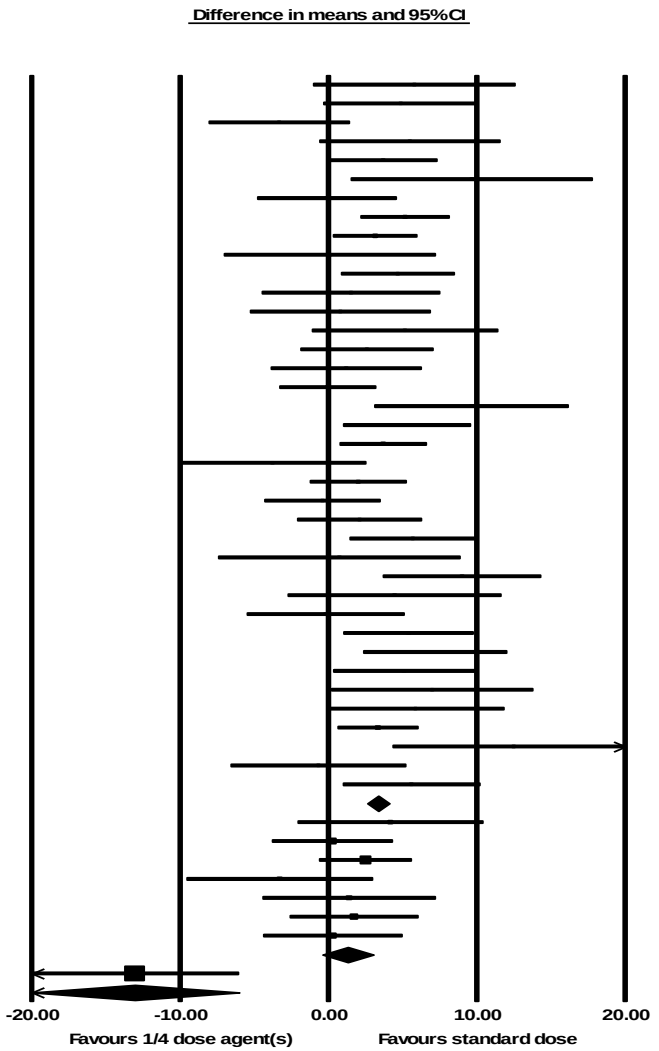
Study name	Subgroup within study	Difference in means	Standard error	Lower limit	Upper limit
Bergstrand, 1984	ACEI	-5.9	2.1	-10.0	-1.8
DeQuattro, 1997	ACEI	-0.2	1.7	-3.5	3.1
Gomez, 1989	ACEI	-0.0	1.9	-3.7	3.6
De Brujin, 1994	ACEI	-2.2	1.7	-5.5	1.1
Gradman, 1997	ACEI	-0.8	1.9	-4.6	2.9
Sedman, 1989	ACEI	-2.1	1.5	-5.0	0.7
Study 01-05, 2006	ACEI	-4.7	1.6	-7.8	-1.7
Moser, 1991	ACEI	-1.7	1.8	-5.3	1.9
Reif, 1996	ARB	-4.1	1.6	-7.1	-1.0
Meineke, 1997	ARB	-1.6	1.9	-5.3	2.0
EC009	ARB	-1.9	1.7	-5.2	1.4
EC403, 1996	ARB	-2.3	1.9	-6.1	1.6
866-204	ARB	-3.9	1.5	-6.8	-0.9
866-305, 1999	ARB	-4.1	1.3	-6.7	-1.6
Oparil, 1996	ARB	-2.3	1.0	-4.3	-0.4
866-10, 1999	ARB	-3.9	1.1	-6.1	-1.8
866-09, 2001	ARB	-1.1	1.1	-3.3	1.0
Neutel, 1997	ARB	-3.8	1.4	-6.5	-1.1
Williams, 1992	BB	-3.5	1.3	-6.1	-0.9
Frishman, 2006	BB	-3.5	1.6	-6.6	-0.4
Schoenberger, 1989	BB	-2.4	1.3	-4.9	0.2
NEB - 302, 2003	BB	-4.4	1.2	-6.7	-2.0
Casadei, 1992	BB	-1.7	1.0	-3.6	0.3
Mehta, 1993	CCB	-1.3	1.4	-4.0	1.5
Omboni, 1998	CCB	-1.7	1.4	-4.5	1.2
Frick, 1988	CCB	-0.1	1.7	-3.5	3.2
Mcmahon, 1989	CCB	-0.0	1.6	-3.1	3.0
Canter, 1994	DIURETIC	-1.2	2.2	-5.4	3.0
Jounela, 1994	DIURETIC	-0.9	2.1	-5.0	3.3
Villamil, 2007	DIURETIC	-1.7	0.8	-3.4	-0.1
McGill, 2001	DIURETIC	-1.4	2.0	-5.2	2.5
Frishman, 1994	OTHER	-1.9	0.9	-3.7	-0.2
Pool, 1997	OTHER	-1.0	1.8	-4.6	2.6
Kochar, 1999	OTHER	-2.6	1.3	-5.2	-0.0
Roca-Cusachs, 2001	OTHER	-1.4	2.1	-5.6	2.7
Papademetriou, 2006	OTHER	-3.2	1.0	-5.0	-1.3
		-2.4	0.2	-2.8	-1.9



