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

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Summary

Background Globally, most patients with hypertension are treated with monotherapy, and control rates are poor because monotherapy only reduces blood pressure by around 9/5 mm Hg on average. There is a pressing need for blood pressure-control strategies with improved efficacy and tolerability. We aimed to assess whether ultra-low-dose combination therapy could meet these needs.

Methods We did a randomised, placebo-controlled, double-blind, crossover trial of a quadpill—a single capsule containing four blood pressure-lowering drugs each at quarter-dose (irbesartan 37.5 mg, amlodipine 1.25 mg, hydrochlorothiazide 6.25 mg, and atenolol 12.5 mg). Participants with untreated hypertension were enrolled from four centres in the community of western Sydney, NSW, Australia, mainly by general practitioners. Participants were randomly allocated by computer to either the quadpill or matching placebo for 4 weeks; this treatment was followed by a 2-week washout, then the other study treatment was administered for 4 weeks. Study staff and participants were unaware of treatment allocations, and masking was achieved by use of identical opaque capsules. The primary outcome was placebo-corrected 24-h systolic ambulatory blood pressure reduction after 4 weeks and analysis was by intention to treat. We also did a systematic review of trials evaluating the efficacy and safety of quarter-standard-dose blood pressure-lowering therapy against placebo. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12614001057673. The trial ended after 1 year and this report presents the final analysis.

Findings Between November, 2014, and December, 2015, 55 patients were screened for our randomised trial, of whom 21 underwent randomisation. Mean age of participants was 58 years (SD 11) and mean baseline office and 24-h systolic and diastolic blood pressure levels were 154 (14)/90 (11) mm Hg and 140 (9)/87 (8) mm Hg, respectively. One individual declined participation after randomisation and two patients dropped out for administrative reasons. The placebo-corrected reduction in systolic 24-h blood pressure with the quadpill was 19 mm Hg (95% CI 14–23), and office blood pressure was reduced by 22/13 mm Hg (p=0.0001). During quadpill treatment, 18 (100%) of 18 participants achieved office blood pressure less than 140/90 mm Hg, compared with six (33%) of 18 during placebo treatment (p=0.0013). There were no serious adverse events and all patients reported that the quadpill was easy to swallow. Our systematic review identified 36 trials (n=4721 participants) of one drug at quarter-dose and six trials (n=312) of two drugs at quarter-dose, against placebo. The pooled placebo-corrected blood pressure-lowering effects were 5/2 mm Hg and 7/5 mm Hg, respectively (both p<0.0001), and there were no side-effects from either regimen.

Interpretation The findings of our small trial in the context of previous randomised evidence suggest that the benefits of quarter-dose therapy could be additive across classes and might confer a clinically important reduction in blood pressure. Further examination of the quadpill concept is needed to investigate effectiveness against usual treatment options and longer term tolerability.

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Introduction High blood pressure is a leading cause of preventable morbidity and mortality,1 and the benefits of blood pressure-lowering treatments are well established.2,3 Despite the plethora of blood pressure-lowering medicines available, and the fact that, once found to have high blood pressure, most patients receive some treatment, findings of multiple large-scale population studies show poor blood pressure control in many patients globally.4 Many factors contribute to poor blood pressure control, including low adherence rates, complex guidelines recommending multiple up-titration steps, and treatment inertia. Most treated patients only receive monotherapy, which has low potency even at high doses.5 Furthermore, the increasingly strong evidence showing benefits of more intensive blood pressure lowering6,7 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. However, there is uncertainty about effects at ultra-low doses and whether combinations can achieve clinically relevant blood pressure reductions. We, therefore, sought to assess efficacy and tolerability of ultra-low-dose combination therapy by conducting a systematic review of quarter-dose blood pressure-lowering therapies and a randomised trial of a quadpill containing four common blood pressure-lowering medications, each at quarter-dose.

