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

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1. 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 randomised controlled trials with at least one quarter-dose and one placebo and/or 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 mmHg ($p<0.001$). Six comparisons were of dual quarter-dose therapy vs. placebo, observing a -6.7/ -4.4 mmHg ($p<0.001$) blood pressure reduction. There were no trials of triple quarter-dose combination vs. placebo but one quadruple quarter-dose study observed a blood pressure reduction of -22.4/ -13.1 mmHg vs. placebo ($p<0.001$). Compared to 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 ($p<0.001$) mmHg 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 to standard dose monotherapy.

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

Blood pressure lowering, combination therapy, quarter dose, meta-analysis, systematic review, safety, hypertension, high blood pressure

INTRODUCTION

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 low-dose combinations may provide the best ratio of side effects to blood pressure reduction, since at low doses most side effects are avoided and most benefit is realised.[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 very large blood pressure reduction from quadruple quarter dose combination therapy compared to monotherapy[8] and a small trial recently completed also showed large reductions compared to placebo.[9] We therefore conducted a systematic review of randomised 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 (supplementary file 1) 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 - June 2016), MEDLINE (inception - June 2016), Cochrane Central Registry of Controlled Trials (CCRCT/CENTRAL) (inception - June 2016) and the Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites. Searches of trial registers were performed for any ongoing trials including World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP), Australia New Zealand Clinical Trial Register (ANZCTR) and Clinical Trials Registry – India (CTRI). 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 supplementary material (please see http://hyper.ahajournals.org, web appendix 1).

During the initial phase of the search, two reviewers (AB, MC) 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 (AR) resolved any disagreement on the included articles.

Types of Studies

Randomised controlled trials (either parallel or crossover) with a treatment and follow up of at least two weeks were sought. Up-titration studies must have had blood pressure or safety data for at least the first two weeks before

titration occurred. Studies were included only if there were efficacy or safety data that were measured for at least one of the five major classes of blood pressure lowering medications: calcium channel blockers (CCBs), beta-blockers (BBs), angiotensin receptor II antagonists (ARBs), angiotensin converting enzyme inhibitors (ACE-Is) and thiazide diuretics (TZs). All included medications were registered for use by the Food and Drug Administration (FDA) or European Medicines Advisory (EMA), 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 and/or standard dose monotherapy (in order 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 (BNF), Martindale and Monthly Index of Medical Specialties (MIMS), similar to the method of Law et al.[7] The World Health Organisation Defined Daily Dose (WHO-DDD) 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 two exceptions. A quarter dose of hydrochlorothiazide (HCTZ) of 6 mg and 5 mg were utilized 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 (AB, MC) independently extracted data using a standard extraction form. The variables extracted included study design, sample size, mean age, percentage female, randomisation, blinding, intervention, dose(s), follow up, % lost to follow-up and study outcomes. In studies where numerical 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 two being used.

The two reviewers (AB, MC) also independently assessed the risk of bias in each trial based on the Cochrane Collaboration's risk of bias tool[12] (please see http://hyper.ahajournals.org, S10). 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 (AR) resolved any differences.

Data analysis

One reviewer (AB) 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 (AR) resolving any disagreements. The data were analysed according to intention-to-treat when possible. Binary outcomes were analysed using the Mantel-Haenszel approach and summarised as risk ratios with 95% confidence intervals. Continuous outcomes were summarised as difference in means with 95% confidence intervals. Individual trial results were pooled using fixed-effect meta-analysis with inverse variance weighting. Heterogeneity was quantified by Q test, I^2 and tau statistics [14,15] (please see http://hyper.ahajournals.org, S2). Publication bias was assessed and reported using a funnel plot (please see http://hyper.ahajournals.org), S8).