Legend. DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Figure S3. Systolic blood pressure lowering of quarter dose agent(s) compared to standard dose therapy of all comparisons

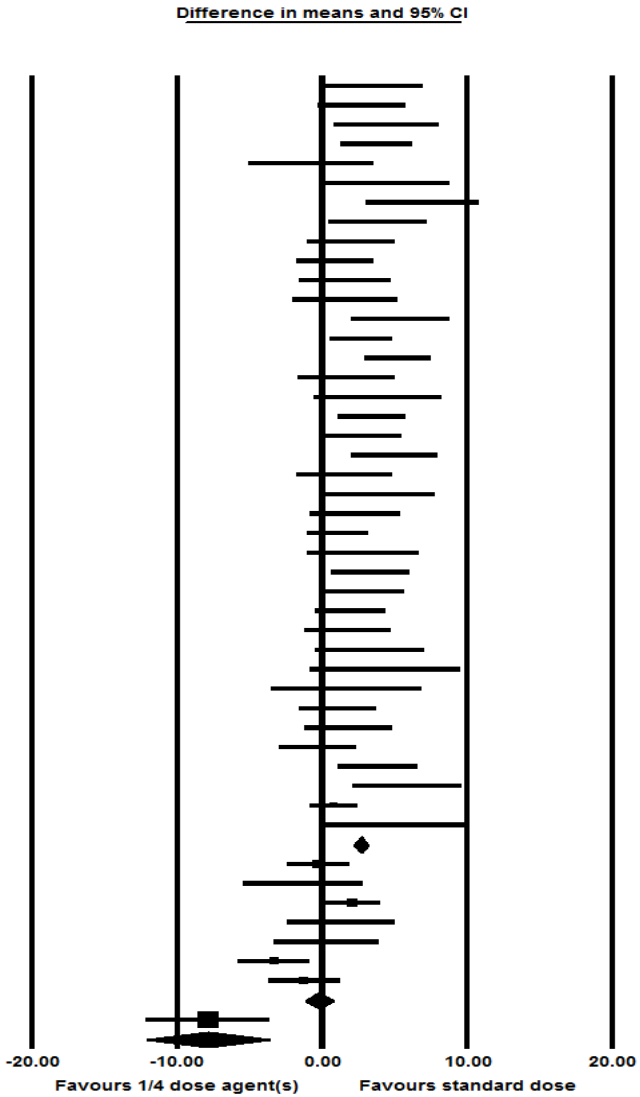
Study name	Subgroup within study	Comparison	Statistics for each study			
			Difference in means	Standard error	Lower limit	Upper limit
Bergstrand, 1984	ACEI	0.25-1	5.8	3.5	-1.0	12.6
De Brujin, 1994	ACEI	0.25-1	4.9	2.7	-0.3	10.1
DeQuattro, 1997	ACEI	0.25-1	-3.3	2.4	-8.1	1.4
Gomez, 1989	ACEI	0.25-1	5.5	3.1	-0.6	11.6
Gradman, 1997	ACEI	0.25-1	3.7	1.9	0.1	7.3
Roca-Cusachs, 2001	ACEI	0.25-1	9.7	4.2	1.5	17.8
Sedman, 1989	ACEI	0.25-1	-0.1	2.4	-4.8	4.6
866-09, 2001	ARB	0.25-1	5.2	1.5	2.2	8.2
866-10, 1999	ARB	0.25-1	3.2	1.4	0.3	6.0
866-204	ARB	0.25-1	0.1	3.6	-7.0	7.2
866-305, 1999	ARB	0.25-1	4.7	1.9	0.9	8.5
EC403, 1996	ARB	0.25-1	1.5	3.1	-4.5	7.5
Meineke, 1997	ARB	0.25-1	0.8	3.1	-5.3	6.9
Neutel, 1997	ARB	0.25-1	5.2	3.2	-1.1	11.4
Oparil, 1996	ARB	0.25-1	2.6	2.3	-1.9	7.1
Reif, 1996	ARB	0.25-1	1.2	2.6	-3.9	6.3
Study 01-05, 2006	ARB	0.25-1	-0.0	1.7	-3.3	3.2
Casadei, 1992	BB	0.25-1	9.7	3.3	3.1	16.2
Devi, 2011	BB	0.25-1	5.3	2.2	1.0	9.6
Frishman, 1994	BB	0.25-1	3.7	1.5	0.8	6.6
Frishman, 2006	BB	0.25-1	-3.8	3.2	-10.1	2.6