**Methods**

**Systematic review**

We did a systematic review of all randomised trials of quarter-dose blood pressure therapy, identifying potentially relevant studies from searches of Embase, MEDLINE, and the Cochrane Central Registry of Controlled Trials, with each source searched from inception to June, 2016; we also searched the websites of the US Food and Drug Administration and the European Medicines Agency. MEDLINE search terms are provided in the appendix (pp 1, 2). We searched trial registers for any ongoing trials, including WHO’s International Clinical Trials Registry platform, the Australian New Zealand Clinical Trials Registry, and the Clinical Trials Registry—India. We also retrieved studies from reference lists of key clinical trials, systematic reviews, and published articles, and reviewed the reference lists of eligible studies and systematic reviews (appendix pp 3–6, 14). We included randomised controlled trials of adult participants (≥18 years of age) in which quarter-standard-dose blood pressure-lowering drugs were compared with placebo for the following drug classes: angiotensin-converting-enzyme inhibitors; angiotensin receptor II blockers; β blockers; calcium-channel blockers; and thiazide and thiazide-like diuretics. Quarter-dose was a quarter of the standard dose, defined as the most frequently reported usual maintenance dose recorded by therapy and found that one and two drugs at quarter-dose led to placebo-corrected blood pressure reductions of 5/2 mm Hg and 7/5 mm Hg, respectively. These reductions were not associated with any difference in side-effects compared with placebo. Our trial provides the first placebo-controlled data on four quarter doses, indicating a 22/13 mm Hg reduction in blood pressure.

**Implications of all the available evidence**

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

**Research in context**

**Evidence before this study**

Findings of a systematic review and meta-analysis of 354 randomised, double-blind, placebo-controlled trials of blood pressure-lowering therapy showed that half-standard-dose achieved almost 80% as much blood pressure lowering as did standard dose, and that the blood pressure-lowering effect of different classes of drugs was additive. Although most benefits were maintained at half-dose, most side-effects were avoided. Findings of another trial showed that four drugs at quarter-dose achieved greater blood pressure reduction than did each component at standard dose.

**Added value of this study**

We systematically reviewed the literature on placebo-controlled, quarter-dose blood pressure-lowering therapy and found that one and two drugs at quarter-dose led to placebo-corrected blood pressure reductions of 5/2 mm Hg and 7/5 mm Hg, respectively. These reductions were not associated with any difference in side-effects compared with placebo. Our trial provides the first placebo-controlled data on four quarter doses, indicating a 22/13 mm Hg reduction in blood pressure.

**Clinical trial design and participants**

The Quadpill study was a randomised, placebo-controlled, double-blind, crossover trial (figure 1). We recruited participants from four centres in the community, predominantly through general practices, in western Sydney, NSW, Australia. We judged participants eligible if they met the following inclusion criteria: adults aged 18 years and older; office systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg, or both; and not taking any blood pressure drugs. Exclusion criteria included: definite contraindication to one or more component agents in the quadpill; the responsible clinician judged that a change in current therapy would place the patient at risk; severe or accelerated hypertension; pregnancy; inability to provide informed consent; and 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. We obtained informed consent from all participants.
Randomisation and masking
We randomly allocated participants in a 1:1 ratio to either: a group receiving the quadpill for 4 weeks, followed by a 2-week placebo washout, then placebo for 4 weeks; or a group receiving placebo, then washout, then the quadpill for the same periods. The quadpill was a single encapsulated pill containing four common blood pressure-lowering drugs, each at quarter-standard-dose, as defined above (irbesartan 37.5 mg, amlodipine 1.25 mg, hydrochlorothiazide 6.25 mg, and atenolol 12.5 mg). We selected the most commonly used drug from each class in Australia. We obtained quarter-doses by halving half-dose tablets using a pill-splitting device, without crushing, and we weighed the pills to ensure accuracy of halving doses. We then encapsulated the quarter doses using gelatine capsules (DBCaps; Capsugel, Morristown, NJ, USA). All trial medicines were prepared and packaged at a manufacturing facility licensed with a Certificate of Good Manufacturing Practice by the Therapeutic Goods Administration of Australia.

Treatment allocations were done at random via a computer-assisted randomisation sequence and were masked to study staff enrolling participants, care providers, outcome assessors, and participants. The placebo capsule appeared identical and contained four placebo tablets of similar weight to those in the quadpill. We gave participants a single daily capsule quadpill or placebo throughout the trial. We instructed patients to take the capsules at the same time each day, preferably in the morning. In addition to the study drugs, we provided all participants with education on healthy lifestyle options, as recommended by local blood pressure management guidelines that were current at the time.11