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

In order to analyse all randomised comparisons of quarter dose therapy vs. placebo and vs. standard dose monotherapy, some participants contributed to more than one analysis and not all comparisons within multi-arm trials were included. For example, Frishman et al[17] conducted a 4x3 factorial dose response trial of two agents, with 12 cells labeled A-L in the table below:

		Thiazide dose		
		0	¼	1
Beta-blocker dose	0	A	B	C
	¼	D	E	F
	1	G	H	I
	4x	J	K	L

These cells contributed to the different analyses in the following way:

Comparison	Cells included in comparison(s)
¼ vs. placebo	D vs. A, B vs. A
¼ vs. standard dose	B vs. ½(C+G), D vs. ½(C+G)
Dual ¼ vs. placebo	E vs. A
Dual ¼ vs. standard dose	E vs. C, E vs. G

Variability data were absent in 12 trials, in which cases the Standardard deviation (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 Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT),[20] and for uric acid from the review by Weidmann et al.[21] Meta-regression was used to undertake subgroup analysis of the effect that age and treatment period (>6 weeks) had on efficacy. Also, three sensitivity analyses were undertaken, to compare fixed-effect vs. random effects

models, standardised vs. non-standardised blood pressure differences, and the impact of imputation for studies with missing variability data.

RESULTS

Search results

The initial search identified 1,730 studies, with 1,554 screened following exclusion of duplicate citations (figure 1). 58 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 (please see http://hyper.ahajournals.org). web appendix 2).

Study characteristics

S1 of the online supplement details the characteristics of included studies (please see http://hyper.ahajournals.org). On average the trials were published 17 years ago, and 85% of trials had eligibility criteria based solely on DBP. Of the 42 studies, 38 reported quarter-dose monotherapy, seven reported dual quarter-dose combination therapy and two reported quadruple quarter-dose therapy compared to 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 vs. placebo. Fourteen trials[w8,10,12-13,15,17-18,20,21,22,24,34-35,37] were factorial dose response trials, testing several doses of two agents. Only one out of the 42 studies did not have at least one arm containing standard dose monotherapy, and all but two included a placebo control arm. Overall, there were 20,284 participants with a mean age of 54 years, 61% were male and mean baseline blood pressure was 154/101 mmHg.

Efficacy

Quarter-dose therapy vs. placebo

The efficacy in blood pressure lowering of single quarter-dose therapy vs. placebo was assessed in 4,721 participants in 36 trials (Figure 2). Overall, placebo-corrected single quarter-dose therapy reduced blood pressure by -4.7 (95%CI -5.4, -3.9)/ -2.4 (-2.8, -1.9) mmHg. There was broad consistency in treatment effect across the five major treatment classes (I^2 SBP: 3, DBP: 0), and each was separately significant except for CCBs.

Six trials measured the efficacy of dual quarter-dose therapy compared to 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, -4.8)/ -4.4 (-5.5, -3.3) mmHg. 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 vs. placebo. One study[w40] measured efficacy of quadruple quarter-dose therapy vs. placebo and showed an office blood pressure reduction of -22.4 (-28.3, -16.5)/ -13.1 (-17.3, -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 mmHg and -10.4/-12.5 mmHg, respectively.

Quarter-dose therapy vs. standard dose monotherapy

Figure 3 illustrates the comparisons of single, dual and quadruple quarter-dose therapy compared to 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 mmHg (2.2, 3.1) (I^2 SBP: 24.3, DBP:

10.2). Dual quarter-dose therapy showed an equivalent blood pressure lowering effect compared to standard dose monotherapy. Only one study[8] assessed blood pressure lowering with quadruple quarter-dose therapy vs. standard dose monotherapy, and showed a substantially greater blood pressure reduction in the quarter dose group of -13.1 (-20.1, -6.1) / -7.9 (-12.1, -3.7) mmHg.

Safety and tolerability

Adverse events

Fifteen studies provided data on adverse events. Overall, compared to placebo, no significant difference in the risk of adverse events in the 14 single quarter-dose comparisons [RR 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 to 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 to 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.”(personal communication, J Feely). 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.

