Quarter-dose quadruple combination therapy for initial treatment of hypertension – placebo-controlled crossover randomised trial and systematic review

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Abstract

Background: There is a pressing need for blood pressure control strategies with improved efficacy and tolerability. We examine whether using ultra-low dose quadruple combination therapy provides an approach with greater efficacy and tolerability.

Methods: We conducted a systematic review of trials evaluating the efficacy and safety of quarter-standard dose BP-lowering therapy against placebo and a randomised, placebo-controlled, double-blind, cross-over trial of a 'quadpill': a single capsule containing four BP-lowering medicines each at quarter-dose (irbesartan 37.5mg, amlodipine 1.25mg, hydrochlorothiazide 6.25mg and atenolol 12.5mg). Participants with untreated hypertension received either quadpill or matching placebo for four weeks, followed by a two-week wash-out and then the other treatment for four weeks. The primary outcome was placebo-corrected 24-hour systolic ambulatory BP reduction after four weeks.

Findings: Our systematic review identified 36 trials (n=4,721) of single quarter-dose and six trials (n=312) of dual quarter-dose therapy against placebo. The pooled placebo-corrected BP-lowering effects were 5/2mmHg and 7/5mmHg (both $p<0.0001$) respectively, and there were no side effects from either regimen. The trial is complete and stopped recruiting due to inadequate funding. It randomised 20 patients, whose mean age was 60 years and mean baseline office and 24-hour systolic BP levels were 154/90 and 138/87mmHg, respectively. Two patients dropped out for administrative reasons. The placebo-corrected reduction in systolic 24-hour BP on quadpill was 19mmHg (95%CI 14-23) and office BP was reduced by 22/13mmHg ($p<0.001$). During quadpill treatment 18/18 (100%) achieved office BP<140/90mmHg, compared to 6/18 (33%) during placebo treatment ($p=0.0013$). There were no serious adverse events and all patients reported that the quadpill was easy to swallow.

Interpretation: This small trial in the context of previous randomised evidence indicates that the benefits of quarter-dose therapy are additive across classes, and are likely to confer a clinically important BP reduction. Further examination of the quadpill concept is needed to examine effectiveness against usual treatment options and longer term tolerability.

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Clinical trial registration no. ACTRN12614001057673

INTRODUCTION

High blood pressure (BP) is a leading cause of preventable morbidity and mortality,[1] and the benefits of BP lowering treatments are well established.[2,3] Despite the plethora of BP lowering medicines available and the fact that most patients receive some treatment, multiple large-scale population studies demonstrate poor BP control in many patients globally.[4]

Multiple factors contribute to poor BP control including low adherence rates, complex guidelines recommending multiple up-titration steps and treatment inertia. The majority of treated patients only receive monotherapy,[4] which has low potency even at high doses.[5] Furthermore the increasingly strong evidence of benefits of more intensive BP lowering[6,7] highlights the need for new treatment strategies that are more efficacious, while remaining tolerable. Low-dose combination therapy holds considerable promise in this regard, since at low doses most side effects are avoided and most benefits are maintained.[8]

However, there is uncertainty about effects at ultra-low doses and whether combinations can achieve clinically relevant BP reductions. We therefore sought to assess efficacy and tolerability of ultra-low dose combination therapy by conducting a systematic review of quarter-dose BP lowering therapies and a trial of a 'quadpill', containing four common BP lowering medications each at quarter-dose.

METHODS

Systematic review

We conducted a systematic review of all randomised trials of quarter-dose BP therapy, identifying potentially relevant studies from searches of EMBASE, MEDLINE and Cochrane Central Registry of Controlled Trials, with each source searched from inception to June 2016; and the Food and Drug Administration and European Medicines Agency websites. Medline search terms are in appendix 1. 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. Reference lists of eligible studies and systematic reviews were also reviewed. (Appendix Figure 1) We included randomised controlled trials of adult participants (≥18 years of age) examining quarter-standard dose BP-lowering drugs against placebo for the following drug classes: angiotensin converting enzyme inhibitors, angiotensin receptor II blockers, beta-blockers, calcium channel blockers and thiazide and thiazide-like diuretics. Quarter dose was quarter of the standard dose, defined as the most frequently reported usual maintenance dose recorded by the British National Formulary,[9] Martindales and Monthly Index of Medical Specialties.[10] Two reviewers (AB, MC) independently extracted data using a standard extraction form. A third reviewer (AR) resolved any differences. Data were analysed using Comprehensive Meta-analysis Software (v3, Englewood NJ). We a fixed-effect model to estimate the effects on BP lowering and on adverse events of quarter dose BP lowering against placebo. Effect on BP was assessed using the mean

change in systolic BP (SBP) and diastolic BP (DBP) from baseline to end-of-study, with standardisation to a baseline of 150/95mmHg.[8] Adverse events included all that were reported by trials at follow up.