Procedures
We did 24-h ambulatory blood pressure monitoring four times (figure 1): at baseline (off study drug); at 4 weeks (period one treatment or placebo); at 6 weeks (after 2-week placebo washout); and at 10 weeks (period two treatment or placebo). Ambulatory blood pressure monitoring machines were calibrated according to the manufacturer’s specification. We recorded office blood pressure three times at each study visit using an Omron T9P blood pressure monitor (HEM-759-C1; Omron Healthcare, Hoofddorp, Netherlands). We averaged the second and third readings for study analysis. We took readings while participants were seated and rested, but not while they had been left unattended.11 Furthermore, at week 4 and week 10, we did blood biochemistry analyses and administered a questionnaire for clinical side-effects and medication compliance. At study end, we assessed drug acceptability and tolerability. We recorded all adverse events and asked patients specifically about clinical adverse events associated with blood pressure-lowering drugs—ie, dizziness, blurred vision, syncope or collapse, chest pain or angina, shortness of breath, cough, wheeze, pedal oedema, skin rash, or itching. The study doctor (JT) and a clinical cardiologist, in consultation with the principal investigator if needed, judged the severity of adverse events and whether they were related to study treatment. We provided study drugs and investigations at no cost to participants and we reimbursed nominal amounts to cover travel and parking costs.

Outcomes
The primary outcome was reduction in mean 24-h systolic blood pressure at 4 weeks using ambulatory blood pressure monitoring. Secondary outcomes included: reduction in mean 24-h diastolic blood pressure and in daytime and night-time systolic and diastolic blood pressure at 4 weeks; reduction in office systolic and diastolic blood pressure, as measured by a standardised automated blood pressure cuff; the proportion of participants with controlled blood pressure at 4 weeks (defined as <135/85 mm Hg 24-h ambulatory blood pressure and <140/90 mm Hg office blood pressure); adverse events and prespecified adverse events with laboratory-associated parameters (ie, rise in alanine aminotransferase and aspartate aminotransferase of more than three times the upper limit of normal, or doubling if baseline levels were known to be elevated; a drop in estimated glomerular filtration rate by more than 20%, as estimated from serum creatinine; and a change in levels of sodium, potassium, and uric acid); and assessment of acceptability and tolerability.
We planned a sample size of 50 patients to provide 90% power at an α of 0·05, to detect a difference in systolic blood pressure of 12 mm Hg between the quadpill and placebo, assuming an SD of the within-patient difference of 12 mm Hg and taking into account the possibility of a 10% loss to follow-up. The study ended at 1 year at the end of the budget and staffing time allocated and the original sample size was not reached. Analyses were by intention to treat. All tests were two-sided. All statistical analyses were unadjusted for prognostic covariates. We reported compliance to study drug using data for pills (doses) taken and missed doses over the study period. We used a linear mixed model to estimate the effect of the treatment on change in mean 24-h systolic blood pressure from baseline for each treatment period (primary outcome), according to the Kenward and Roger approach.12 We included all available data in the model; no missing data were imputed. If a patient had missing data for one period, we used data from the available period. We did a sensitivity analysis including only patients with data available from both periods. We also adjusted the denominator degrees of freedom of Kenward and Roger13 to optimise for the small sample size.

We tested for carry-over with an unpaired t test of the main outcome, with order as an effect. We tested period effect by using a paired t test comparing the main outcome in period one (baseline to week 4) with main outcome in period two (week 6 to week 10) from the same patient. As well as the Kenward and Roger approach, we also did a sensitivity analysis using a standard paired t test to compare the change in primary outcome between different periods.

We analysed continuous secondary endpoints with baseline values (eg, daytime/night-time ambulatory systolic/diastolic blood pressure) similarly to the primary endpoint. We analysed other continuous variables without a baseline value in each period 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), sex, and body-mass index (BMI ≤30 vs >30 kg/m²). We also did subgroup analyses for each variable. We did trial analyses using SAS version 9.4.

This trial is registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12614001057673.

Role of the funding source
The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. KV, KR, CKC, and AR had full access to all data in the study. CKC and AR had final responsibility for the decision to submit for publication.

Results
Between November, 2014, and December, 2015, 55 patients were screened for the Quadpill trial, and 21 individuals were judged eligible and randomly allocated to a treatment group (figure 2). Baseline characteristics of the study population are shown in table 1. One patient declined participation before study drug initiation and two participants withdrew at the end of the first treatment period for social reasons (figure 2). Therefore, 18 patients had complete data for the primary outcome.