NEB - 302, 2003	BB	0.25-1	2.0	1.7	-1.2	5.3
Papademetriou, 2006	BB	0.25-1	-0.4	2.0	-4.3	3.5
Schoenberger, 1989	BB	0.25-1	2.1	2.1	-2.1	6.3
Williams, 1992	BB	0.25-1	5.7	2.2	1.4	10.0
Roca-Cusachs, 2001	CCB	0.25-1	0.7	4.2	-7.4	8.9
Frick, 1988	CCB	0.25-1	9.0	2.7	3.7	14.4
Mcmahon, 1989	CCB	0.25-1	4.5	3.7	-2.7	11.7
Mehta, 1993	CCB	0.25-1	-0.2	2.7	-5.5	5.1
Omboni, 1998	CCB	0.25-1	5.4	2.2	1.0	9.8
Frishman, 1994	DIURETIC	0.25-1	7.2	2.5	2.4	12.0
Papademetriou, 2006	DIURETIC	0.25-1	5.1	2.4	0.3	9.9
Canter, 1994	DIURETIC	0.25-1	7.0	3.5	0.2	13.8
Jounela, 1994	DIURETIC	0.25-1	5.9	3.1	-0.1	11.9
Villamil, 2007	DIURETIC	0.25-1	3.3	1.4	0.6	6.1
McGill, 1994	DIURETIC	0.25-1	12.5	4.2	4.3	20.7
Pool, 1997	OTHER	0.25-1	-0.7	3.0	-6.6	5.3
Kochar, 1999	OTHER	0.25-1	5.6	2.4	1.0	10.2
			3.4	0.4	2.6	4.1
Roca-Cusachs, 2001	Combination	2x0.25-1	4.2	3.2	-2.1	10.5
Frishman, 1994	Combination	2x0.25-1	0.3	2.1	-3.8	4.3
Papademetriou, 2006	Combination	2x0.25-1	2.5	1.6	-0.6	5.6
Pool, 1997	Combination	2x0.25-1	-3.3	3.2	-9.6	3.0
Kochar, 1999	Combination	2x0.25-1	1.4	3.0	-4.4	7.2
Benetos, 2000	Combination	2x0.25-1	1.7	2.2	-2.6	6.1
Chrysant, 1996	Combination	2x0.25-1	0.3	2.4	-4.4	5.0
			1.3	0.9	-0.4	3.0
Mahmud, 2006	Combination	4x0.25-1	-13.1	3.6	-20.1	-6.0
			-13.1	3.6	-20.1	-6.0



