Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial

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Summary

Background Treatment inertia is a recognised barrier to blood pressure control, and simpler, more effective treatment strategies are needed. We hypothesised that a hypertension management strategy starting with a single pill containing ultra-low-dose quadruple combination therapy would be more effective than a strategy of starting with monotherapy.

Methods QUARTET was a multicentre, double-blind, parallel-group, randomised, phase 3 trial among Australian adults (≥18 years) with hypertension, who were untreated or receiving monotherapy. Participants were randomly assigned to either treatment, that started with the quadpill (containing irbesartan at 37·5 mg, amlodipine at 1·25 mg, indapamide at 0·625 mg, and bisoprolol at 2·5 mg) or an indistinguishable monotherapy control (irbesartan 150 mg). If blood pressure was not at target, additional medications could be added in both groups, starting with amlodipine at 5 mg. Participants were randomly assigned using an online central randomisation service. There was a 1:1 allocation, stratified by site. Allocation was masked to all participants and study team members (including investigators and those assessing outcomes) except the manufacturer of the investigational product and one unmasked statistician. The primary outcome was difference in unattended office systolic blood pressure at 12 weeks. Secondary outcomes included blood pressure control (standard office blood pressure <140/90 mm Hg), safety, and tolerability. A subgroup continued randomly assigned allocation to 12 months to assess long-term effects. Analyses were per intention to treat. This trial was prospectively registered with the Australian New Zealand Clinical Trials Registry, ACTRN12616001144404, and is now complete.

Findings From June 8, 2017, to Aug 31, 2020, 591 participants were recruited, with 743 assessed for eligibility, 152 ineligible or declined, 300 participants randomly assigned to intervention of initial quadpill treatment, and 291 to control of initial standard dose monotherapy treatment. The mean age of the 591 participants was 59 years (SD 12); 356 (60%) were male and 235 (40%) were female; 483 (82%) were White, 70 (12%) were Asian, and 38 (6%) reported as other ethnicity; and baseline mean unattended office blood pressure was 141 mm Hg (SD 13)/85 mm Hg (SD 10). By 12 weeks, 44 (15%) of 300 participants had additional blood pressure medications in the intervention group compared with 115 (40%) of 291 participants in the control group. Systolic blood pressure was lower by 6·9 mm Hg (95% CI 4·9–8·9; p<0·0001) and blood pressure control rates were higher in the intervention group (76%) versus control group (58%; relative risk [RR] 1·30, 95% CI 1·15–1·47; p<0·0001). There was no difference in adverse event-related treatment withdrawals at 12 weeks (intervention 4·0% *vs* control 2·4%; p=0·27). Among the 417 patients who continued, uptitration occurred more frequently among control participants than intervention participants (p<0·0001). However, at 52 weeks mean unattended systolic blood pressure remained lower by 7·7 mm Hg (95% CI 5·2–10·3) and blood pressure control rates higher in the intervention group (81%) versus control group (62%; RR 1·32, 95% CI 1·16–1·50). In all randomly assigned participants up to 12 weeks, there were seven (3%) serious adverse events in the intervention group and three (1%) serious adverse events in the control group.

Interpretation A strategy with early treatment of a fixed-dose quadruple quarter-dose combination achieved and maintained greater blood pressure lowering compared with the common strategy of starting monotherapy. This trial demonstrated the efficacy, tolerability, and simplicity of a quadpill-based strategy.

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Research in context

Evidence before this study

A systematic review and meta-analysis of quarter-dose blood pressure-lowering therapy, published in 2017, highlighted the potential benefits of quarter-dose combination therapy in comparison to standard dose monotherapy. An updated search of MEDLINE, from Jan 1, 2016, to July 21, 2021, using the search strategy from this review identified another 67 references, title screening excluded 49, abstract screening excluded a further 11. Seven studies of combination therapy progressed to full-text review. None met the criteria of quarter-dose combination therapy compared with monotherapy or placebo, although the authors were aware of one trial. Overall, there was only one unblinded study comparing quadruple quarter-dose combination therapy to standard doses of the four components. This showed short-term benefits favouring the ultra-low-dose combination. A small randomised, placebo-controlled, crossover trial of quadruple quarter-dose combination therapy demonstrated significant blood pressure reductions in the short term and served as proof of concept to pursue this trial. A small trial also compared a losartan–amlodipine–chlorthalidone combination in triple quarter, triple third, and triple half doses to monotherapy. Collectively these studies indicated the potential for large blood pressure reductions with quadruple quarter-dose therapy compared with monotherapy, but provided few data on tolerability and none compared with the guideline recommended therapy of uptitration if blood pressure is not controlled after initial monotherapy.

Added value of this study

This is, to our knowledge, the first randomised trial that demonstrates that a quarter-dose quadruple combination (quadpill) early in treatment of patients with hypertension is a more effective strategy than initial monotherapy. It is the first to show that uptitration on top of blinded initial therapy does not achieve catch-up in the initial monotherapy group. Despite consistently higher rates of up-titrated blood pressure medicines in the control group, this group did not catch up in blood pressure control and blood pressure levels were lower in the intervention group throughout 12-month follow-up. Blood pressure control rates were also higher than seen in previous trials of single-pill combinations, with control at less than 140/90 mm Hg at 6 months and 12 months of 76% and 81%, respectively. This is the first trial to demonstrate safety of this strategy, and also that tolerability was maintained, but not improved, against this comparator regimen.

Implications of all the available evidence

These findings indicate that a single-pill, quadruple, quarter-dose combination can achieve sustained blood pressure control quickly and safely for the large majority of patients. Initial monotherapy remains the most used strategy globally, and as a result blood pressure control rates remain suboptimal, often due to treatment inertia. This study supports a greater focus by clinicians, medication manufacturers, and consumers on using combination therapy. Clinical practice guidelines should be updated to incorporate evidence on the effectiveness and safety of strategies that use low-dose combination medications as initial or early treatment of patients with hypertension. The findings add further weight to the existing trend in guideline recommendations to actively discourage the use of monotherapy while encouraging the greater use of effective and safe combination therapies.