The difference in mean 24-h systolic blood pressure between quadpill and placebo periods was 18·7 mm Hg.
(95% CI 14–2–23–0), and in 24-h diastolic blood pressure was 14·2 mm Hg (11·5–16·9). Similarly, the difference in office systolic and diastolic blood pressure was 22·4 mm Hg (16·5–28·3) and 13·1 mm Hg (8·9–17·3), respectively (table 2). Daytime ambulatory systolic blood pressure, daytime ambulatory diastolic blood pressure, night-time ambulatory systolic blood pressure, and night-time ambulatory diastolic blood pressure were all significantly lower with the quadpill (table 2). All participants (18/18 [100%]) achieved office systolic and diastolic blood pressure less than 140/90 mm Hg while on the quadpill, compared with six (33%) of 18 while on placebo (risk ratio [RR] 3·01, 95% CI 1·54–5·89; p=0·0013). Ambulatory blood pressure less than 135/85 mm Hg was achieved by 15 (83%) of 18 participants while on the quadpill compared with seven (39%) of 18 while on placebo (RR 2·14, 95% CI 1·25–3·65; p=0·0128).

Data are mean (SD), unless otherwise stated. *Difference in change between quadpill and placebo period.

### Table 2: Effects of quadpill and placebo on blood pressure variables

<table>
<thead>
<tr>
<th>Study drug allocated when adverse event occurred</th>
<th>Treatment period when adverse event occurred</th>
<th>Severity*</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Relation to study drug*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal illness Quadpill</td>
<td>First</td>
<td>Mild</td>
<td>None</td>
<td>Resolved</td>
<td>Not related</td>
</tr>
<tr>
<td>Headache</td>
<td>Quadpill</td>
<td>First</td>
<td>Mild</td>
<td>Resolved</td>
<td>Not related</td>
</tr>
<tr>
<td>Dry nose</td>
<td>Placebo</td>
<td>Second</td>
<td>Mild</td>
<td>Resolved</td>
<td>Not related</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Neither</td>
<td>Between first and second</td>
<td>Mild</td>
<td>Resolved</td>
<td>Not related</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Quadpill</td>
<td>First</td>
<td>Mild</td>
<td>Temporarily discontinued study drug</td>
<td>Related</td>
</tr>
<tr>
<td>Increased urinary frequency†</td>
<td>Quadpill</td>
<td>First</td>
<td>Mild</td>
<td>Resolved</td>
<td>Possibly related</td>
</tr>
<tr>
<td>Increased urinary frequency†</td>
<td>Placebo</td>
<td>Second</td>
<td>Mild</td>
<td>Resolved</td>
<td>Possibly related</td>
</tr>
<tr>
<td>Respiratory-tract infection</td>
<td>Quadpill</td>
<td>Second</td>
<td>Mild</td>
<td>Resolved</td>
<td>Not related</td>
</tr>
</tbody>
</table>

*Judged by the study doctor (JT) and a clinical cardiologist, in consultation with the principal investigator if needed. †Reported by one male patient during the intervention period and the same patient in the placebo period; we instructed him to consult a local doctor for urological assessment.

### Table 3: Adverse events

(95% CI 14–2–23–0), and in 24-h diastolic blood pressure was 14·2 mm Hg (11·5–16·9). Similarly, the difference in office systolic and diastolic blood pressure was 22·4 mm Hg (16·5–28·3) and 13·1 mm Hg (8·9–17·3), respectively (table 2). Daytime ambulatory systolic blood pressure, daytime ambulatory diastolic blood pressure, night-time ambulatory systolic blood pressure, and night-time ambulatory diastolic blood pressure were all significantly lower with the quadpill (table 2). All participants (18/18 [100%]) achieved office systolic and diastolic blood pressure less than 140/90 mm Hg while on the quadpill, compared with six (33%) of 18 while on placebo (risk ratio [RR] 3·01, 95% CI 1·54–5·89; p=0·0013). Ambulatory blood pressure less than 135/85 mm Hg was achieved by 15 (83%) of 18 participants while on the quadpill compared with seven (39%) of 18 while on placebo (RR 2·14, 95% CI 1·25–3·65; p=0·0128).