Clinical trial

Design and participants

The Quadpill study was a randomised, placebo-controlled, double-blind cross-over trial (Figure 1). Participants were randomised (1:1) to a group receiving the quadpill for four weeks, followed by a two-week placebo washout and then placebo for four weeks; or to a group receiving placebo, then washout, then Quadpill for the same periods. Participants were recruited from the community, predominantly through general practices in Western Sydney, Australia. Participants were eligible if they met the following inclusion criteria: 1) adults aged 18 years and over; 2) office SBP>140mmHg and/or DBP> 90mmHg on two readings on separate days; 3) baseline ambulatory SBP >135mmHg and/or DBP >85mmHg; and 4) not taking any BP medications. Exclusion criteria included: 1) definite contraindication to one or more component medications in the quadpill; 2) the responsible clinician considered that a change in current therapy would place the patient at risk; 3) severe or accelerated hypertension; 4) pregnancy; 5) inability to provide informed consent; and 6) medical illness with anticipated life expectancy less than 3 months. The study protocol was approved by the Human Research and Ethics committee at The University of Sydney and funded by a Vanguard Grant and Ross Hohnen prize from the National Heart Foundation of Australia (Grant number 100227), University of Sydney Bridging Grant and National Health and Medical Research Council of Australia program grant. Informed consent was obtained from all participants. The study is registered with the Australian and New-Zealand Clinical Trials Registry (ACTRN 12614001057673).

Intervention and randomisation

The quadpill was a single encapsulated pill containing four common BP lowering medicines each at quarter-standard dose (irbesartan 37.5mg, amlodipine 1.25mg, hydrochlorothiazide 6.25mg and atenolol 12.5mg). Quarter- doses were obtained by halving half- doses using a pill splitting device, without crushing, and were weighed to ensure accuracy of halving doses. The quarter doses were then encapsulated using gelatine capsules (DBCaps- Capsugel).[11] All trial medicines were prepared and packaged at a Therapeutic Goods Australia – Certificate of Good Manufacturing Practice licensed manufacturing facility.

Treatment allocations were at random via a computer assisted randomisation sequence and were blinded to both study staff and participants. The placebo capsule appeared identical and contained four placebo tablets of similar weight to those in the quadpill. Participants were administered a single daily capsule quadpill or placebo throughout the trial. Patients were instructed to take the capsules at the same time each day, preferably in the morning. In addition to the study drugs, all participants were provided education on healthy lifestyle options as recommended by then current local BP management guidelines.[12]

Outcomes and data collection

The primary outcome was reduction in mean 24-hour SBP at 4 weeks using ambulatory BP monitoring (ABP). The secondary outcomes included:

1) Reduction in mean 24-hour DBP and in daytime and night-time SBP and DBP at 4 weeks
2) Reduction in office SBP and DBP as measured by a standardised automated BP cuff
3) Proportion with controlled BP at 4 weeks, defined as <135/85mmHg 24-hour ABP and <140/90mmHg office BP
4) Adverse events and pre-specified adverse events with laboratory-associated parameters: rise in transaminases (ALT/AST) more than three times the upper limit of normal or doubling if baseline levels known to be elevated; drop in estimated glomerular filtration rate by >20% as estimated from serum creatinine; change in sodium, potassium and uric acid levels
5) Assessment of acceptability and tolerability

Patients underwent 24-hour ABP monitoring 4 times - baseline (off study drug), 4 weeks (on phase 1 treatment or placebo), 6 weeks (after 2 week placebo washout) and 10 weeks (on phase 3 treatment or placebo). The ABP units were calibrated at regular intervals by the laboratory according to the manufacturer's specification. Office BP was recorded three times at each visit using an OMRON T9P (HEM-759-C1). The second and the third readings were averaged for study analysis. In addition, at week 4 and week 10 blood biochemistry and a questionnaire for clinical side effects and medication compliance were administered. At study end, drug acceptability and tolerability were assessed. We recorded all adverse events. In addition, we specifically asked about clinical adverse events possibly associated with BP lowering medications: dizziness, blurred vision, syncope/collapse, chest pain/angina, shortness of breath, cough, wheeze, pedal oedema, skin rash, or itching. Study medications and investigations were provided at no cost to participants and nominal amounts to cover travel and parking costs were reimbursed.

Statistical considerations:

A sample size of 50 patients was planned to provide 90% power at α =0.05 to detect a SBP difference of 12mmHg between the intervention and control, assuming a SD of the within patient difference of 12mmHg and taking into account the possibility of a 10% loss to follow-up. The study ended at one year at the end of the budget and staffing time allocated and the original sample size was not reached.

Analyses were conducted on an intention to treat basis. All tests were two-sided. All statistical analyses were unadjusted for prognostic covariates. We reported compliance to the study drug using data on pills (doses) taken and missed doses over the time period. We used a linear mixed model to estimate the effect of the treatment on change in BP from baseline for each treatment period, according to the Kenward and Roger approach.[13] All available data were included in the model; no missing data were imputed. If a patient had missing data for one period, data from the available period were used. A sensitivity analysis was done including only patients with data available from both periods to see if the effect of treatment was modified. We also adjusted the denominator degrees of freedom of Kenward and Roger (2009)[14] to optimize for the small sample size.

We tested for carry over with an unpaired t-test of the main outcome with order as an effect. Period effect was tested by using a paired t-test comparing the main outcome in period 1 with main outcome in period 2 from the same patient. We also performed a sensitivity analysis using normal paired t-test to compare primary outcome between different period (different treatment) from the same patient, ignoring the baseline level of each period.