Legend. DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Figure S4. Diastolic blood pressure lowering of quarter dose agent(s) compared to standard dose therapy of all comparisons

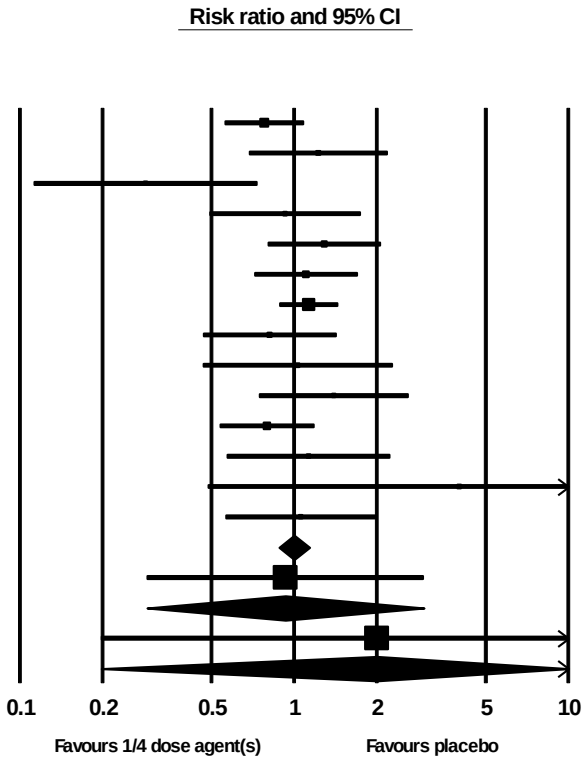
Study name	Subgroup within study	Comparison	Difference in means	Standard error	Lower limit	Upper limit
866-09, 2001	ARB	0.25-1	3.5	1.7	0.1	6.9
866-10, 1999	ARB	0.25-1	2.7	1.5	-0.3	5.7
866-204	ARB	0.25-1	4.4	1.8	0.8	8.0
866-305, 1999	ARB	0.25-1	3.7	1.2	1.3	6.2
Bergstrand, 1984	ACEI	0.25-1	-0.8	2.2	-5.1	3.5
Canter, 1994	DIURETIC	0.25-1	4.4	2.2	0.1	8.7
Casadei, 1992	BB	0.25-1	6.9	2.0	3.1	10.8
De Brujin, 1994	ACEI	0.25-1	3.8	1.7	0.5	7.1
DeQuattro, 1997	ACEI	0.25-1	1.9	1.5	-1.1	4.9
Devi, 2011	OTHER	0.25-1	0.9	1.4	-1.8	3.5
EC009	ARB	0.25-1	1.6	1.6	-1.5	4.7
EC403, 1996	ARB	0.25-1	1.5	1.8	-2.0	5.1
Frick, 1988	CCB	0.25-1	5.3	1.7	2.0	8.7
Frishman, 1994	BB	0.25-1	2.7	1.1	0.6	4.8
Frishman, 1994	DIURETIC	0.25-1	5.2	1.1	2.9	7.4
Frishman, 2006	BB	0.25-1	1.6	1.7	-1.7	4.9
Gomez, 1989	ACEI	0.25-1	3.8	2.2	-0.5	8.1
Gradman, 1997	ACEI	0.25-1	3.4	1.2	1.1	5.7
Kochar, 1999	OTHER	0.25-1	2.8	1.4	0.1	5.4
McMahon, 1989	CCB	0.25-1	4.9	1.5	2.0	7.9
Mehta, 1993	CCB	0.25-1	1.5	1.7	-1.7	4.8
Meineke, 1997	ARB	0.25-1	3.9	2.0	0.0	7.7
Moser, 1991	ACEI	0.25-1	2.3	1.6	-0.8	5.4
NEB - 302, 2003	BB	0.25-1	1.0	1.1	-1.1	3.1
Neutel, 1997	ARB	0.25-1	2.8	2.0	-1.0	6.6
Omboni, 1998	CCB	0.25-1	3.3	1.4	0.7	6.0
Oparil, 1996	ARB	0.25-1	2.9	1.4	0.2	5.6
Papademetriou, 2006	BB	0.25-1	1.9	1.2	-0.5	4.3
Papademetriou, 2006	DIURETIC	0.25-1	1.8	1.5	-1.2	4.7
Pool, 1997	OTHER	0.25-1	3.3	1.9	-0.5	7.0
Roca-Cusachs, 2001	ACEI	0.25-1	4.3	2.6	-0.8	9.5
Roca-Cusachs, 2001	CCB	0.25-1	1.6	2.6	-3.5	6.8
Schoenberger, 1989	BB	0.25-1	1.1	1.3	-1.6	3.7
Sedman, 1989	ACEI	0.25-1	1.8	1.5	-1.2	4.7
Study 01-05, 2006	ARB	0.25-1	-0.3	1.3	-3.0	2.3
Williams, 1992	BB	0.25-1	3.8	1.4	1.1	6.5
Jounela, 1994	DIURETIC	0.25-1	5.8	1.9	2.1	9.6
Villamil, 2007	DIURETIC	0.25-1	0.8	0.8	-0.9	2.4
McGill, 2001	DIURETIC	0.25-1	5.2	2.5	0.3	10.1
			2.6	0.2	2.2	3.1
Frishman, 1994	Combination	2x0.25-1	-0.3	1.1	-2.4	1.8
Kochar, 1999	Combination	2x0.25-1	-1.4	2.1	-5.4	2.7
Papademetriou, 2006	Combination	2x0.25-1	2.1	1.0	0.1	4.0
Pool, 1997	Combination	2x0.25-1	1.3	1.9	-2.4	5.0
Roca-Cusachs, 2001	Combination	2x0.25-1	0.2	1.8	-3.4	3.8
Benetos, 2000	Combination	2x0.25-1	-3.4	1.2	-5.8	-0.9
Chrysant, 1996	Combination	2x0.25-1	-1.3	1.2	-3.7	1.2
			-0.3	0.5	-1.2	0.7
Mahmud, 2006	Combination	4x0.25-1	-7.9	2.2	-12.1	-3.7
			-7.9	2.2	-12.1	-3.7