Tests for both a carry-over effect (p=0·868) and a period effect (p=0·308) were not significant. There were no significant interactions by age, sex, or BMI. In one sensitivity analysis, using a standard comparison (paired t test), results were virtually identical, with a difference in mean 24-h systolic blood pressure between the quadpill and placebo of 18·7 mm Hg (95% CI 14·2–23·2; appendix p 12). Similarly, in a second sensitivity analysis, in which we only included patients who did not have missing data (n=18), results were also virtually identical, with the difference in mean 24-h systolic blood pressure of 18·7 mm Hg (95% CI 14·2–23·2).

Treatment compliance was high, with a mean number of capsules missed in the last week of 0·2 (SD 0·4) for the quadpill and 0·3 (0·6) for placebo. 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. Moreover, 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 prespecified adverse event. One participant reported dizziness while on the quadpill, causing temporary discontinuation of treatment, and one reported increased urinary frequency in quadpill and placebo periods, which were judged related or possibly related to study treatment (table 3).

Mean heart rate was lower with the quadpill treatment than with placebo, with a difference between groups of 6·5 beats per minute (95% CI 2·3–10·6). There was a difference between the quadpill and placebo with respect to changes in creatinine (4·4 mmol/L, 95% CI 0·9–7·8; p=0·02), urate (−0·03 mmol/L, 95% CI −0·01–0·04; p=0·003), and glucose (−0·2 mmol/L, 95% CI −0·02–0·04; p=0·04), but no patient had more than a 12% increase in any variable (appendix p 13). Levels of alanine aminotransferase, aspartate aminotransferase, sodium, potassium, total cholesterol, or LDL-cholesterol did not differ between the quadpill and placebo.

In the systematic review, 36 trials (4721 participants) were identified that reported the efficacy of one blood pressure-lowering drug at quarter-dose compared with placebo (appendix pp 7–11). Pooling these data, quarter-dose blood pressure-lowering drugs reduced systolic blood pressure by 4–7 mm Hg (95% CI 3·9–5·4) and diastolic blood pressure by 2–4 mm Hg (1·9–2·8; figure 3). Adverse events were reported in 14 of these trials (n=1838), with no increase noted in adverse events for one drug at quarter-dose compared with placebo (RR 1·0, 95% CI 0·88–1·10). Furthermore, six trials (n=312) were identified in which two drugs at quarter-dose were compared with placebo. The pooled reduction in systolic and diastolic blood pressure was 6·7 mm Hg (95% CI 4·8–8·6) and 4·4 mm Hg (3·3–5·5), respectively. No increase in side-effects was noted with two drugs at quarter-dose compared with placebo (RR 0·93, 95% CI 0·29–2·9). No trials of three or four drugs at quarter-dose versus placebo were identified in the systematic review.

**Discussion**

Our trial findings show that a capsule containing four blood pressure-lowering drugs each at quarter-dose reduced 24-h ambulatory blood pressure by roughly 19/14 mm Hg and achieved an office blood pressure less than 140/90 mm Hg in all participants. When large effects are seen in small trials, it is especially important to review in the context of past evidence; our systematic review findings and those of previous similar trials are consistent with our finding of a large benefit with minimum side-effects.

As far as we are aware, our findings are the first placebo-corrected results showing the full effects of four drugs at quarter-dose. Together with our systematic review finding that one or two drugs at quarter-dose produces no increase in side-effects compared with placebo—our clinical trial findings suggest considerable potential advantages for a single capsule containing multiple blood pressure-lowering drugs at ultra-low dose. A major novel feature of the proposed quadpill approach is the theoretical advantage of initiating therapy with a highly effective and tolerable combination versus starting with fewer agents and titrating up (which in practice is rarely done well). Thus, initiation of combination therapy at very low doses might, for a worthwhile proportion of patients, achieve the blood pressure targets seen in SPRINT without the multiple titration steps. However, as yet, there is no direct head-to-head evidence for the quadpill approach being better than that used currently, and comparison of the quadpill with existing stepped-care approaches is required in randomised clinical trials.

The main limitations of our trial are the small sample size, short follow-up, and minimum power to assess side-effects. A major barrier to recruitment was identifying untreated individuals with elevated blood pressure within the settings in which we work. The trial did not aim to assess the contributions of each component or the comparison with other strategies. One further issue is the definition of quarter-dose. The strengths of our study include the crossover design and use of ambulatory blood pressure monitoring, hence maximising statistical power, and the use of randomisation and placebo control to minimise bias.