Continuous secondary endpoints with baseline values (e.g. daytime/ night-time ambulatory SBP/DBP) were analysed similarly to the primary endpoint. Other continuous variables without a baseline value in each period were analysed with a paired t-test. We have reported counts and percentages of all adverse events.

We tested for interaction of treatment effect with age (≤60 vs. >60 years), gender, and body mass index (BMI ≤30 vs. >30 kg/m^2). We also carried out subgroup analyses for each variable. Trial analyses were conducted using SAS 9.4 (Cary, NC, USA) software.

Role of funders: The funder had no direct involvement in any of the following: data collection, analysis, interpretation, writing of the manuscript and the decision to submit. K Vo and K Rodgers conducted the statistical analysis for this paper and together with C Chow and A Rodgers had full access to the data. CC and AR were responsible for the decision to submit the manuscript.

Results

In the systematic review we identified 36 trials (4,721 participants) that reported the efficacy of single quarter dose BP lowering compared to placebo. (Appendix table 1) Pooling the data, quarter dose BP-lowering drugs reduced SBP by 4.7mmHg (95% CI -5.4 to -3.9) and DBP by 2.4mmHg (95% CI -2.8 to -1.9). (Figure 2) Further 14 of these trials (n=1,838) reported adverse events in single quarter dose versus placebo. Overall single quarter-dose agents had no increase in adverse events compared to placebo (Risk Ratio [RR] 1.0, 95% CI 0.88 – 1.10). Six trials (n=312) also examined dual quarter dose against placebo and found a reduction in SBP and DBP of 6.7mmHg (95% CI -4.8 to -8.6) and 4.4mmHg (95% CI -3.3 to -5.5) respectively and no increase in side effects compared to placebo (RR 0.93, 95% CI 0.29 – 2.9). No trials of triple or quadruple quarter dose therapy versus placebo were identified.

In the quadpill trial, 55 patients were screened, and 21 participants found eligible, one patient declined prior to drug initiation. Twenty were randomised between November 2014 and December 2015 and two withdrew at the end of the first treatment period because of social reasons (Figure 3). Baseline characteristics of the study population are shown in Table 1.

The difference in mean 24-hour SBP between quadpill and placebo periods was –18.7mmHg (95% CI -23.0 to -14.3) and 24-hour DBP was –14.2mmHg (94% CI -16.9 to -11.5). Similarly the difference in office SBP was -22.4mmHg (95% CI 16.5 to 28.3) and office DBP –13.1mmHg (95% CI 8.9 to 17.3). Daytime ASBP, daytime ADBP, night-time ASBP and night-time ADBP were all significantly lower with quadpill (Table 2). All participants achieved an office SBP <140 and DBP<90mmHg on the quadpill compared to

6/18 (33%) while on placebo (RR 3.01, 95% CI 1.54; 5.89; p=0.0013). ABP<135/85mmHgwas achieved by 15/18 (83%) while on the quadpill compared to 7/18 (39%) while on placebo, (RR 2.14, 95% CI 1.25-3.65; p=0.0053)

Tests for both a carryover effect (t=-0.17, p=0.868) and a period effect (t=-1.05, p=0.308) were not significant. There were no significant interactions by age, sex or BMI. In sensitivity analysis using a standard comparison (paired t-test), results were virtually identical with a difference in mean 24-hour SBP between the quadpill and placebo periods of -18.7mmHg (95% CI -23.1 to -14.2). Similarly, in a second sensitivity analysis that included only patients with complete data (n=18) from both periods, results were also virtually identical with the difference in mean 24-hour SBP of -18.7 (95% CI -23.2 to -14.2).

Treatment compliance was high with the mean number of capsules missed in the last week 0.2 (SD 0.4) for quadpill and 0.3 (SD 0.6) for placebo. All 18 participants who finished the study completed the end-of-study acceptability questionnaire, with all reporting the study medication was either very easy (n=13) or easy (n=5) to swallow. In addition, all 18 participants reported it was either very likely (n=10) or likely (n=8) they would take the quadpill if available for use.

There were no serious adverse events and no patients had a pre-specified adverse events. One participant reported dizziness while on the quadpill causing temporary discontinuation of treatment; one reported vertigo during the washout period on placebo; and one reported urinary frequency in quadpill and placebo phases (see Table 3).

The mean heart rate was lower on Quadpill treatment, difference between groups of 6.5 beats per minute (95% CI 2.3 to 10.6). There was a difference in changes in creatinine (4.4, 95% CI 0.9 – 7.8 mmol/L; p=0.02) and urate (0.03, 95% CI 0.001 – 0.04 mmol/L; p=0.003) in the quadpill compared to the placebo treatment periods, but no patient had more than a 12% increase in either variable. There were no significant differences in ALT, AST, sodium, potassium, total cholesterol or LDL-cholesterol. (Appendix table 3)

The results of the systematic review together with the office BP reduction in the quadpill trial are summarised in Figure 2.