Introduction

High blood pressure remains the leading modifiable cause of disease burden globally.[1] Even in countries where blood pressure-lowering medications are available and affordable, many—if not most—treated individuals do not achieve blood pressure control.[2] Still, by far the most common approach to hypertension management globally is to start patients on monotherapy. Although multiple medications are usually required to achieve blood pressure control, treatment inertia and concerns regarding adverse events are common barriers to the effective use of multiple medications, resulting in persistent monotherapy for many patients with hypertension.

Low-dose, single-pill combinations hold considerable promise to help overcome these barriers.[3,4] Dose-response studies of individual agents indicate most benefits are achieved and most side-effects avoided at low doses.[3,5] The quadpill concept describes that of a single pill combining four types of blood pressure-lowering medications, with each medicine included at a quarter of the standard dose for hypertension.[5] Previous small short-term studies suggested the quadpill had better blood pressure-lowering efficacy than standard dose monotherapy,[6] and large benefits compared with placebo.[4] A larger trial testing triple half dose[7] against usual care in Sri Lanka also provided promising results but was open label, so could not provide blinded assessment of comparative tolerability and also did not have long-term follow-up to assess whether these initial benefits were sustained.[8] This quadruple ultra-low-dose treatment for hypertension (QUARTET) trial was designed to examine the potential of a simple and scalable hypertension management strategy, which might address multiple barriers to hypertension control, including treatment inertia and concerns about adverse events.

The primary objective of QUARTET was to determine whether hypertension management starting with a single pill containing quarter-standard doses of four types of blood pressure-lowering medicines (ie, the quadpill) is more effective than an approach that starts with standard dose monotherapy. Our secondary aims were to assess the tolerability and safety of this approach, and the long-term durability of blood pressure control in an extended analysis.

Methods

Study design

QUARTET was a multicentre, parallel-group, active control, double-blind, randomised, controlled, phase 3 trial of patients with high blood pressure. The primary outcome assessment was at 12 weeks and a subgroup continued follow-up to 12 months to examine long-term efficacy and tolerability. Patients were recruited from ten primary care centres and hospital outpatient clinics in four states of Australia (ie, NSW, TAS, VIC, and WA). The Western Sydney Local Health District Human Research Ethics Committee provided lead ethics approval (HREC/15/WMEAD/422). The protocol is available in the appendix (pp 11–67).

Participants

Adults (≥18 years) were potentially eligible if currently untreated or receiving monotherapy, with each group having specific blood pressure eligibility criteria—ie, (1) a standard observed clinic systolic blood pressure between 140 mm Hg and 179 mm Hg or diastolic blood pressure between 90 mm Hg and 109 mm Hg, or both, or a daytime average 24-h ambulatory systolic blood pressure of 135 mm Hg or more, or diastolic blood pressure of 85 mm Hg or more, or both, measured in the last 12 weeks for untreated participants; (2) or a clinic systolic blood pressure between 130 mm Hg and 179 mm Hg or a diastolic blood pressure between 85 mm Hg and 109 mm Hg, or both, or a daytime average ambulatory systolic blood pressure of 125 mm Hg or more or a diastolic blood pressure of 80 mm Hg or more, or both, measured in the last 12 weeks in participants with known hypertension currently treated with one blood pressure-lowering agent. Amendments were made to the inclusion criteria during the recruitment period, the most significant being in June, 2018, enabling patients currently on monotherapy to be included with a lower baseline entry systolic blood pressure to enhance enrolment.[9] Participants gave written informed consent before study procedures.

Recruitment numbers were impacted in the final year (2020) of study recruitment due to directives at various sites to suspend recruitment because of the COVID-19 pandemic. The study was hence stopped before achieving the target sample size.

Randomisation and masking

Participants were randomly assigned to either intervention, initial treatment with the quadpill, or active control, initial treatment with standard dose monotherapy. Randomisation was in a 1:1 allocation ratio using a central computer-based service stratified by site and using permuted blocks of variable size. Unmasked personnel included the data and safety monitoring committee, the statistician who prepared reports for the data and safety monitoring committee, and the data manager responsible for the randomisation module. All other study staff and researchers were masked to group allocation. Masking of randomised study treatment was achieved using encapsulation, with capsules appearing identical in both groups and in the intervention containing the quadpill components and in the control containing standard dose monotherapy and placebo pills. The study drug was made by PCI Pharma Services (Melbourne, VIC, Australia).

Procedures

Participants in the intervention group initially received a quadpill containing quarter-standard doses of four common blood pressure medications—namely, irbesartan at 37·5 mg, amlodipine at 1·25 mg, indapamide at 0·625 mg, and bisoprolol at 2·5 mg. We selected medications that were commonly prescribed in Australia, required single daily dosing, and were able to be cut into quarter doses. Each included medicine was at quarter standard doses, defined as the usual maintenance dose recorded by the British National Formulary, Martindale, and Monthly Index of Medical Specialties.

See Online for appendix

Participants in the control group initially received a capsule, identical to the intervention, containing a standard dose of monotherapy—ie, irbesartan at 150 mg and placebo tablets.

Participants who were on monotherapy at the time of recruitment were asked to stop their treatment at randomisation, and switch to the study treatment. The study was purposefully inclusive of a wide range of treatment regimens among baseline participants on monotherapy, to reflect normal clinical practice. These patients on different regimens would be balanced across groups at baseline. By the first follow-up visit at week 6, the pharmacological effects of baseline therapy would have been fully washed out, given the number of half-lives that would have been completed, and the full effects of study treatment would be established, since this takes only a few weeks.[10]

All study treatment was taken once daily, with no specific direction related to time of day. For both study groups, if at the first follow-up visit (week 6) blood pressure was greater than 140/90 mm Hg, amlodipine at 5 mg once per day was added to the participant's regimen. Randomly assigned treatments and amlodipine, if required, were provided to all participants at no cost. Any additional blood pressure-lowering medication required was initiated at the discretion of the treating doctor. Open-label treatment could be added without the need to unblind. In particular, for participants continuing in the study beyond 12 weeks, advice was provided to their general practitioners regarding maximum recommended doses for additional therapy.

All participants were assessed at baseline, 6 weeks, and 12 weeks. At 12 weeks, participants were invited to participate in the extended follow-up; these invitations were issued up to 1 year before the overall expected study completion. Study treatment blinding was maintained during extended follow-up. Participants who continued

in the trial to 12 months had repeat assessments at 6 months and 12 months.

At baseline, medical history, sociodemographic characteristics, blood tests (standard certified central laboratory), and electrocardiogram (ECG), unless done in the preceding 3 months, were assessed. Blood pressure assessment comprised a clinic recording of blood pressure by research staff using an automated device (office blood pressure) and was followed by three preprogrammed unobserved blood pressure measures occurring while the researcher was outside the room (unattended office blood pressure). The blood pressure measurements were recorded using an Omron HEM907 device according to the Australian National Heart Foundation 2016 guidance.[11] Blood pressure measures were commenced after participants were seated in a quiet room for at least 5 min. An appropriate cuff size was selected and fitted snugly around the upper arm, with the centre of the cuff bladder positioned over the brachial artery. For unattended measures, the blood pressure monitor was programmed to start the first measurement after 5 min of rest and staff having left the room, and the second and third measurements at 1-min intervals thereafter.

Each participant also had 24-h ambulatory blood pressure monitoring (ABPM). The 24-h ambulatory blood pressure was assessed using a Suntech Oscar-2 device programmed to make measurements every 30 min during waking hours and every 60 min during sleep. Sleep and wake time were personalised to minimise disruption to participants' routines. At 6 weeks, the office blood pressure measures were repeated, and participants were assessed for adverse events, changes in medications, or health service use since randomisation. At 12 weeks, these assessments were repeated along with the addition of blood tests, medication adherence, quality of life, and 24-h ABPM. Adherence to the blinded study medication was defined as the number of pills taken per number prescribed×100%. Participants were considered adherent if this measure was more than 80%. For the subgroup continuing to 12 months, the 6-month visit followed the same structure as week 6, and the 12-month visit followed the same structure as week 12, with the addition of a 12-lead ECG.

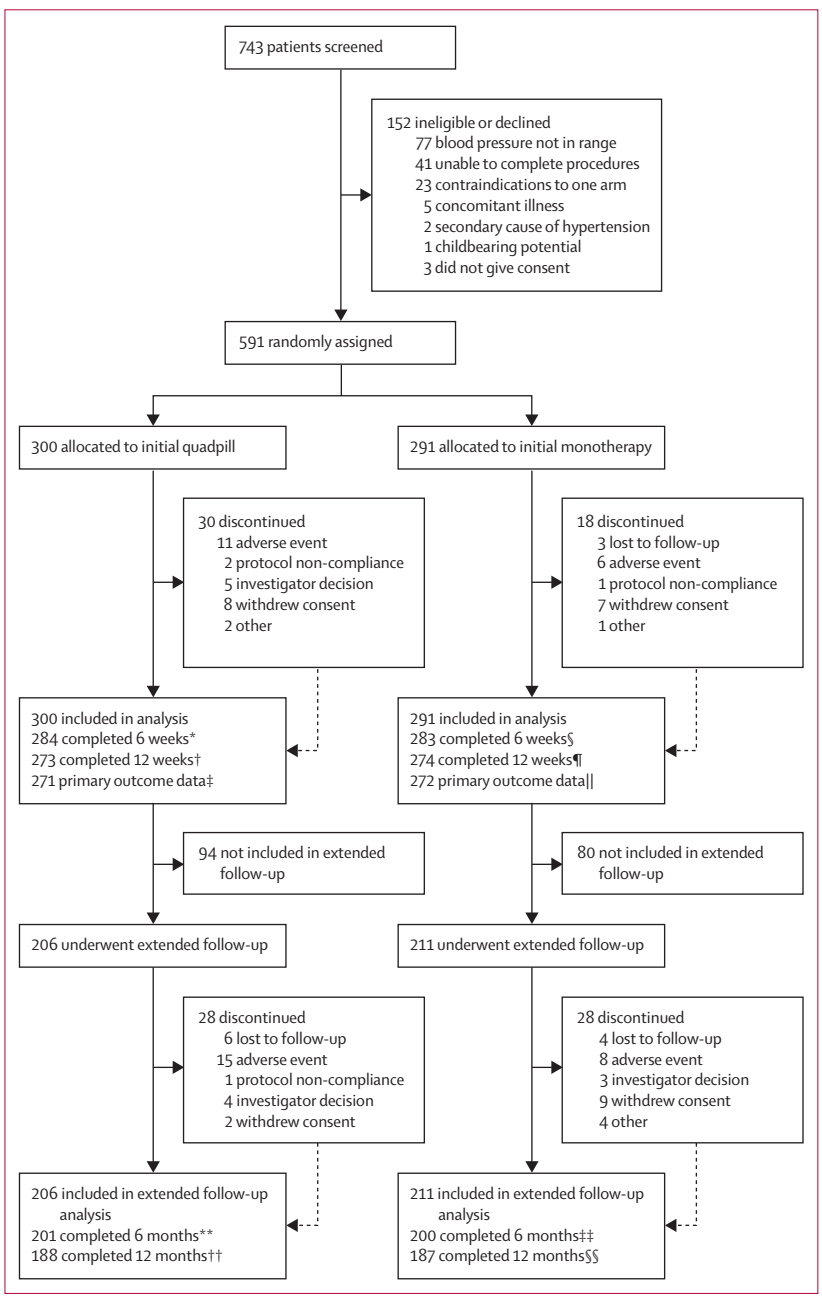

Figure 1: **Trial profile**
*16 discontinued (five adverse event, four investigator decision, seven withdrew consent). †14 discontinued (seven adverse event, two protocol non-compliance, two lost to follow-up, one investigator decision, one withdrew consent, one other). ‡Two did not complete blood pressure measurement. §Eight discontinued (three adverse event, one protocol non-compliance, four withdrew consent). ¶Ten discontinued (four adverse event, three lost to follow-up, three withdrew consent). ||Two did not complete the blood pressure measurement. **Seven discontinued (five adverse event, two investigator decision). ††12 discontinued (eight adverse event, two investigator decision, two withdrew consent). ‡‡12 discontinued (one adverse event, two lost to follow-up, two investigator decision, four withdrew consent, three other). §§15 discontinued (7 adverse event, 2 lost to follow-up, 1 investigator decision, 5 withdrew consent).

Outcomes

The primary outcome was change in mean unattended office systolic blood pressure at 12 weeks. The mean was calculated from three unattended office measures. Secondary outcomes were unattended office diastolic blood pressure at 12 weeks and 52 weeks and unattended systolic blood pressure at 52 weeks; blood pressure control (<140/90 mm Hg standard office blood pressure) at weeks 6, 12, 26 and 52; tight blood pressure control (<120/80 mm Hg standard office blood pressure), ambulatory systolic blood pressure and diastolic blood pressure overall, daytime and night-time at 12 weeks and 52 weeks, percentage requiring step-up treatment at 6 weeks and over 52 weeks; safety; and tolerability.

Safety was assessed as the proportion of participants with any serious adverse event, defined as an untoward

	Intervention (n=300)	Control (n=291)
Age, years	58 (12)	59 (11)
Sex		
Female	122 (41%)	113 (39%)
Male	178 (59%)	178 (61%)
Health-care concession card holder	65 (22%)	72 (25%)
Race or ethnicity		
White	249 (83%)	234 (80%)
Asian	33 (11%)	37 (13%)
Other*	18 (6%)	20 (7%)
Baseline blood pressure treatment		
Not treated†	171 (57%)	147 (51%)
On monotherapy	129 (43%)	144 (49%)
Baseline blood pressure, mm Hg		
Unattended systolic	142 (13)	140 (13)
Unattended diastolic	86 (10)	83 (10)
Office systolic	153 (16)	152 (15)
Office diastolic	89 (10)	88 (11)
24 h ABPM, systolic	144 (11)	143 (11)
24 h ABPM, diastolic	84 (9)	84 (9)
Baseline heart rate, beats per min	71 (11)	71 (11)
Body-mass index, kg/m²	31 (6)	30 (6)
Ever smoked	115 (38%)	110 (38%)
Current smoker	23 (8%)	25 (9%)
Former smoker	92 (31%)	85 (29%)
Alcohol once or more per week	202 (67%)	174 (60%)
Diabetes	21 (7%)	24 (8%)
Chronic kidney disease	0 (0%)	1 (0·3%)
Coronary artery disease	14 (5%)	12 (4%)
Creatinine, µmol/L	76·1 (15·1)	74·7 (13·0)
eGFR, mL/min per 1·73 m²‡	77·0 (10·2)	79·1 (9·0)
Sodium, mmol/L	140·2 (2·2)	140·3 (2·4)
Potassium, mmol/L	4·4 (0·4)	4·4 (0·4)
Total cholesterol, mmol/L	5·3 (1·1)	5·3 (1·1)
HDL cholesterol, mmol/L	1·4 (0·4)	1·4 (0·4)
Fasting glucose, mmol/L	5·6 (1·6)	5·4 (0·9)

Data are mean (SD) or n (%). ABPM=ambulatory blood pressure monitoring. eGFR=estimated glomerular filtration rate. *Included Black, Hispanic, Middle Eastern, Australian Aboriginal or Torres Strait Islander, Pacific Islands, Maori, and other. †Not taking blood pressure-lowering medications, or not currently taking treatment for at least 4 weeks. ‡eGFR estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation.

Table 1: **Baseline characteristics**

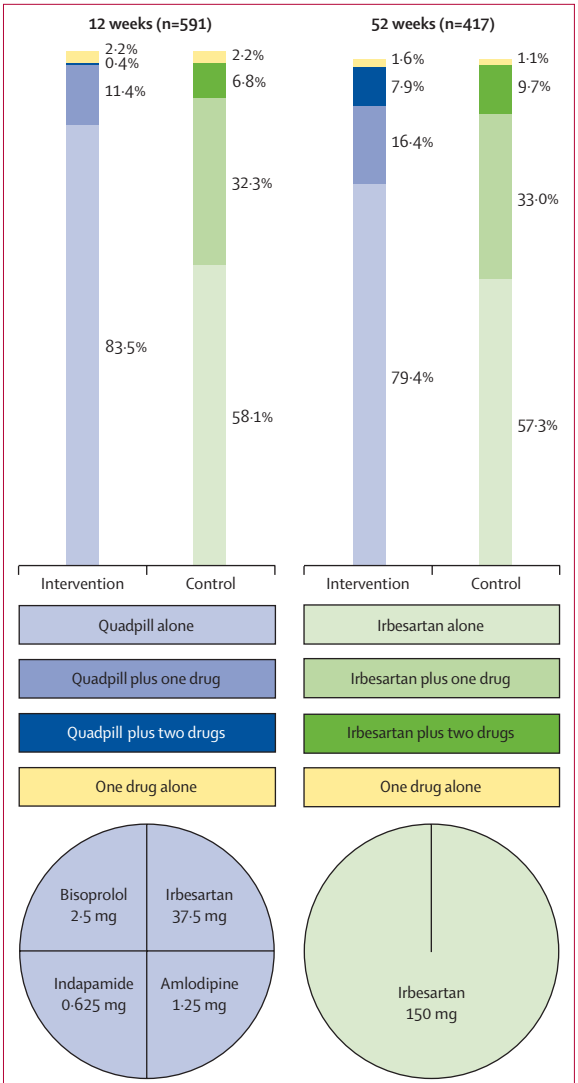

Figure 2: **Blood pressure-lowering treatment at 12 weeks and 52 weeks in intervention and control groups**

medical occurrence—ie, death, life-threatening event, hospitalisation, persistent disability, or congenital anomaly. Tolerability was defined as participant withdrawals from treatments, potentially related side-effects (eg, dizziness; blurred vision; syncope, collapse, or fall; chest pain or angina; shortness of breath; cough; wheeze; ankle oedema; skin rash; itching; gout; hyperkalaemia; hypokalaemia; hyponatraemia; or other), and mean potassium, uric acid, blood glucose, cholesterol and lipid fractions, alanine aminotransferase, aspartate aminotransferase, urine albumin-to-creatinine ratio, and serum creatinine levels.

Statistical analysis

Before the study, we estimated a sample size of 650 patients would provide 90% power at an α of 0·05 to detect a difference of 4 mm Hg in the primary outcome, assuming an SD of 15 mm Hg. The calculations allowed for a 10% data-loss rate.

The analyses of the primary outcome and other continuous outcomes were done using a linear mixed model using all available data. This model included a random intercept for site and visit, treatment allocation, visit-by-treatment interaction, and the baseline measure of the outcome as fixed effects. Repeated measurements were accounted for using an unstructured covariance

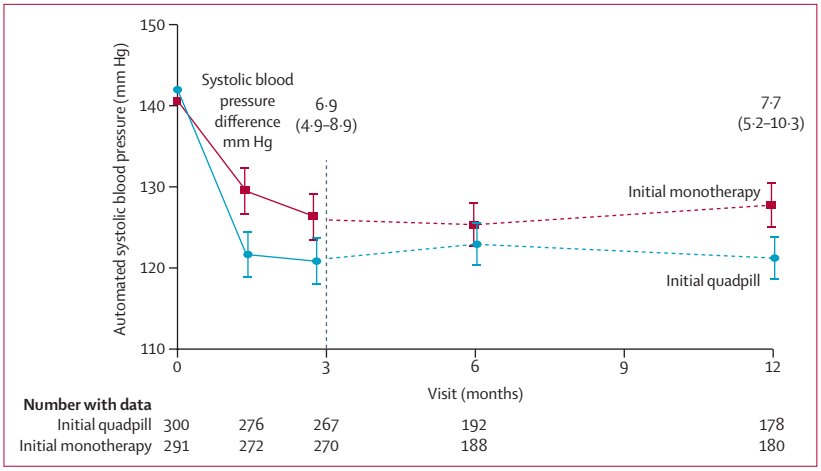

Figure 3: **Mean systolic blood pressure to month 12, by group**
Estimated mean unattended office systolic blood pressure with 95% CIs at baseline, 6 weeks, and 12 weeks in the main study, and at 6 months and 12 months from the extended substudy. Dotted line is placed between studies.

structure. A similar approach was applied to binary endpoints with generalised linear mixed models, using log-binomial regression in place of linear regression.

Analyses were done by intention to treat. For a sensitivity analysis, two different imputation methods were used to assess the impact of missing data on the primary outcome. These were a multiple imputation technique based on the missing at random assumption,[12] and a tipping point analysis. Prespecified subgroup analyses were done on the primary efficacy variable according to the following baseline subgroups: age (split by tertiles), sex, diabetes, education (high or low, where high education was that beyond secondary school), systolic blood pressure at baseline (split by tertiles), diastolic blood pressure at baseline (split by tertiles), blood pressure-lowering treatment at baseline (no treatment versus monotherapy), and participants with cardiovascular disease (yes or no).

The analysis was completed in SAS, version 9.4. No adjustment for multiplicity was performed. The data safety and monitoring committee reviewed overall reports, but no formal interim analyses were done.

The QUARTET trial was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12616001144404).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 8, 2017, to August 31, 2020, 591 participants were recruited, with 743 assessed for eligibility, 152 ineligible or declined, and 300 randomly assigned to intervention of initial quadpill treatment and 291 to control of initial standard dose monotherapy treatment. Of the 591 randomly assigned to quadpill or control, 271 (90%) of 300 intervention participants and 272 (93%) of 291 control participants had complete primary outcome data at 12 weeks (figure 1).

The mean age of the 591 participants was 59 years (SD 12); 356 (60%) were male and 235 (40%) were female; 483 (82%) were White, 70 (12%) were Asian, and 38 (6%) reported as other race or ethnicity (table 1). 318 (54%) of 519 participants were not receiving treatment (25 [4%] previously treated, but not for at least 4 weeks, the remainder not previously treated) and 273 (46%) were on monotherapy. The mean unattended office blood pressure was 141 mm Hg (SD 13)/85 mm Hg (SD 10) and observed office blood pressure 153 mm Hg (SD 15)/89 mm Hg (SD 11). Baseline characteristics were similar in both groups (table 1).

All patients commenced their randomly assigned treatment. 206 (83·1%) of 248 participants in the intervention group and 219 (83·9%) of 261 participants in the control group reported taking study treatment in the morning. As recommended in the protocol, in addition to randomly assigned treatment, physicians could add open-label amlodipine and other blood pressure-lowering drugs to the blinded study drug at each visit. This occurred more frequently in the control group than the intervention group at each follow-up visit (figure 2). By 12 weeks, 44 (15%) of 300 participants in the intervention group had additional blood pressure medications, which was most commonly additional amlodipine alone for 28 (9%) participants; in the control group, 115 (40%) of 291 had additional blood pressure medications, which was most commonly additional amlodipine alone for 95 (33%) participants. At 12 weeks, 225 (87%) of 260 participants in the intervention group adhered to randomly assigned treatment, versus 223 (84%) of 266 participants in the control group.

At 12 weeks, the primary outcome measure of unattended office blood pressure was 120 mm Hg (SD 14)/71 mm Hg (SD 10) in the intervention group and 127 mm Hg (SD 13)/79 mm Hg (SD 10) in the control group, and the mean systolic blood pressure difference between groups was –6·9 mm Hg (95% CI –4·9 to –8·9; p<0·001; figure 3). Findings were broadly consistent across subgroups, although the p value for homogeneity for education was 0·014 (appendix pp 2, 7).

With respect to secondary outcomes, mean unattended diastolic blood pressure was reduced in the intervention group compared with the control group (–5·8 mm Hg, 95% CI –4·4 to –7·2; p<0·0001). Intervention participants were more likely to achieve blood pressure control of less than 140/90 mm Hg on standard office measures (intervention 76% *vs* control 58%; relative risk [RR] 1·30, 95% CI 1·2 to 1·5; p<0·0001) and tight blood pressure control at less than 120/80 mm Hg on standard office measures (intervention 46% *vs* control 26%; RR 1·75, 95% CI 1·38 to 2·22; p<0·0001). The mean 24-h systolic ambulatory blood pressure (ABP) was 7·5 mm Hg

(95% CI –9·0 to –5·9) lower in the quadpill compared with the control group. Average daytime systolic blood pressure and average night-time systolic blood pressure was similarly reduced in the intervention group (–7·8 mm Hg, –9·4 to –6·1) compared with the control group (–6·6 mm Hg, –8·4 to –4·7; appendix p 3).

417 (71%) of 591 participants had extended follow-up—this was 417 (81%) of 513 participants invited to extended follow-up (the remainder were not invited as less <1 year to end of study). The baseline characteristics of extension participants were similar to main study participants (appendix p 4) and the 12-week blood pressure levels were similar in patients who continued follow-up (intervention 121/72 mm Hg *vs* control 126/76 mm Hg) compared with participants who did not (intervention 121/72 mm Hg *vs* control 127/76 mm Hg). For the cohort who continued to 12 months, additional blood pressure medications were more commonly being taken at each of the 6-week, 12-week, 26-week, and 52-week follow-up visits in the control group than in the intervention group (figure 3). At 52 weeks, 158 (77%) of 205 participants were adherent to randomised treatment in the intervention group versus 157 (74%) of 211 participants in the control group.

At 12 months, the mean unattended office blood pressure was 121 mm Hg (SD 13)/71 mm Hg (SD 9) in the intervention group and 128 mm Hg (SD 13)/76 mm Hg (SD 9) in the control group, with a mean unattended systolic blood pressure difference of –7·7 mm Hg (95% CI –5·2 to –10·3; p<0·0001). The mean unattended diastolic blood pressure difference was –6·0 mm Hg (–4·3 to –7·6). Both blood pressure control on standard office measures (intervention 81% *vs* control 62%; RR 1·3, 95% CI 1·2–1·5; p<0·0001) and tight blood pressure control on standard office measures (intervention 53% *vs* control 25%; 2·1, 1·6–2·8; p<0·0001) were achieved more frequently in the intervention group than in the control group. The mean 24-h systolic ABP was –6·0 mm Hg (–8·8 to –3·2) lower in the intervention compared with the control group (tables 2, 3).

In all randomly assigned participants up to 12 weeks, there were seven (3%) serious adverse events in the intervention group (one each of positional vertigo, shortness of breath, non-cardiac chest pain, tonic clonic seizure, fracture of ankle, cholecystitis, and migraine) and three (1%) serious adverse events in the control group (one each of non-cardiac chest pain, pneumonia, and myocardial infarction). There were 12 (4·0%) treatment withdrawals for any event in the intervention group, versus seven (2·4%) in the control group (p=0·27; appendix p 5). During follow-up to 12 weeks, systolic blood pressure of less than 100 mm Hg was recorded in 17 (6·0%) of 282 intervention participants versus seven (2·5%) of 276 control participants, and heart rate of less than 50 beats per min was recorded in 35 (12·4%) of 282 intervention participants versus one (0·4%) of 276 control participants (both p<0·01), whereas the number reporting dizziness was 93 (31·0%) intervention participants versus 74 (25·4%) control participants (RR 1·27, 95% CI 0·98–1·64; p=0·07). There were no serious adverse events due to syncope, falls, or acute kidney injury. There were similar rates of other self-reported side-effects in both groups, and for most serum and blood markers there were no or small differences (table 4).

Among all participants, at 12 months there were 15 (7·3%) in the intervention group versus 14 (6·6%) in the control group reporting serious adverse events.

	Intervention (95% CI)	Control (95% CI)	Mean difference (95% CI)	p value
Unattended automated systolic blood pressure, mm Hg				
Week 6	121 (118 to 123)	131 (128 to 133)	–10 (–12 to –8)	<0·0001
Week 12	121 (118 to 123)	127 (124 to 129)	–6 (–8 to –4)	<0·0001
Week 26	122 (120 to 125)	126 (123 to 129)	–4 (–6 to –1)	0·0035
Week 52	121 (118 to 123)	128 (126 to 131)	–8 (–10 to –5)	<0·0001
Overall	..	..	–7 (–9 to –5)	<0·0001
Unattended automated diastolic blood pressure, mm Hg				
Week 6	71 (69 to 72)	78 (77 to 80)	–8 (–9 to –6)	<0·0001
Week 12	71 (70 to 73)	77 (75 to 78)	–5 (–7 to –4)	<0·0001
Week 26	72 (70 to 74)	76 (75 to 78)	–4 (–6 to –2)	<0·0001
Week 52	71 (69 to 73)	77 (75 to 79)	–6 (–8 to –4)	<0·0001
Overall	..	..	–6 (–7 to –5)	<0·0001
Office systolic blood pressure, mm Hg				
Week 6	130 (126 to 133)	139 (135 to 142)	–9 (–12 to –6)	<0·0001
Week 12	129 (126 to 132)	134 (130 to 137)	–4 (–7 to –2)	0·0015
Week 26	130 (127 to 133)	134 (131 to 137)	–4 (–7 to –1)	0·0031
Week 52	128 (125 to 131)	136 (133 to 139)	–8 (–10 to –5)	<0·0001
Overall	..	..	–6 (–8 to –4)	<0·0001
Office diastolic blood pressure, mm Hg				
Week 6	75 (73 to 76)	82 (80 to 84)	–7 (–9 to –5)	<0·0001
Week 12	76 (74 to 77)	79 (77 to 81)	–4 (–5 to –2)	<0·0001
Week 26	75 (74 to 77)	79 (78 to 81)	–4 (–6 to –2)	<0·0001
Week 52	75 (73 to 77)	79 (78 to 81)	–4 (–6 to –3)	<0·0001
Overall	..	..	–5 (–6 to –4)	<0·0001

Table 2: **Blood pressure by measurement method at weeks 6, 12, 26, and 52 in participants in the extended study**

	Intervention	Control	Absolute rate difference (95% CI)	Relative rate (95% CI)	p value
Blood pressure target achieved (office blood pressure <140/90 mm Hg)					
Week 6	154/201 (77%)	109/208 (52%)	24·2 (15·0–32·8)	1·47 (1·26–1·71)	<0·0001
Week 12	155/205 (76%)	129/211 (61%)	14·5 (5·5–23·1)	1·24 (1·08–1·42)	0·0022
Week 26	149/196 (76%)	128/194 (66%)	10·0 (1·0–18·8)	1·15 (1·01–1·31)	0·0299
Week 52	150/184 (82%)	114/185 (62%)	19·9 (10·7–28·6)	1·32 (1·16–1·50)	<0·0001
Tight blood pressure target achieved (office blood pressure <120/80 mm Hg)					
Week 6	85/201 (42%)	44/208 (21%)	21·1 (12·2–29·7)	1·98 (1·45–2·70)	<0·0001
Week 12	92/205 (45%)	60/211 (28%)	16·4 (7·2–25·3)	1·58 (1·21–2·06)	0·0009
Week 26	83/196 (42%)	47/194 (24%)	18·1 (8·8–27·0)	1·76 (1·30–2·38)	0·0003
Week 52	97/184 (53%)	46/185 (25%)	27·9 (18·0–36·9)	2·07 (1·56–2·75)	<0·0001

Data are n/N (%) unless otherwise specified.

Table 3: **Hypertension control at weeks 6, 12, 26, and 52 in the extended cohort**

	Intervention (n=300)	Control (n=291)	Relative risk (95% CI)	Mean difference (95% CI)	p value
Side-effects					
Dizziness	93 (31·0%)	74 (25·4%)	1·27 (0·98 to 1·64)	..	0·07
Pedal oedema	21 (7·0%)	22 (7·6%)	0·96 (0·54 to 1·69)	..	0·88
Muscle cramps	66 (22·0%)	61 (21·0%)	1·09 (0·80 to 1·47)	..	0·60
Hypersensitivity	28 (9·3%)	30 (10·3%)	0·93 (0·57 to 1·52)	..	0·79
Gastrointestinal complaints	37 (12·3%)	36 (12·4%)	1·03 (0·67 to 1·59)	..	0·89
Musculoskeletal complaints	38 (12·7%)	45 (15·5%)	0·85 (0·57 to 1·27)	..	0·41
Headache	43 (14·3%)	43 (14·8%)	1·00 (0·68 to 1·47)	..	0·99
Other	109 (36·3%)	104 (35·7%)	1·05 (0·85 to 1·30)	..	0·64
Laboratory measures					
Sodium, mmol/L	139·8 (2·5)	140·2 (2·2)	..	−0·4 (−0·8 to 0·0)	0·06
Potassium, mmol/L	4·3 (0·4)	4·4 (0·4)	..	−0·2 (−0·2 to −0·1)	<0·0001
Uric acid, mmol/L	0·4 (0·08)	2·0 (26·2)	..	−1·6 (−5·0 to 1·7)	0·34
Fasting glucose, mmol/L	5·8 (1·7)	5·4 (1·1)	..	0·4 (0·1 to 0·7)	0·018
Total cholesterol, mmol/L	5·2 (1·0)	5·3 (1·0)	..	−0·04 (−0·24 to 0·17)	0·72
HDL cholesterol, mmol/L	1·3 (0·4)	1·4 (0·4)	..	−0·06 (−0·1 to 0·0)	0·14
Alanine aminotransferase, U/L	30·0 (17·9)	28·9 (14·6)	..	1·1 (−1·8 to 4·0)	0·45
Aspartate aminotransferase, U/L	25·2 (9·4)	25·6 (8·9)	..	−0·4 (−2·0 to 1·3)	0·67
Urea, mmol/L	6·1 (1·8)	5·7 (1·4)	..	0·5 (0·2 to 0·8)	0·001
Creatinine, µmol/L	79·3 (17·7)	75·3 (14·9)	..	4·0 (1·1 to 6·8)	0·006
UACR, mg/mmol	1·1 (1·8)	1·6 (6·7)	..	−0·4 (−1·3 to 0·5)	0·35
eGFR, mL/min per 1·73m²	76·2 (12·1)	77·4 (10·5)	..	−2·9 (−5·6 to −0·2)	0·04

Data are n (%) or mean (SD), unless otherwise specified. UACR=urine albumin-to-creatinine ratio. eGFR=estimated glomerular filtration rate.

Table 4: **Tolerability at 12 weeks**

In the cohort with extended follow-up, 15 (7·3%) participants in the intervention group versus eight (3·8%) participants in the control group (RR 1·92, 95% CI 0·83–4·35; p=0·12) had treatment discontinuation due to any adverse event (appendix p 6).

Our first sensitivity analysis for missing data (multiple imputation strategy) was consistent with the main analysis. Our second sensitivity tipping point analysis revealed that it would take unrealistic blood pressures in the patients with missing data (eg, <50 mm Hg or >250 mm Hg) to remove our finding of efficacy of intervention versus control.

Discussion

This trial showed that a strategy of starting with quarter-dose quadruple combination therapy achieved and maintained blood pressure control more effectively than starting with standard dose monotherapy. The study used a range of blood pressure measurement methods, including the method most used in clinic settings, and a consistent treatment effect was seen. There were no differences in rates of severe adverse events or adverse event-related treatment discontinuations between the two approaches.

The quadpill strategy is simple and effective. In this study, most of the intervention participants only needed the quadpill to achieve blood pressure control. The control group started with a standard dose of a commonly used, highly tolerable medication and uptitration was implemented at each visit according to current guidelines. Uptitration occurred more frequently in the control group compared with the intervention group, but even so, blood pressure was not controlled as effectively as in the intervention group at 12 weeks nor at 1 year. The difference between the two groups did not appear to reduce between 12 weeks and 12 months, perhaps suggesting residual treatment inertia.

The strengths of this trial are that it provides a blinded assessment of this novel strategy compared with the most commonly used current blood pressure management strategy, with a sufficient period of follow-up. Earlier studies have indicated large blood pressure reductions with quadruple quarter-dose therapy compared with monotherapy[6] or placebo,[4] but these were small trials with imprecise efficacy estimates, and provided little or no data on tolerability or maintenance of effect over the long term. A trial[13] of initial triple half-dose combination therapy done in Sri Lanka showed benefits on blood pressure lowering compared with usual care at 6 months. However, that trial was unblinded, which could introduce biases whereby awareness of the study drug allocation might influence concomitant care and lead to differential reporting of adverse effects between groups.[13,14] The generalisability to other clinical settings was also unclear.

A secondary aim of our study was to assess if initial use of a quadpill was safe and had fewer adverse effects than standard care. There was no excess in serious adverse events, or acute kidney injury associated with the quadpill, but there were no types of adverse effects that occurred less frequently in the quadpill group compared with standard care. Historically, dual ultra-low-dose (also termed subtherapeutic dose) combinations have been used to reduce adverse effects while maintaining the efficacy of monotherapy.[15,16] In the QUARTET trial drug-specific adverse effects are not reduced with a quadpill compared with an angiotensin receptor blocker-based approach; however, angiotensin receptor blockers have little difference in tolerability compared with placebo, unlike other forms of monotherapy, especially at higher doses.[3,17–19] Further research should assess comparative efficacy and tolerability compared with other regimens, such as initial dual combination therapy now recommended for numerous patient groups in recent guidelines.[20–22] However, the current trial results are relevant as monotherapy remains the most common initial treatment, even in high-income countries.[23]

Evidence of benefits from lowering blood pressure beyond traditional targets[20,21,24] has further magnified the implementation challenge. For example, the change in targets in the 2017 US guideline update increased the proportion of US adults with treated hypertension who have blood pressure levels above goal from 39% to 53%.[25] In the context of previous supportive evidence,[26] the SPRINT trial[27] has been highly influential in changing guidelines globally. Although the SPRINT population were on more medications at entry and were likely to be at higher risk, the blood pressure reductions achieved in the QUARTET and SPRINT intervention groups were similar, as were mean baseline blood pressure levels. In QUARTET, this blood pressure reduction was achieved largely in one step—this simplicity is a key potential advantage. Implementation research is now required to understand how ultra-low dose combinations can best be integrated into current treatment algorithms globally.[28]

Achieving blood pressure control remains a substantial challenge.[2,29] There are many reasons for poor blood pressure control, including social and health system determinants, poor adherence, and clinical inertia. The comparison group blood pressure control rate of around 60% in this trial is similar to that seen in high-income countries, indicating the potential utility of this novel approach in such settings.[30,31] A strategy that confers an additional 7 mm Hg systolic blood pressure reduction would, if maintained long-term, be expected to confer an additional 11% lower risk of ischemic heart disease and an additional 18% lower risk of stroke and heart failure.[24] There is also considerable potential in low-income and middle-income countries, where the majority of people with hypertension globally reside, where less than one-third are treated, and only around 30% of those who are treated achieve blood pressure control.[30,32] Initial use of ultra-low-dose combination therapy has the potential to significantly improve blood pressure control in such settings if challenges of availability, affordability, and health system integration can be overcome.[29,33] A description of this strategy should be incorporated into hypertension guidelines, although currently implementation is limited by availability of suitable products.

Limitations of this trial are that it did not reach its recruitment target, because implementation was impacted by the COVID-19 pandemic. The reduced sample size limits precision, especially for comparisons of some secondary outcomes and for subgroup analyses. The extended follow-up provides data on the continued efficacy and tolerability of this approach to 12 months, but not on long-term cardiovascular outcomes. Although randomised trials to date show that the benefits of blood pressure-lowering drugs are mediated through the degree of blood pressure reduction,[34] there are no direct data on low-dose combinations. Patient adherence was assessed by pill count only, which has known limitations. Our definition of quarter-dose was based on a definition of standard dose derived from published formularies,[3,5] but there is geographical variation in doses used and standard dose is not always the most commonly used dose. Another limitation is the fact that participating clinicians had much lower rates of treatment inertia than would be commonly observed—eg, fewer than half of people with uncontrolled office blood pressure at week 6 in the control group remained on monotherapy after week 12, whereas much higher rates of treatment inertia are generally observed.[35] This result will lead to underestimation of the benefits of the quadpill.

In conclusion, this trial has demonstrated the simplicity, tolerability, and effectiveness of a quadpill-based strategy compared with the common strategy of initial standard dose monotherapy. This new paradigm holds promise for achieving better blood pressure control for people with hypertension around the world.

Contributors

CKC wrote the first draft with input from AR and ERA. KR conducted all statistical analyses. CKC, AR, and ERA had full access to all the data tables. All authors commented on multiple drafts and supported the decision to submit by CKC.

Declaration of interests

The George Institute for Global Health (TGI) has submitted patent applications with respect to low fixed-dose combination products for the treatment of cardiovascular or cardiometabolic disease. AR and CKC are listed as inventors. AR is employed by TGI and seconded part-time to George Medicines (GM). George Health Enterprises (GHE) and its subsidiary, GM, have received investment funds to develop fixed-dose combination products, including combinations of blood pressure-lowering drugs. GHE is the social enterprise group of TGI. AR and CKC do not have direct financial interests in these patent applications or investments. All other authors declare no competing interests.

Data sharing

De-identified participant data will be made available to researchers 1 year after the publication date of the Article. Data shared will include individual participant data that underlie the results reported in this Article, after de-identification. The study protocol and statistical analysis plan will be available. Access will be via application with a study proposal to the study steering committee via the chair (the corresponding author of this Article). Data will only be shared with the approval of the steering committee and on signing of a data access agreement.

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