We recorded significant increases in creatinine, urate, and glucose in our study, although no patient had more than a 12% increase in any measure. There were no...
longer term follow-up data and any clinical implications are uncertain. The small increases in urate are consistent with previous dose-response analyses for effects of hydrochlorothiazide26 and observations with respect to glucose and atenolol.19 Lower systemic pressure can reduce glomerular perfusion pressure and lead to longer term renal benefits for people with raised intraglomerular pressure and proteinuria.26–29 However, trials have also shown an increase in adverse renal outcomes with intensive blood pressure lowering.7,24,25 Long-term randomised data are required to determine the clinical implications of the creatinine differences observed in this study.

There has been one previous trial of four-drug quarter-dose blood pressure lowering, involving 110 untreated individuals with blood pressure greater than 140/90 mm Hg.14 In that trial, a 26/15 mm Hg reduction was recorded in blood pressure, from a baseline of 160/96 mm Hg, with therapy comprising amlopidine 1·25 mg, atenolol 12·5 mg, bendroflumethiazide 0·625 mg, and captopril 50 mg. That trial was unable to estimate a placebo-corrected reduction in blood pressure but did report significantly greater reductions with the four-drug quarter-dose therapy than those seen with each monotherapy at standard dose. Compared with individual agents, the combination showed a greater systolic blood pressure reduction than amlopidine (8 mm Hg, 95% CI 1–14), atenolol (9 mm Hg, 2–16), bendroflumethiazide (11 mm Hg, 4–18), and captopril (7 mm Hg, 1–14). In that trial, no side-effects were reported in the quadpill group and the only two withdrawals were in the atenolol group. The only other trial to date of low-dose antihypertensive therapy with more than two agents assessed three-drug half-dose therapy versus placebo in a crossover trial and showed a similarly large blood pressure reduction of 18/10 mm Hg (p<0·001).13 The placebo-corrected reduction with one-drug and two-drug standard-dose therapy at similar blood pressure levels is around 9/5 mm Hg and 17/9 mm Hg, respectively.26

Poor blood pressure control is a global problem.4,27 Initiating treatment with two-drug combination therapy has been advocated9 as a more effective means to achieve blood pressure control rapidly and with fewer clinic visits.29 Our study draws on the same underlying principles but extends the idea further to initiating treatment with multiple ultra-low-dose agents in a single capsule.30 By comparison with existing approaches to blood pressure-lowering therapy, administration of a single quadruple combination capsule is likely to achieve more blood pressure-lowering than up-titrating monotherapy, since doubling the dose for blood pressure drugs from half-dose or from standard dose provides only about 1–2 mm Hg further reduction in systolic or diastolic blood pressure.3 Moreover, a quadpill approach could address treatment inertia related to the clinician and patient because it reduces the reliance on stepped titration, which is rarely completed in practice. A quadpill 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 burden40 and use of lower doses to minimise side-effects.4

In summary, our study is the first placebo-controlled trial to indicate that quarter-dose four-drug combination therapy could be efficacious in lowering blood pressure. It presents a novel approach that could achieve substantially greater blood pressure control with a single pill, which could have widespread clinical applicability. Further trials are required to assess contributions of different components, and the long-term efficacy and safety in a broader population, both for initial treatment and among patients with inadequate control or side-effects while receiving monotherapy.

Contributors

CKC is the chief investigator of the clinical trial, led the writing of the protocol and successful funding application, supervised JT, and drafted the report. JT is a PhD student who primarily implemented the trial protocol. AB, MB, and TU supported trial recruitment. KV ran all statistical analyses, supervised by KR, who was the primary writer of the statistical analysis plan. CKC, AR, and GH contributed to trial design. AR and CKC had the idea for the trial. AB drafted the protocol and data collection forms for the systematic review, did the search, data abstraction, and data checking as first reviewer, led the statistical analysis, and drafted the systematic review report. CKC contributed to the idea for the systematic review, revision of the protocol, and review of data analyses. MC contributed to the literature search, trial identification, data abstraction, and data checking as second reviewer, and reviewed data analyses. H-MD contributed to data checking as third reviewer, and review of data analyses. EA assisted with data checking and analysis. AR had the idea for the systematic review and supervised research staff working on the project. RW, AS, AP, BN, DP, HK, JT, JC, MN, CMR, GH, MW, SH, and ST contributed to review of the protocol and data analyses. All authors contributed to critical review of this report.

Declaration of interests

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Articles


Acknowledgments

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