Discussion

This study found that a capsule containing four quarter-dose BP lowering drugs reduced 24-hour ambulatory BP by 19/14mmHg and achieved office BP <140/90mmHg in all participants. This BP lowering effect is consistent with the findings of our systematic review that single quarter-dose therapy produces a 5/2mmHg BP reduction against placebo and that dual quarter-dose therapy produces additional effects on BP.[8] Together with findings from our systematic review that single or dual quarter-dose therapy produces no increase in side effects compared to placebo, these findings indicate

considerable potential advantages for a single capsule containing multiple BP lowering drugs in ultra-low dose.

There has been one prior trial of quadruple quarter-dose BP-lowering versus monotherapy, involving 110 untreated individuals with BP >140/90mmHg.[15] That trial observed a 26/15mmHg reduction in BP from a baseline of 160/96mmHg with therapy comprising amlodipine 1.25mg, atenolol 12.5mg, bendroflumethiazide 0.625mg and captopril 50mg, which was significantly greater than the reduction seen with each monotherapy at standard dose - compared with individual agents, the combination showed a greater systolic BP reduction than amlodipine (8 mmHg, 95% CI 1 to 14mmHg), atenolol (9, 2 to 16 mmHg), bendroflumethiazide (11, 4 to 18mmHg) and captopril (7, 1 to 14mmHg). The only other trial to date of low-dose antihypertensive therapy with more than two agents assessed triple half-dose therapy vs. placebo in a crossover trial and demonstrated a similarly large BP difference of 18/10mmHg ($p<0.001$).[16]

The main limitations of this trial is the small sample size and short follow-up duration and the minimal power it had to evaluate side effects. A major barrier to recruitment was identifying untreated individuals with elevated BP within the settings in which we work. The systematic review findings and previous related trials[15,16] suggest consistency in effect sizes and supports the minimal side effects observed. The strengths of this study include the randomised cross-over design maximising statistical power and minimising bias.

Small but statistically significant increases in creatinine and urate were observed in this trial, with no patient experiencing more than a 12% increase in either measure. There were no longer term follow-up data and any clinical implications are uncertain. Lower systemic pressure can reduce glomerular perfusion pressure and lead to longer term renal benefits for people with raised intraglomerular pressure and proteinuria.[17,18] [19,20] However, trials have also observed an increase in adverse renal outcomes with intensive BP lowering.[7,21,22] To determine the clinical implications of the creatinine differences observed in this study, studies with further long-term data are required.

Sub-optimal BP control is a global problem.[4,23] Initiating treatment with dual combination therapy has been advocated[24] as a more effective means to achieve BP control rapidly and with fewer clinical visits.[25] Our study draws on the same underlying principles but extends the concept further to initiating treatment with multiple ultra-low dose agents in a single capsule.[26] In comparison to existing approaches to BP lowering therapy, administration of a single quadruple combination capsule is likely to achieve more BP lowering than up-titrating monotherapy, since doubling the dose for BP drugs from half-dose to full dose provides only about 1-2mmHg further reduction in BP.[8] In addition a quadpill approach could address physician and patient-related treatment inertia as it reduces the need for stepped titration. It also addresses the individual variation in responsiveness to different agents through provision of a combination with a range of modes of action. Improved adherence is also likely as a result of both decreased pill burden[27] and use of lower doses to minimise side effects.[8]

In summary, this is the first placebo-controlled trial demonstrating that quarter-dose quadruple combination therapy is highly efficacious in lowering BP. It presents a novel approach that could achieve

substantially greater BP control with a single pill, which may have wide-spread clinical applicability. Further trials are required to assess the long-term efficacy and safety in a broader population, both for initial treatment and among patients with inadequate control and/or side effects while receiving monotherapy.

Panel: Research in context

Evidence before this study

Systematic review and meta-analysis of 354 randomised double-blind placebo-controlled trials of BP lowering therapy[8] identified that doubling of dose from half to full standard dose produced on average a 22% increase in BP reduction, and that the BP lowering effect of different classes of drugs were additive. While most benefits are maintained at half-dose, most side effects were avoided. One trial demonstrated a quadruple quarter-dose therapy achieved greater BP reduction than each component at standard dose.[15]

Added value of this study

We systematically reviewed the literature on placebo controlled quarter-dose BP-lowering therapy and found placebo-corrected BP reductions with single and dual quarter-dose BP lowering of 5/2mmHg and 7/5mmHg respectively. These reductions were not associated with any difference in side effects compared to placebo. Our trial provides the first placebo-controlled data on a four agent quarter-dose 'quadpill' containing irbesartan 37.5mg, amlodipine 1.25mg, hydrochlorothiazide 6.25mg and atenolol 12.5mg, combined into a single capsule). We observed a BP reduction of 19/14 mmHg in 24 hour SBP compared to placebo, and 18/18 patients achieved BP <140/90mmHg while receiving Quadpill compared to 6/8 while receiving placebo ($p<0.001$).

Implications of all the available evidence

This study provides proof of concept for an innovative approach of using ultra-low-dose quadruple combination therapy to achieve substantial BP reductions. Further studies are required to examine the generalisability of these findings and assess the longer term effects on efficacy, safety and tolerability compared to usual care.

Contributions

Systematic review: AB drafted the protocol and data collection forms, conducted search, data abstraction and data checking as first reviewer, led statistical analysis and drafted the systematic review paper. CC contributed to the conception of the review, revision of the protocol, review of data analyses. MC contributed to the literature search, trial identification, data abstraction and data checking as second reviewer; and review of data analyses. H-M D contributed to data checking as second reviewer; and review of data analyses. AR conceived the systematic review and supervised research staff working on the project. RW, AS, AP, BN, DP, HK, JT, JC, MN, CR, GH, MW, SH, ST contributed to reviewing the protocol and data analyses.

Quadpill trial: CC is the chief investigator, led the writing of the protocol and successful funding application, supervised JT and drafted the paper. JT is a PhD student who primarily implemented the study protocol, AB, MB, TU supported study recruitment. KV ran all statistical analysis supervised by KR who was primary writer of the statistical analysis plan. CC, AR, GH contributed to study design.

AR and CC conceived the initiative. All authors contributed critical review of this manuscript

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Disclosures

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George Health Enterprises, the social enterprise arm of The George Institute for Global Health, has received investment to develop fixed-dose combinations containing aspirin, statin and BP lowering drugs.

Table 1 Baseline characteristics of trial participants

Characteristics	
Mean age, years (SD)	58 (11)
24-hour SBP/ DBP (mmHg)	140 (9)/ 87 (8)
Office BP (mmHg)	154 (14) / 90 (11)
Mean months since diagnosis of hypertension (SD)	4.2 (5.4)
Female, n (%)	11 (52%)
University education	9 (43%)
Diabetes	2 (10%)
Hyperlipidaemia	5 (24%)
Previous myocardial infarction	0 (0%)
Coronary artery revascularisation	0 (0%)
Cerebrovascular disease	0 (0%)
Previous depression	4 (19%)
Current smoker	5 (46%)

SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure

Table 2 Effects of quadpill and placebo on blood pressure parameters

	Quadpill treatment period		Placebo treatment period			
Parameter	**Baseline (week 0 or week 6)**	**End of treatment (week 4 or week 10)**	**Baseline (week 0 or week 6)**	**End of treatment (week 4 or week 10)**	**Difference in change between Quadpill and Placebo period in mmHg (95% CI) ***	**p-value ***
Mean BP levels (mmHg)						
Mean 24hr SBP	138.4	119.6	137.1	138.2	-18.7 (-23.2; -14.2)	<0.0001
Daytime ASBP	141.7	121.4	140.3	143.7	-22.3 (-26.9; -17.7)	<.0001
Daytime ADBP	89.9	75.7	87.9	91.1	-15.3 (-18.1; -12.6)	<.0001
Night-time ASBP	128.8	114.4	126.2	125.4	-10.4 (-18.3; -2.6)	0.0128
Night-time ADBP	77.7	66.8	77.8	79.4	-12.5 (-17.1; -7.9)	<.0001
Mean 24hr DBP	86.7	73.3	85.1	87.6	-14.2 (-16.9; -11.5)	<.0001
Office SBP	149.9	122.1	145.8	144.6	-22.4 (-28.3; -16.5)	<.0001
Office DBP	87.4	71.8	86.1	84.8	-13.1 (-17.3; -8.8)	<.0001

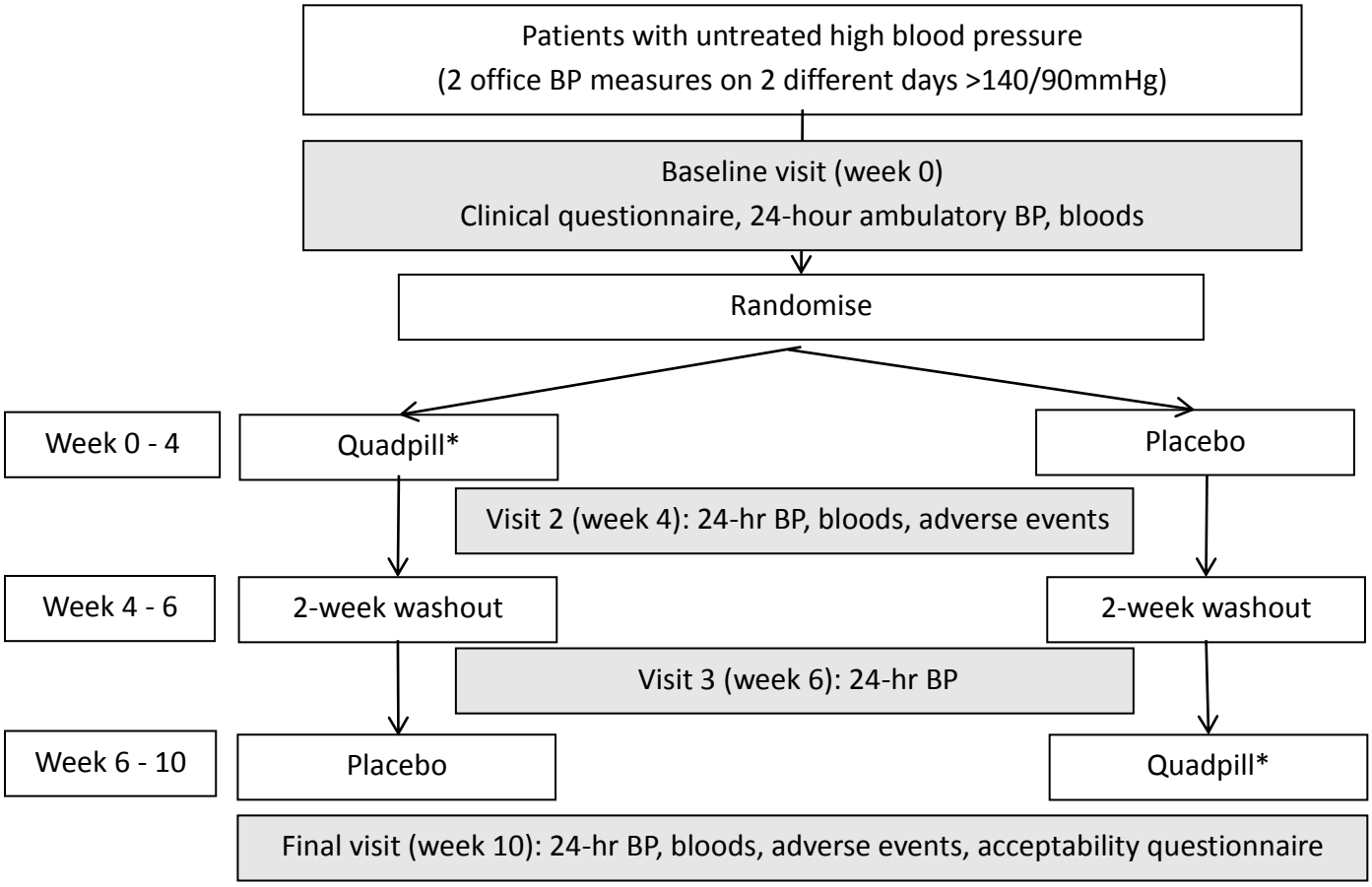
BP**:** blood pressure; SBP: systolic blood pressure; ASBP: ambulatory systolic blood pressure; ADBP: ambulatory diastolic blood pressure; DBP diastolic blood pressure; ABP: ambulatory blood pressure; CI: confidence interval; N/A: not applicable

Table 3 – Adverse events

Event	Study drug allocated when occurred	Treatment period when occurred	Severity	Action Taken	Outcome	Relationship
Gastro Illness	Quadpill	1st	Mild	None	Resolved	Not Related
Headache	Quadpill	1st	Mild	None	Resolved	Not Related
Dry Nose	Placebo	2nd	Mild	None	Resolved	Not Related
Vertigo	Neither	Between 1st & 2nd	Mild	None	Resolved	Not Related
Dizziness	Quadpill	1st	Mild	Temporarily discontinued study drug	Resolved	Related
Urinary Frequency*	Quadpill	1st	Mild	None	Resolved	Possibly Related
Urinary Frequency*	Placebo	2nd	Mild	None	Resolved	Possibly Related
Respiratory Tract Infection	Quadpill	2nd	Mild	None	Resolved	Not Related

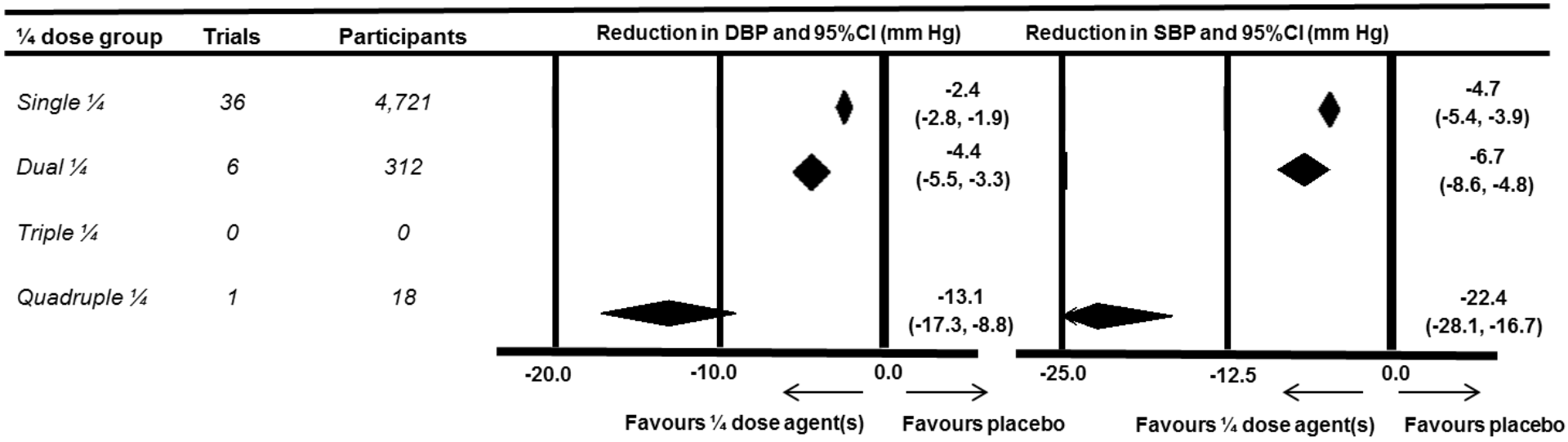
* Urine Frequency was reported by one male patient during the intervention phase and same patient in the placebo phase. He was instructed to consult local doctor for urologic assessment.

Figure 1 Study design for randomised trial



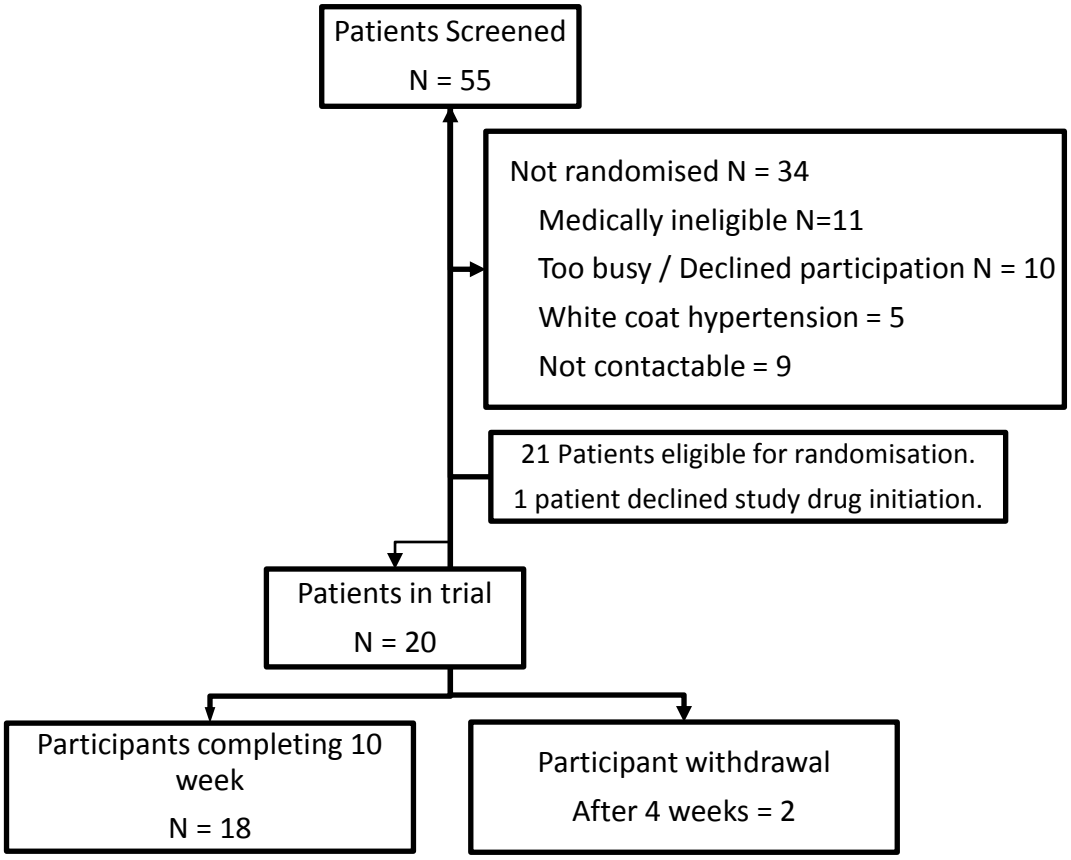
*quadpill = irbesartan 37.5mg, amlodipine 1.25mg, hydrochlorothiazide 6.25mg, atenolol 12.5mg; BP: blood pressure

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



Data on single quarter and dual quarter dose are from the systematic review. Data on quadruple quarter dose is from the Quadpill trial described in this paper.

Figure 3 Study flow diagram



Appendix

Appendix 1: Medline Search and eligible trials

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

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Web table 1. 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	-
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%
anter, 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 (½, 3/4, 1) vs. placebo	726	55	37%	Stage I-III diastolic primary hypertension	in office, sitting, trough	95<DBP<114	153/101	DBP, SBP, adverse events	6	7%
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	in office, supine	95<DBP<115	159/101	DBP, SBP, adverse events, treatment discontinuation, potassium	6	11%

							essential hypertension						
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, ½, 1) vs. placebo	683	55	15%	Mild-moderate hypertension	in office, sitting	95<DBP	151/100	DBP, SBP, uric acid	8	8%
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 hypertension	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%	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, ½, 1.5) vs. placebo	548	52	39%	Mild-moderate essential hypertension	in office, sitting	95<DBP<110	150/100	DBP, SBP	8	-
Reif, 1996	USA	double blind, 6 groups, parallel	Candesartan (¼, ½, 1, 2, 4) vs. placebo	360	55	34%	Systemic hypertension	in office, sitting, trough	95<DBP<115	153/100	DBP, SBP, adverse events, treatment discontinuation	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 hypertension	in office, sitting	90<DBP<110	158/99	DBP, SBP	6	9%
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%