Legend. DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Figure S5. Adverse events of quarter dose agent(s) compared to placebo of all comparisons

Group by Comparison	Study name	Subgroup within study	Dosage	AE / Total		Risk ratio	Lower limit	Upper limit
				Intervention	Placebo			
0.25	Reif, 1998	ARB	0.250	28 / 59	39 / 64	0.779	0.558	1.086
0.25	McMahon, 1989	CCB	0.250	16 / 42	14 / 45	1.226	0.685	2.195
0.25	Omboni, 1998	CCB	0.250	5 / 58	15 / 50	0.287	0.112	0.735
0.25	Frick, 1989	CCB	0.250	14 / 55	14 / 51	0.927	0.491	1.750
0.25	Moser, 1990	ACEI	0.250	22 / 38	14 / 31	1.289	0.802	2.070
0.25	EC009, 1994	ARB	0.250	21 / 39	19 / 39	1.105	0.716	1.705
0.25	Oparil, 1996	ARB	0.250	70 / 140	65 / 147	1.131	0.884	1.446
0.25	DeQuattro, 1997	ACEI	0.250	13 / 41	21 / 54	0.815	0.465	1.427
0.25	Gomez, 1989	ACEI	0.250	9 / 41	10 / 47	1.032	0.465	2.290
0.25	Schoenberger, 1989	BB	0.250	19 / 77	13 / 74	1.395	0.745	2.613
0.25	mitrovic, 2003	ARB	0.250	21 / 45	26 / 44	0.797	0.536	1.184
0.25	study 01-05	ARB	0.250	14 / 63	12 / 61	1.130	0.569	2.243
0.25	Jounela, 1994	HCTZ	0.250	4 / 22	1 / 22	4.000	0.485	32.997
0.25	Villamil, 2007	HCTZ	0.250	18 / 194	17 / 195	1.057	0.563	1.985
0.25						0.999	0.878	1.136
2x0.25	Chrysant, 1996	Combination	2x0.25	5 / 43	5 / 40	0.928	0.290	2.970
2x0.25						0.928	0.290	2.970
4x025	Thakkar, 2016	Combination	4x025	2 / 19	1 / 19	2.000	0.198	20.244
4x025						2.000	0.198	20.244