Biochemical adverse effects

Table 2 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 to 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 to single quarter-dose TZ, dual ¼ BB + ¼ TZ and dual ¼ ACE-I + ¼ TZ. Similar trends were seen in two 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 to 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 to placebo (0.03, 95% CI 0.001 – 0.04 mmol/L; p=0.003). Standard dose TZ resulted in greater uric acid concentration vs. single quarter-dose TZ, vs. dual ¼ ARB + ¼ TZ and vs. dual ¼ BB + ¼ TZ. These findings are comparable to one trial which only reported percentage change from baseline.[24] There was a also a small difference in creatinine compared with quadruple quarter dose therapy compared to 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, 2017 reported a reduction

of 6·5 beats per minute (95% CI 2·3–10·6) compared to placebo and Mahmud and Feely, 2006 reported a reduction from baseline of 6 SD 3 beats per minute.

Quality of evidence

The Trim and Fill approach did not suggest evidence of publication bias (please see http://hyper.ahajournals.org). S8). The risk of bias was assessed in all 42 studies (please see http://hyper.ahajournals.org, S10).

Overall, eight studies described the method of sequence generation; seven 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, one single-blinded and one 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) (please see http://hyper.ahajournals.org, S9).

Sensitivity analyses

The mean blood pressure reduction for a single quarter dose vs. placebo was essentially the same using the random effects model [-4.7 (-5.4, -3.9)/-2.3 (-2.8, -1.9) mmHg], compared to the fixed-effect model [-4.7 (-5.4, -3.9)/ -2.4 (-2.8, -1.9)] mmHg]. Exclusion of studies with missing data on variability also did not substantially affect this estimate [-5.0 (-5.7, -4.2)/-2.4 (-2.9, -1.8)

mmHg]. Finally, pooling of non-standardised changes in blood pressure, rather than changes standardised to a baseline blood pressure of 150/95 mmHg provided an overall estimate of -5.0 (-5.8, -4.3)/ -2.9 (-3.4, -2.3) mmHg for quarter dose therapy vs. 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 about -4.7/ -2.4 mmHg compared to 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 two small trials that indicated 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 since 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. 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. Lastly, defining standard dose involved some assumptions, but to minimise their impact the authors used data from four 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.[9] 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 half dose blood pressure treatment was approximately 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. This 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, hydrochlorothiazide 12.5 mg) with placebo and also observed a large blood pressure reduction, of -17.9/ -9.8 mmHg.[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 3-4 mmHg 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 1-2mmHg 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 USA (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 to sequential monotherapy or stepped care.[28] Quarter doses are available for many beta-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 i.e. 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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Novelty and Significance

What Is New?

There are few data on the efficacy or tolerability of ultra-low dose blood pressure combinations.

What Is Relevant?

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

Quadruple quarter-dose therapy appears to be around twice as efficacious as standard dose monotherapy, but there are few data on side effects

Summary

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

FIGURE LEGENDS

Figure 1

Figure 2 - 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. Data presented as difference in means (lower confidence limit, upper confidence limit). Heterogeneity (Q value, p-value, I2 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, 37. SBP: 3.7, 0.36, 18.2. Trial and participant numbers represent single quarter dose vs. placebo DBP analysis. Quarter dose vs. placebo SBP analysis trials=34, participants=4,573. Mean difference (mmHg) = 1/4 dose(s) – placebo

Figure 3 - DBP- diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval. Data presented as difference in means (lower confidence limit, upper confidence limit). Heterogeneity (Q value, p-value, I2 statistic) observed for single quarter dose vs. standard dose, DBP: 37, 0.5, 0. SBP: 46, 0.1, 22. Observed for dual quarter dose vs. standard dose, DBP: 13, 0.04, 55. SBP: 4, 0.69, 0) Trial and participant numbers represent single quarter dose vs. standard dose DBP analysis. Quarter dose vs. standard dose SBP analysis trials=35, participants=5,146. Mean difference (mmHg) = 1/4 dose(s) – standard dose

Figure 4 - CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker. Risk ratio presented as risk ratio (lower confidence interval, upper confidence interval). Heterogeneity (Q value, p-value, I2

statistic) observed for single quarter dose vs. placebo: 6, 0.8, 0 observed for single quarter vs. standard dose: 17, 0.11, 35 observed for dual quarter vs. standard dose: 0.4, 0.52, 0

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
Beta-blocker					
atenolol	75mg	25-50 mg	50-100 mg	50-100 mg	**50 mg**
metoprolol	150 mg	100-200 mg	100-200 mg	100-200 mg	**100 mg**
bisoprolol	10 mg	10 mg	10 mg	10 mg	**10 mg**
carvedilol	37.5 mg	25 mg	25 mg	25-50 mg	**25 mg**
nebivolol	5 mg	5 mg	5- 40 mg	5 mg	**5 mg**
penbutolol	40 mg	-	20-40 mg	-	**40 mg**
CCB					
amlodipine	5 mg	5 - 10 mg	5 - 10 mg	2.5 - 10 mg	**5 mg**
lercanidipine	10 mg	10-20 mg	10-20 mg	10 mg	**10 mg**
nitrendipine	20 mg	-	20 mg	-	**20 mg**
verapamil	240 mg	240- 480 mg	240 mg	240 mg	**240 mg**
ACE Inhibitor					
captopril	50 mg	25-150 mg	100-150 mg	50-100 mg	**100 mg**
benazepril	7.5 mg	-	20-40 mg	-	**20 mg**
fosinopril	15 mg	10-40 mg	10-40 mg	10-40 mg	**10 mg**
lisinopril	10 mg	20 mg	20 mg	10-20 mg	**20 mg**
quinapril	15 mg	20-40 mg	20-40 mg	10-40 mg	**20 mg**
trandolapril	2 mg	1-2 mg	1 - 2 mg	1- 2 mg	**2 mg**
enalapril	10 mg	20 mg	10-20 mg	10-40 mg	**20 mg**
ARB					
valsartan	80 mg	80 mg	80-160 mg	80 mg	**80 mg**
irbesartan	150 mg	150 -300 mg	150 mg	150 mg	**150 mg**
candesartan	8 mg	8 mg	8 mg	8-16 mg	**8 mg**
telmisartan	40 mg	40 mg	20-80 mg	40 mg	**40 mg**

olmesartan	20 mg	10-20 mg	20 mg	20 mg	**20 mg**
azilsartan	-	40 mg	40 mg		**40 mg**
TZ					
hydrochlorothiazide	25 mg	-	25-50 mg	-	**25 mg**
bendroflumethazide	2.5 mg	2.5 mg	2.5 mg	-	**2.5 mg**

Legend. Standard dose was defined as the most reported usual maintenance dose recorded by the British National Formulary (BNF), Martindale and Monthly Index of Medical Specialties (MIMS). If no consensus was found, the World Health Organisation Defined Daily Dose (WHO-DDD) 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. CCB - Calcium Channel Blocker, ACE – Angiotensin-Converting-Enzyme, ARB – Angiotensin Receptor Blocker, TZ - Thiazide

Table 2. 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)					
¼ ACEI	Placebo	1	88	0.14 (-0.15, 0.43)	0.35
	Standard dose ACEI		85	0.01 (-0.29, 0.31)	0.95
¼ BB	Placebo	1	115	0.21 (-0.05, 0.47)	0.11
	Standard dose BB		121	0.10 (-0.15, 0.35)	0.43
¼ TZ	Placebo	4	294	-0.02 (-0.19, 0.16)	0.85
	Standard dose TZ		227	0.27 (0.08, 0.45)	0.01*
¼ ACEI + ¼ TZ	Placebo	1	83	0.03 (-0.27, 0.33)	0.85
	Standard dose ACEI		88	-0.22 (-0.51, 0.07)	0.14
	Standard dose TZ		85	0.36 (0.06, 0.66)	0.02*
¼ ARB + ¼ TZ	Placebo	1	77	-0.05 (-0.36, 0.26)	0.75
	Standard dose TZ		75	0.22 (-0.1, 0.54)	0.17
¼ BB + ¼ TZ	Placebo	1	84	0.07 (-0.25, 0.39)	0.67
	Standard dose BB		90	-0.04 (-0.35, 0.27)	0.80
	Standard dose TZ		67	0.39 (0.05, 0.73)	0.02*
****¼ BB + ¼ TZ**	Standard dose CCB	1	160	0.2 (-0.02, 0.42)	0.07
¼ BB + ¼ TZ + ¼ ARB + ¼ CCB	Placebo	1	19	0.1 (-0.1, 0.2)	0.90
Uric acid (µmol/L)					
¼ BB	Placebo	1	115	1.0 (-24.7, 26.7)	0.94
	Standard dose BB		121	-12.0 (-37.1, 13.1)	0.35
¼ TZ	Placebo	3	200	9.4 (-10.8, 29.6)	0.36
	Standard dose TZ		182	-35.9 (-56.5, -15.2)	0.001*
¼ ARB + ¼ TZ	Placebo	1	77	11.7 (-19.7, 43.1)	0.47
	Standard dose TZ		75	-39.8 (-71.5, -8,1)	0.01*
¼ BB + ¼ TZ	Placebo	1	84	-2.0 (-33.9, 29.9)	0.90
	Standard dose BB		90	-15.0 (-46.2, 16.2)	0.35
	Standard dose TZ		67	-48.0 (-82.0, -14.0)	0.01*
****¼ BB + ¼ TZ**	Standard dose CCB	1	160	29.0 (7.3, 50.7)	0.01*
¼ ARB + ¼ BB + ¼ CCB + ¼ TZ	Placebo	1	19	100.0 (5.0, 195.0)	0.03*

Legend. CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker., TZ – Thiazide diuretic, 1- standard dose, ¼ - quarter dose. Presented as mean difference (lower confidence interval, upper confidence interval). * represents P-value<0.05. ** signifies a trial that did not compare a dual combination with its component quarter doses. Mean difference = 1/4 dose(s) – (placebo or standard dose). Potassium: TZ vs. placebo 0.522, 0.91, 0. TZ vs. 1 dose 0.17, 0.98, 0; Uric acid: TZ vs. placebo: 0.15, 0.93, 0. TZ vs. 1 dose: 0.5, 0.80, 0.

Figure 1. PRISMA Flow Diagram

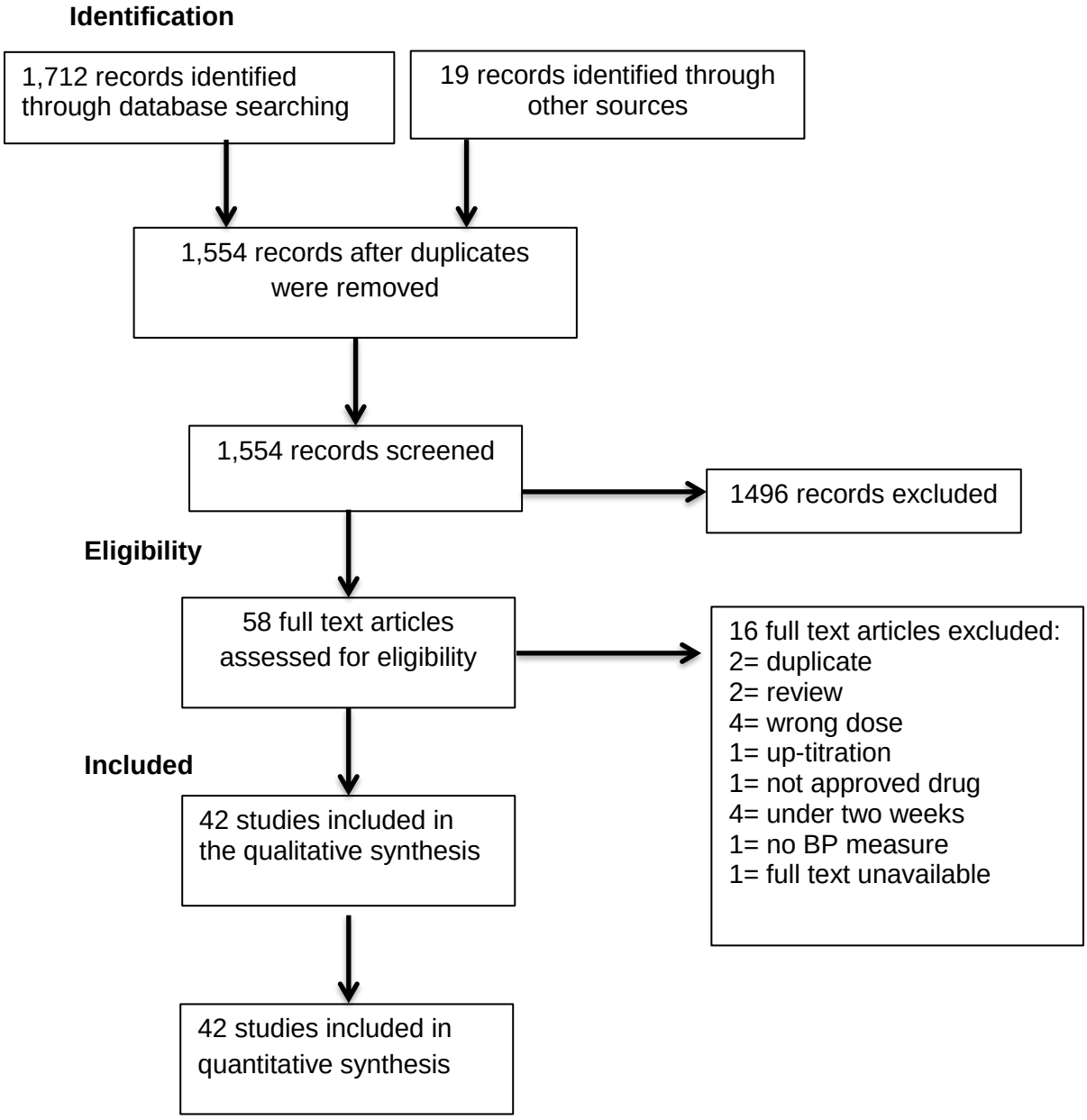


Figure 2: Efficacy of single, dual and quadruple quarter-dose therapy on blood pressure lowering, compared to placebo

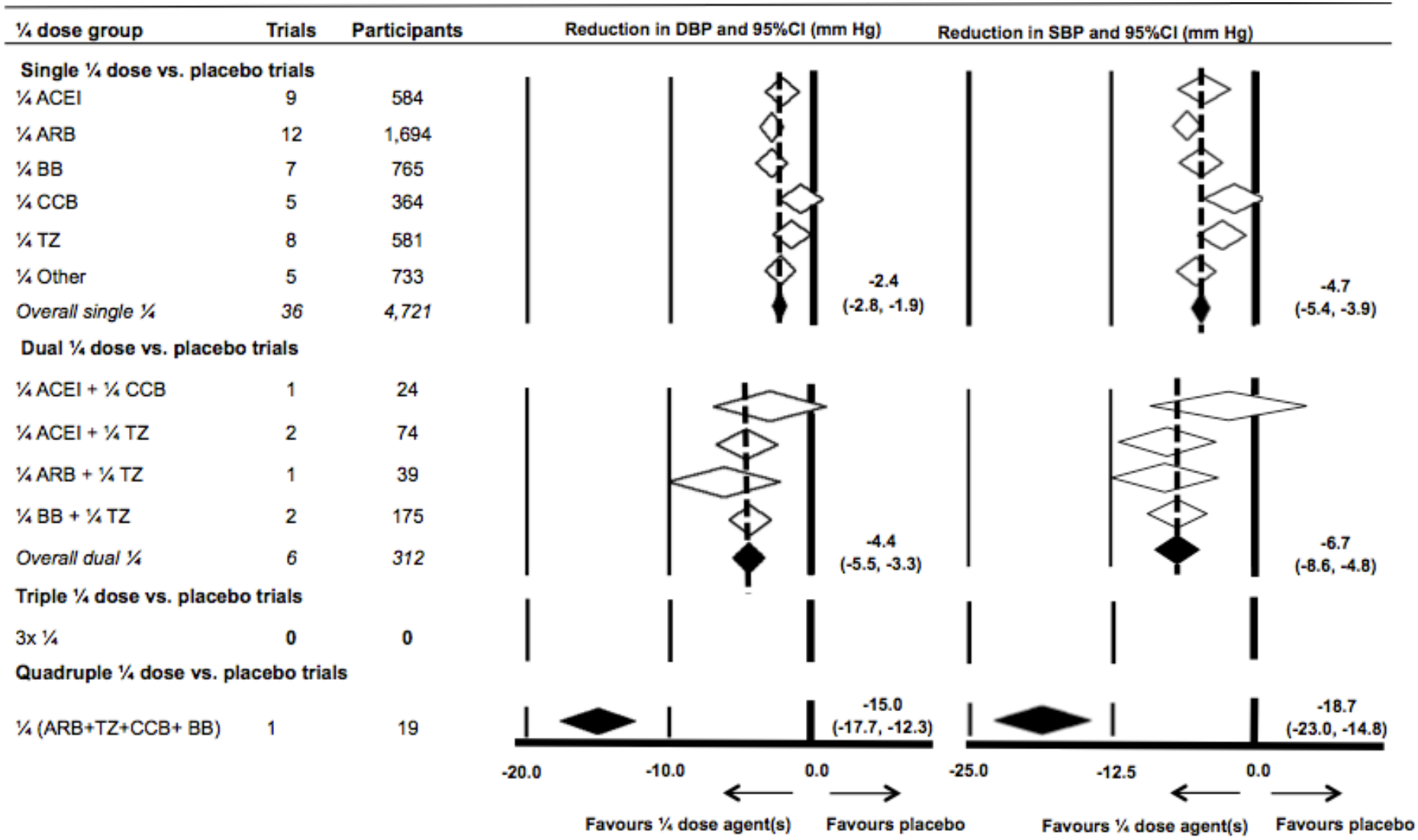


Figure 3. Efficacy in blood pressure lowering of number of quarter-dose agents compared to standard dose monotherapy

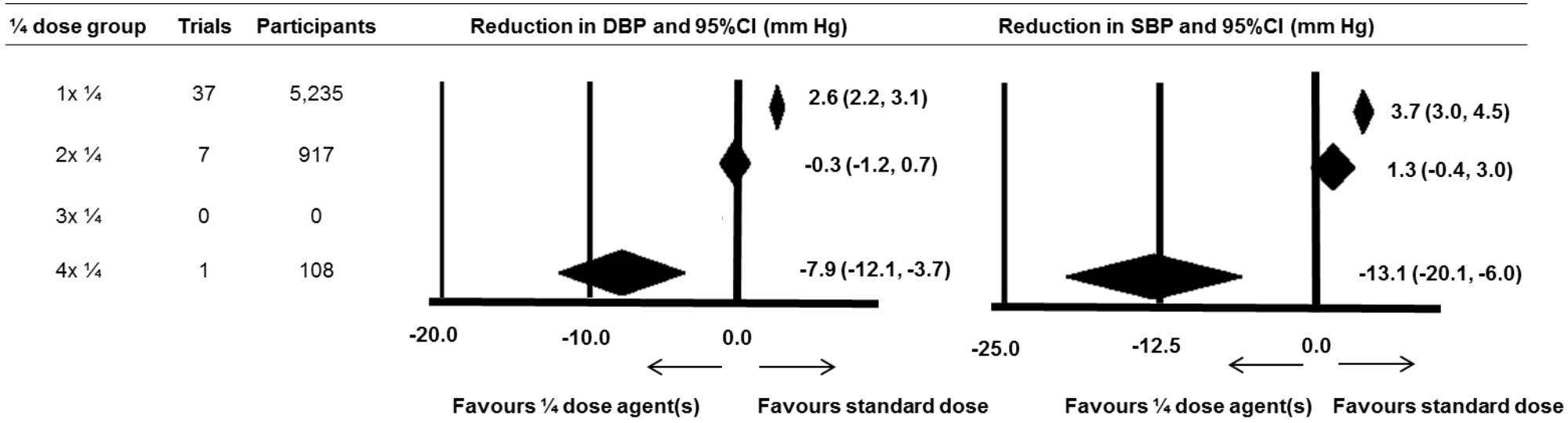


Figure 4. Risk of adverse events with increasing number of quarter-dose agents compared to placebo and standard dose monotherapy