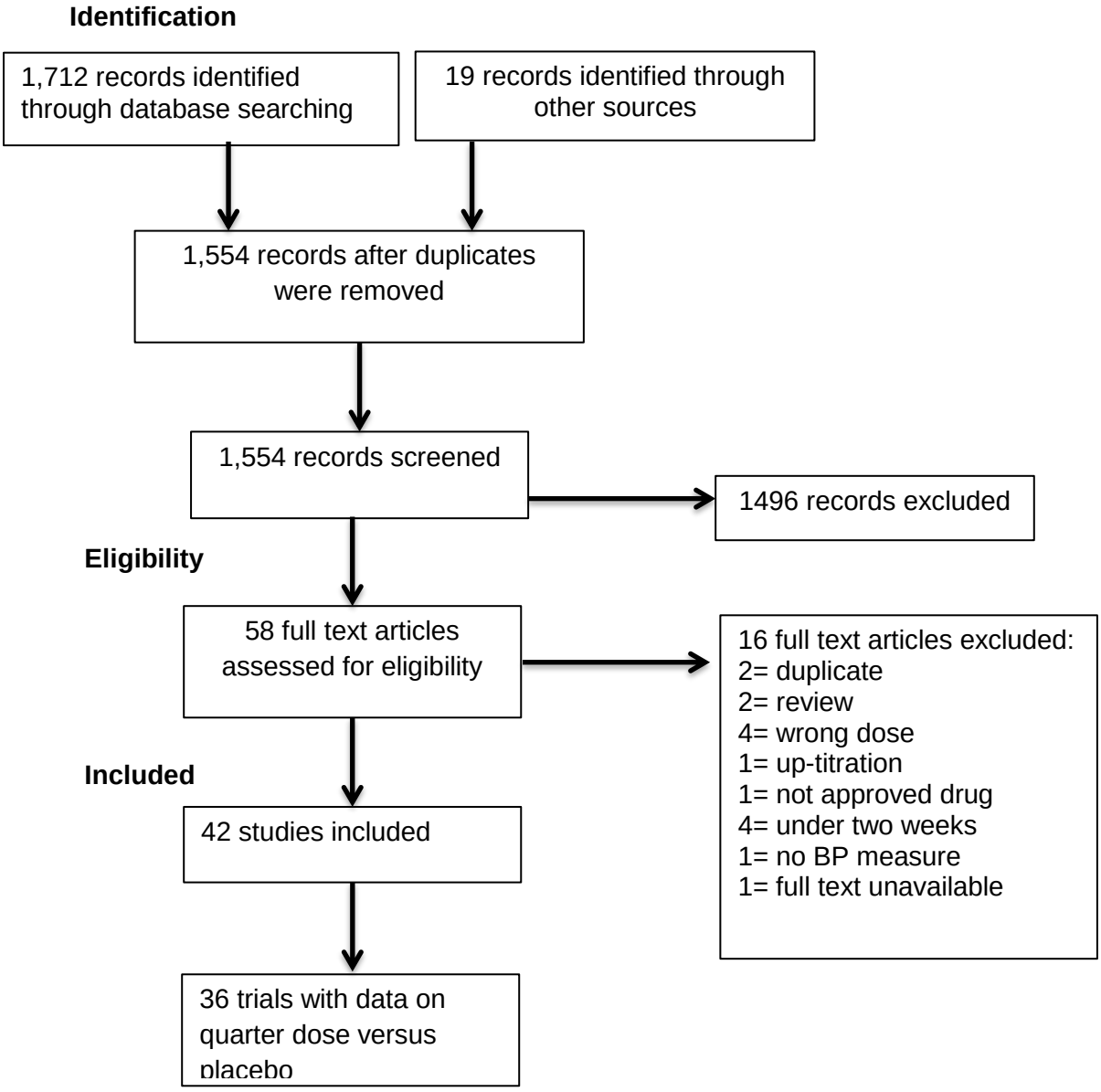
Web Table 2 Effects on 24-hour mean SBP, by treatment period and sequence allocation (mmHg)

	Treatment period		
Treatment sequence	**1**	**2**	**Within-individual difference: Quadpill - Placebo**
Quadpill then Placebo			
Mean (SD)	-21.1 (6.8)	5.3 (6.6)	-26.7 (9.2)
Sample size	10	9	9
Placebo then Quadpill			
Mean (SD)	-3.0 (17.9)	-16.4 (7.5)	-13.4 (22.9)
Sample size	9	9	9
Treatment effect			
Mean (SD)			-18.7 (2.1) & (95% CI-23.0; -14.3)
p-value			<.0001
Sample size			19

Web Table 3 – Biochemical changes

	Difference of changes in quadpill treatment period versus placebo treatment period (95% CI)	p-value *
Creatinine (µmol/L)	4.4 (0.9; 7.8)	0.017
ALT (µmol/L)	3.1 (-4.3; 10.5)	0.38
AST (µmol/L)	-7.3 (-24.1; 9.5)	0.37
Sodium (mmol/L)	-0.6 (-1.8; 0.6)	0.32
Potassium (mmol/L)	-0.04 (-0.2; 0.1)	0.62
Urate (mmol/L)	0.03 (0.01; 0.04)	0.003
Total Cholesterol	0.2 (-0.2; 0.6)	0.27
LDL Cholesterol (mmol/L)	0.2 (-0.2; 0.5)	0.31

Web Figure 1 PRISMA Flow Diagram



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