Legend. DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Figure S6. Publication bias in studies that assessed single quarter dose vs. placebo (n=33) after Trim and Fill

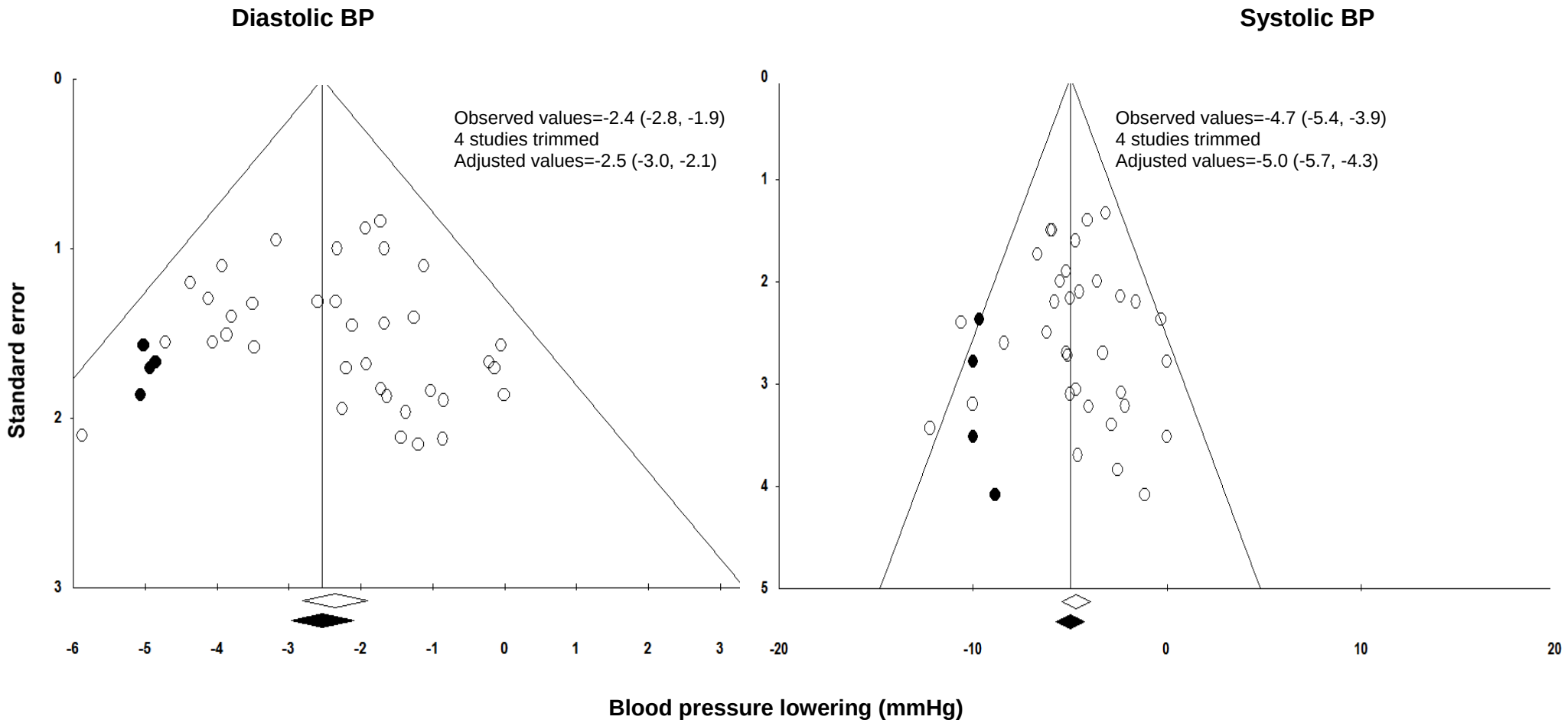


Figure S7. Subgroup analyses assessing the effect of treatment period (>6 weeks) and age (years) on blood pressure lowering

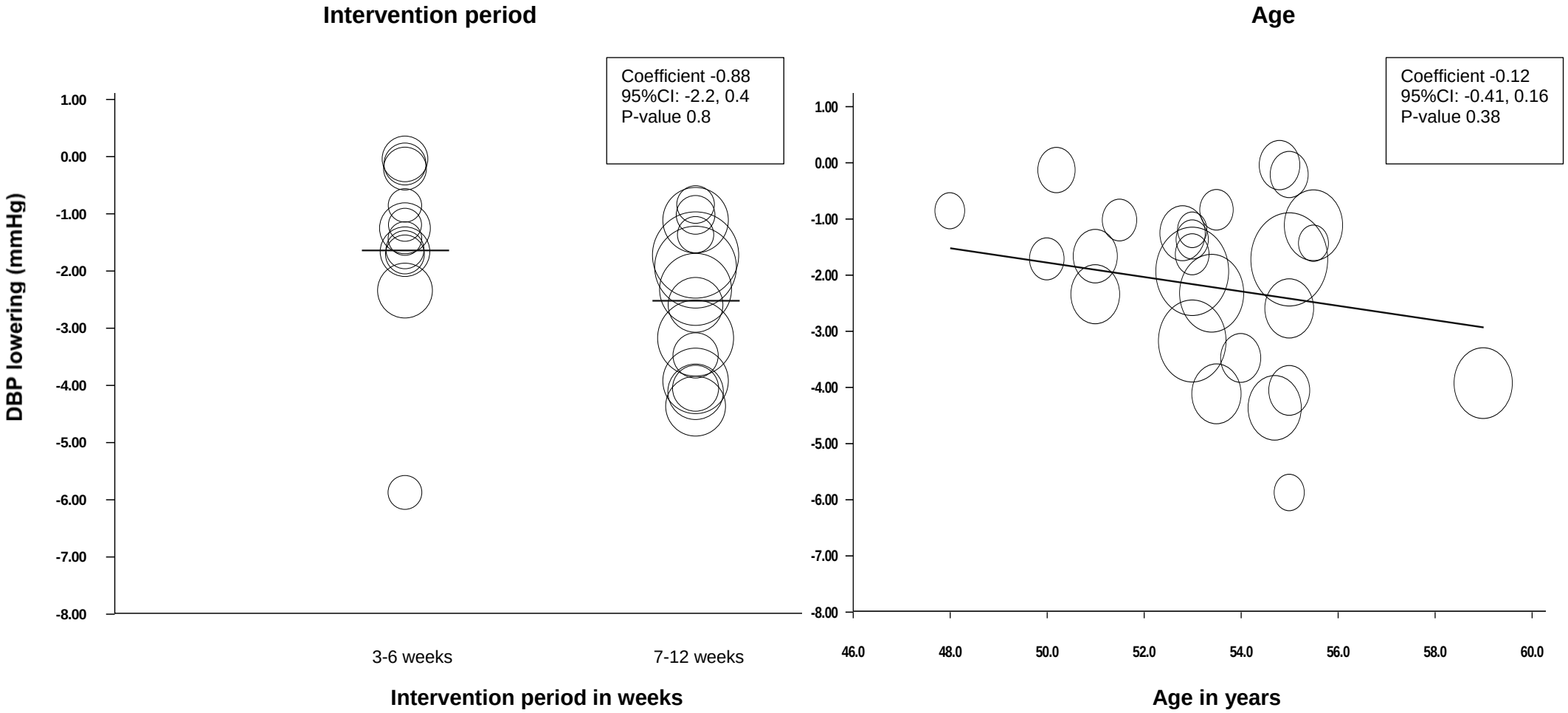

Intervention period
Coefficient -0.88
95%CI: -2.2, 0.4
P-value 0.8
DBP lowering (mmHg)
1.00
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
-7.00
-8.00
3-6 weeks
7-12 weeks
Intervention period in weeks
Age
Coefficient -0.12
95%CI: -0.41, 0.16
P-value 0.38
46.0
48.0
50.0
52.0
54.0
56.0
58.0
60.0
Age in years

Figure S8. Risk of bias

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias