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

Acronym: QUARTET

Short Title: Initial quadruple quarter-dose combination vs monotherapy in hypertension

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ABSTRACT

Background

Treatment inertia is a recognised barrier to blood pressure (BP) control and simpler effective treatment strategies are needed. QUARTET hypothesized 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

This was a multi-centre double-blind, parallel group randomised trial among Australian adults with hypertension, untreated or receiving monotherapy. Participants were randomised to either treatment, that started with the quadpill (containing irbesartan 37.5mg, amlodipine 1.25mg, indapamide 0.625mg, bisoprolol 2.5mg) or control, that started with monotherapy (irbesartan 150mg). If BP was not at target additional medications were added in both groups, starting with amlodipine 5mg. The primary outcome was difference in unattended office systolic BP at 12 weeks. Secondary outcomes included BP control (standard office BP <140/90mmHg), safety, and tolerability. A sub-group continued randomised allocation to 12-months to assess long-term effects.

Findings

There were 591 participants randomised, mean age 59 years, 60% male with baseline mean unattended office BP of 141/85mmHg. By 12 weeks, 15% had additional BP medications in the intervention arm compared to 40% in the control arm. Systolic BP was lower by 6.9mmHg (95% confidence interval [CI] 4.9 to 8.9mmHg; $p<0.0001$) and BP control rates were higher (76% vs 58%, relative risk [RR] 1.30 (95% CI 1.15-1.47), $p<0.0001$) in intervention vs control. There was no difference in adverse event-related treatment withdrawals at 12 weeks, (4.0% vs 2.4%, $p=0.27$). Among the 417 patients that continued, up-titration occurred more frequently among control compared to intervention participants. However, at 52 weeks mean unattended systolic BP remained lower (7.7mmHg (95% CI 5.2-10.3) and BP control rates higher (81% vs 62%, RR 1.32; 95% CI 1.16-1.50) in intervention vs control.

Interpretation

A strategy with early treatment of a fixed-dose quadruple quarter-dose combination achieved and maintained greater BP 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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Introduction

High blood pressure (BP) remains the leading modifiable cause of disease burden globally.¹ Even in countries where BP-lowering medications are available and affordable, many if not most treated individuals do not achieve BP control.² Still by far the most common approach to hypertension management globally is to start patients on monotherapy. While multiple medications are usually required to achieve BP control, treatment inertia and concerns regarding adverse events are common barriers 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 BP-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 to placebo.⁴ . A larger trial testing triple half-dose⁷ 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 The Quadruple Ultra-low-dose tReatment for hypErTension (QUARTET) trial was designed to examine the potential of a potentially 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, in a double blind randomised controlled trial, whether hypertension management starting with a single pill containing quarter-standard doses of four types of BP lowering medicines (“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 in an extended analysis the long-term durability of BP control.

METHODS

Study design

QUARTET was a multi-centre, parallel group, active control, double blind randomized controlled 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 10 primary care centres and hospital outpatient clinics in 4 states of Australia. The QUARTET trial was registered on the Australian New Zealand Clinical Trial Registry ([ACTRN12616001144404](https://www.anzctr.org.au/Trial/Registration/TrialRegistration.aspx?ACTRN12616001144404)). The Western Sydney Local Health District Human Research Ethics Committee provided lead ethics approval (HREC/15/WMEAD/422).

Participants

Participants were potentially eligible if currently untreated or receiving monotherapy, with each group having specific BP eligibility criteria: (1) a standard observed clinic SBP between 140 and 179mmHg and/or diastolic blood pressure (DBP) between 90 and 109mmHg, or a daytime average 24-hour ambulatory SBP $\geq$ 135mmHg and/or DBP $\geq$ 85mmHg measured in the last 12 weeks for

untreated participants; or (2) a clinic SBP between 130 and 179mmHg and/or a DBP between 85 and 109mmHg, or a daytime average ambulatory SBP ≥ 125 mmHg and/or a DBP ≥ 80 mmHg measured in the last 12 weeks in those with known hypertension currently treated with one BP-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 SBP to enhance enrolment.⁹ Participants gave written informed consent prior to study procedures.

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

Intervention and control

Participants were randomised 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. Unblinded personnel included the Data and Safety Monitoring Committee (DSMC), the statistician who prepared reports for the DSMC and the data manager responsible for the randomisation module. All other study staff and researchers were blinded. Blinding of randomised study treatment was achieved using encapsulation with capsules appearing identical in both arms 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 - Pharmaceutical Packaging Professionals in Melbourne, Australia.

Procedures

Intervention participants initially received an encapsulated single pill (quadpill) containing quarter standard doses of four common blood pressure medications: irbesartan 37.5mg, amlodipine 1.25mg, indapamide 0.625mg, bisoprolol 2.5mg. 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 (BNF), Martindale and Monthly Index of Medical Specialties (MIMS).

Control participants initially received an identical capsule containing a standard dose of monotherapy, irbesartan 150mg 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 purposefully was inclusive of a wide range of treatment regimens among those baseline participants on monotherapy, to reflect normal clinical practise. These would be balanced across groups at baseline. By the time of 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 have 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 (83.1% in the intervention and 83.9% in control reported taking study treatment in the morning). For both

study arms, if at 6 weeks clinic BP was greater than 140/90mmHg then amlodipine 5mg once daily was added. Randomised treatments and amlodipine, if required, were provided to all participants at no cost. Any additional BP 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 prior to 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 and 12 months.

At baseline, medical history, socio-demographic characteristics, blood tests (standard certified central laboratory) and electrocardiogram (ECG), unless done in preceding three months, were assessed. Blood pressure assessment comprised a clinic recording of BP by research staff using an automated device ('office BP') and was followed by three pre-programmed unobserved BP measures occurring while the researcher was outside the room ('unattended office BP'). The BP measurements were recorded using an Omron HEM907 device according to the Australian National Heart Foundation 2016 guidance. BP measures were commenced after participants were seated in a quiet room for at least 5 minutes. 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 BP monitor was programmed to start the first measurement after 5 minutes of rest and staff having left room, and the second and third measurements at one-minute intervals thereafter.

Each participant also had 24-hour ambulatory blood pressure monitoring (ABPM). The 24-hour ambulatory BP was assessed using a Suntech Oscar-2 device programmed to make measurements every 30 minutes during waking hours and every 60 minutes during sleep. Sleep and wake time were personalised to minimise disruption to participants' routines. At 6 weeks the office BP 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-hour ABPM. Adherence to the blinded study medication is defined as number of pills taken/number prescribed x100%, and participants considered adherent if this was >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.

Outcomes

The primary outcome was change in mean unattended office SBP at 12 weeks. The mean was calculated from three unattended office measures. Secondary outcomes were unattended office DBP, blood-pressure control (<140/90 mmHg standard office BP), tight blood-pressure control (<120/80 mmHg standard office BP), ambulatory SBP and DBP, safety, and tolerability.

Safety was assessed as the proportion with any serious adverse event (SAE) defined as an untoward medical occurrence - death, life-threatening event, hospitalisation, persistent disability, or

congenital anomaly. Tolerability was defined as participant withdrawals from treatments, potentially related side-effects (dizziness, blurred vision, syncope/ collapse/ fall, chest pain/ angina, shortness of breath, cough, wheeze, ankle oedema, skin rash, itching, gout, hyperkalaemia, hypokalaemia, hyponatraemia, other) and mean potassium, uric acid, blood glucose, cholesterol and lipid fractions, ALT, AST, UACR (urine albumin-to-creatinine ratio) and serum creatinine levels.

Statistical analysis

Prior to the study we estimated a sample size of 650 patients would provide 90% power at $\alpha=0.05$ to detect a difference of 4mmHg in the primary outcome, assuming an SD of 15mmHg. The calculations allowed for a 10% data loss rate.

The analyses of the primary outcome and other continuous outcomes were performed using a linear mixed model using all available data. This 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 structure. A similar approach was applied to binary endpoints with generalized 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,¹¹ and a tipping point analysis. Pre-specified subgroup analyses were conducted on the primary efficacy variable according to the following baseline subgroups: age (split by tertiles), sex, diabetes, education (high/ low where high education is that beyond secondary school), systolic BP at baseline split by tertiles, diastolic BP at baseline split by tertiles, BP lowering treatment at baseline (no treatment versus monotherapy) and participants with cardiovascular disease (yes/no). The analysis was completed in SAS 9.4 (SAS Institute, Cary, NC, USA). No adjustment for multiplicity was performed. The DSMC reviewed overall reports but no formal interim analyses were performed.

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 randomised to intervention of initial quadpill treatment and 291 to control of initial standard dose monotherapy treatment. Of the 591 randomised, 90% (271/300) of intervention participants and 93% (272/291) of controls had complete primary outcome data at 12 weeks. (Figure 1)

The mean age was 59 years (SD 12), 60% were male, 82% were white. Overall 54% were not receiving treatment (4% previously treated but not for at least 4 weeks, the remainder not previously treated) and 46% were on monotherapy. The mean unattended office BP was

141/85mmHg and observed office BP 153/89mmHg. Baseline characteristics were similar in both groups (see Figure Legends

Figure 1 – Consort Diagram

Figure 2 – Blood pressure lowering treatment at 12 weeks and 52 weeks in intervention and control arms

Figure 3 – Mean systolic blood pressure to month 12, by group.

Estimated mean unattended office systolic blood pressure with 95% confidence intervals at baseline, 6 and 12 weeks in the main study and at 6months and 12 months from the extended sub-study

Figure 4 – Difference in change from baseline in systolic blood pressure at 12 weeks, by subgroup

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See appendix “Quartet Acknowledgments”

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Disclosures

The George Institute for Global Health (TGI) has submitted patent applications in respect of low fixed-dose combination products for the treatment of cardiovascular or cardiometabolic disease. Professor Rodgers and Professor Chow are listed as inventors. Professor Rodgers is employed by The George Institute for Global Health (TGI) and seconded part-time to George Medicines Pty Ltd (GM). George Health Enterprises Pty Ltd (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 arm of TGI. Professor Rodgers and Professor Chow do not have direct financial interests in these patent applications or investments.

Data sharing

De-identified participant data will be made available to researchers 1 year after the publication date of the main results paper. 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 paper). Data will only be shared with the approval of the steering committee and on signing of a data access agreement.

Table 1).

All patients commenced their randomised treatment. As recommended in the protocol, in addition to randomised treatment, physicians could add open label amlodipine and other BP lowering drugs on top of the blinded study drug at each visit. This occurred more frequently in the control group compared to the intervention group at each follow-up visit, as shown in Figure 2. By 12 weeks, in the intervention arm 44(15%) had additional BP medications, which was most commonly additional amlodipine alone for 28 (9.3%); for the control arm 115 (40%) had additional BP medications, which was most commonly additional amlodipine alone for 95 (32.6%) (Figure 2). Adherence to randomised treatment was 86.5% (225/260) in the intervention group vs 83.8% (223/266) in the control group at 12 weeks.

At 12 weeks the primary outcome measure of unattended office BP was 120/71mmHg in the intervention group and 127/78mmHg in the control group and the mean systolic BP difference between groups was -6.9 mmHg; 95% CI -4.9 to -8.9mmHg; $p<0.001$ (Figure 3). Findings were broadly consistent across sub-groups, although the p-value for homogeneity for education had $p=0.014$ (Figure 4, Supp. Table 1).

With respect to secondary outcomes, mean unattended diastolic BP was reduced in intervention compared to control (-5.8mmHg, 95% CI -4.4 to -7.2mmHg; $p<0.0001$). Intervention participants were more likely to achieve BP control of $<140/90$ mmHg on standard office measures (76% vs 58%, relative risk [RR] 1.30, 95%CI 1.2 to 1.5; $p<0.0001$) and tight BP control at $<120/80$ mmHg on standard office measures (46% vs 26%, RR 1.75, 95% CI 1.38 to 2.22; $p<0.0001$). The mean 24-hour ambulatory systolic BP (ABP) was 7.5 mmHg (95% CI -9.0; -5.9) lower in the quadpill compared to the irbesartan arm. Daytime 24-hr SBP and nighttime 24-hr SBP was similarly reduced in the intervention compared to control, -7.8 mmHg, 95% CI -9.4, -6.1) and -6.6 (-8.4, -4.7) respectively. (Table 2a, b)

A total of 417 (70.6%) participants had extended follow-up, this was 81% (417/513) of those invited to extended follow-up. The baseline characteristics of extension participants were similar to main study participants (Supp. Table 2) and the 12-week BP levels were almost identical in those who continued follow-up (121/72, vs 126/76 in intervention vs control) compared to those who did not (121/72 vs 127/76 in intervention vs control). For the cohort that continued to 12 months, additional BP meds were more commonly being taken at each of the 6, 12, 26 and 52 week follow-up visits in the control vs intervention group (Figure 2) At 52 weeks 158/205 (77.1%) were adherent to randomised treatment in the intervention vs 157/211 (74.4%) in the control arms.

At 12 months mean unattended office BP was 121/71mmHg in the intervention group and 128/76mmHg in the control group with a mean unattended systolic BP difference of -7.7mmHg; 95% CI -5.2 to -10.3 mmHg; $p<0.0001$). The mean unattended diastolic BP difference was -6.0mmHg (95% CI -4.3 to -7.6mmHg). Both BP control on standard office measures (81% vs 62%, RR 1.3 95% CI 1.2-1.5; $p<0.0001$) and tight BP control on standard office measures (53% vs 25%, RR 2.1, 95% CI 1.6-2.8; $p<0.0001$) were achieved more frequently in the intervention arm compared to control arm. The mean 24-hour systolic ABP was -6.0 mmHg (95% CI -8.75; -3.17) lower in the intervention compared to the control arm (Table 3a,b).

In all randomised participants up to 12 weeks there were 7 (3%) vs 3 (1%) SAEs. There were 12 (4.0%) versus 7 (2.4%) treatment withdrawals for any adverse event, in the intervention vs control arms respectively ($p=0.27$) (Supp Table 3,4). During follow-up to 12 weeks in the intervention vs control groups SBP $<100\text{mmHg}$ was recorded in 17/282 (6.0%) vs 7/276 (2.5%) and heart rate $<50\text{BPM}$ was recorded in 35/282 (12.4%) vs 1/276 (0.4%), both $p<0.01$, whereas the number reporting dizziness was 93 (31.0%) vs 74 (25.4%), RR 1.27 (0.98; 1.64, $p=0.07$). There were no SAEs 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 to 12 months there were 15 (7.3%) versus 14 (6.6%) reporting SAEs in the intervention and control arms respectively. In the cohort with extended follow-up 15 (7.3%) versus 8 (3.8%), RR 1.92 (0.83, 4.35), $p=0.1186$ had treatment discontinuation due to any adverse event in intervention vs control arms respectively (Supp. Table 5,6).

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 (e.g. $<50\text{mmHg}$ or $>250\text{mmHg}$) to remove our finding of efficacy of intervention vs control.

DISCUSSION

This trial showed that a strategy of starting with quarter-dose quadruple combination therapy achieved and maintained BP control more effectively compared to starting with standard dose monotherapy. Importantly the study employed a range of BP 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 attractiveness of the quadpill strategy is in its simplicity and efficacy. In this study the large majority of intervention participants only needed the quadpill to achieve BP control. The control arm of this study 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 much more frequently in the control group compared to the intervention group but despite this BP was not controlled as effectively as in the intervention arm 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 BP management strategy, with a sufficient period of follow-up. Prior studies have indicated large BP reductions with quadruple quarter-dose therapy compared to monotherapy⁶ 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 of initial triple half-dose combination therapy done in Sri Lanka showed benefits on BP lowering compared to 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.^{12,13} The generalisability to other clinical settings was also unclear.

A secondary aim of this study was to assess if initial use of a quadpill was safe and had fewer adverse effects compared to 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 to 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 – in contrast, the strategy assessed in this trial increased efficacy but did not reduce side-effects.^{14,15} While this trial indicates that drug-specific adverse effects are not reduced with a quadpill compared to angiotensin receptor blocker-based approach, it should be noted that angiotensin receptor blockers have little difference in tolerability compared to placebo, unlike other forms of monotherapy, especially at higher doses.^{3,16,17} For example, low-dose triple therapy reduces pedal oedema compared to the maximal dose of amlodipine.¹⁸ Further research should assess comparative efficacy and tolerability compared to other regimens, such as initial dual combination therapy now recommended for numerous patient groups in recent guidelines.¹⁹⁻²¹ However the current trial results are highly relevant to current practise since monotherapy remains the most common initial treatment, even in high income countries.²²

Evidence of benefits from lowering BP beyond traditional targets^{19,20,23} 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 BP levels above goal from 39% to 53%.²⁴ In the context of previous supportive evidence,²⁵ the SPRINT trial²⁶ has been highly influential in changing guidelines globally. While the SPRINT population were on more medications at entry and were likely higher risk, it is noteworthy that the BP reductions achieved in the QUARTET and SPRINT intervention groups were almost identical, as were mean baseline BP levels. In QUARTET however, this BP 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.²⁷

Achieving BP control remains a substantial challenge.^{2,28} There are many reasons for poor BP control including social and health system determinants, poor adherence and clinical inertia. The comparison group BP 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.^{29,30} A strategy that confers an additional 7mmHg SBP 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.²³ There is also considerable potential in low- and middle-income countries, where the vast majority of people with hypertension globally reside and where less than one-third are treated and only around 30% of those treated achieve BP control.^{29,31} Initial use of ultra-low dose combination therapy has the potential to significantly improve BP control in such settings if challenges of availability, affordability and health system integration can be overcome.^{28,32} Description of this strategy should be incorporated into hypertension guidelines, though currently implementation is limited by availability of suitable products.

Limitations of this trial are that it did not reach its recruitment target, as implementation was impacted by the coronavirus 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 longer term cardiovascular outcomes. While randomised trials to date demonstrate that most or all of the benefits of BP lowering drugs are mediated through the degree of BP reduction,³³ there are no direct data on low-dose combinations. Patient adherence was assessed by pill count only which has known limitations. We also note that our definition of quarter-dose was based upon a definition of standard dose derived from published formularies,^{3,5} but there is geographic 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 – for example, less than half of people with uncontrolled office BP at week 6 in the control group remained on monotherapy after week 12, whereas much higher rates of treatment inertia are generally observed.³⁴ This will lead to underestimation of the benefits of the quadpill in settings with higher rates of treatment inertia.

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.

Research in context

Evidence before this study

A systematic review and meta-analysis of quarter dose BP lowering therapy published in 2017 highlighted the potential benefits of quarter-dose combination therapy in comparison to standard dose monotherapy, suggesting greater efficacy with quadruple combinations and comparable efficacy with fewer adverse events with dual combinations.⁵ An updated search of MEDLINE from 2016 to 21 July 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 to monotherapy or placebo, although the authors were aware of one trial.¹⁸ Overall, there was only one unblinded study comparing quadruple quarter-dose combination therapy to standard doses of the four components showed short-term benefits favouring the ultra-low dose combination.⁶ 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.⁴ A small trial also compared a losartan-amlodipine-chlorthalidone combination in triple ¼, triple 1/3 and triple ½ doses to monotherapy. Collectively these studies indicate the potential for large BP reductions with quadruple quarter dose therapy compared to monotherapy, but provided few data on tolerability and none compared to the guideline recommended therapy of uptitration if BP is not controlled after initial monotherapy.

Added value of this study

This trial is the largest and longest randomised double-blinded evaluation of quadruple quarter dose combination therapy assessing efficacy and tolerability. The intervention strategy of initial quadpill provided better blood pressure reductions, and a higher proportion of participants experienced blood pressure control at 12 weeks compared to the control strategy of initial monotherapy. The large majority of intervention participants only needed the quadpill to achieve BP control. While uptitration was frequent in the control and more frequent compared to the intervention group, BP was not controlled as effectively as in the intervention arm at 12 weeks and at 1 year. There was no excess in serious adverse events, or withdrawals due to adverse events in the quadpill group.

Implications of all the available evidence

Initial monotherapy remains the most used strategy globally, but BP control rates remain suboptimal, often due to treatment inertia. Quarter-dose quadruple combination therapy presents a simple, tolerable, and efficient strategy for achieving blood pressure control. It provides an approach to achieving better BP control with a single pill more quickly and with fewer up-titration steps.

Figure Legends

Figure 1 – Consort Diagram

Figure 2 – Blood pressure lowering treatment at 12 weeks and 52 weeks in intervention and control arms

Figure 3 – Mean systolic blood pressure to month 12, by group.

Estimated mean unattended office systolic blood pressure with 95% confidence intervals at baseline, 6 and 12 weeks in the main study and at 6months and 12 months from the extended sub-study

Figure 4 – Difference in change from baseline in systolic blood pressure at 12 weeks, by subgroup

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See appendix “Quartet Acknowledgments”

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Disclosures

The George Institute for Global Health (TGI) has submitted patent applications in respect of low fixed-dose combination products for the treatment of cardiovascular or cardiometabolic disease. Professor Rodgers and Professor Chow are listed as inventors. Professor Rodgers is employed by The George Institute for Global Health (TGI) and seconded part-time to George Medicines Pty Ltd (GM). George Health Enterprises Pty Ltd (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 arm of TGI. Professor Rodgers and Professor Chow do not have direct financial interests in these patent applications or investments.

Data sharing

De-identified participant data will be made available to researchers 1 year after the publication date of the main results paper. 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 paper). Data will only be shared with the approval of the steering committee and on signing of a data access agreement.

Table 1: Baseline characteristics

	Intervention n=300	Control n=291
Age, mean $\pm$ SD (years)	58 $\pm$ 12	59 $\pm$ 11
Female sex- no. (%)	122 (41%)	113 (39%)
Health care concession card holder- no. (%)	65 (22%)	72 (25%)
Ethnicity - no. (%)		
White	249 (83%)	234 (80%)
Asian	33 (11%)	37 (13%)
Other	18 (6%)	20 (7%)
Baseline blood pressure treatment no. (%)		
Not treated*	171 (57%)	147 (51%)
On monotherapy	129 (43%)	144 (49%)
Baseline blood pressure, mean $\pm$ SD (mmHg)		
Unattended systolic	142 $\pm$ 13	140 $\pm$ 13
Unattended diastolic	86 $\pm$ 10	83 $\pm$ 10
Office systolic	153 $\pm$ 16	152 $\pm$ 15
Office diastolic	89 $\pm$ 10	88 $\pm$ 11
24 Hour ABPM – systolic	144 $\pm$ 11	143 $\pm$ 11
24 Hour ABPM – diastolic	84 $\pm$ 9	84 $\pm$ 9
Baseline heart rate, mean $\pm$ SD (beats per minute)	71 $\pm$ 11	71 $\pm$ 11
Body mass index, mean $\pm$ SD (kg/m ²)	31 $\pm$ 6	30 $\pm$ 6
Ever smoked- no. (%)	115 (38%)	110 (38%)
Current smoker- no. (%)	23 (8%)	25 (9%)
Former smoker- no. (%)	92 (31%)	85 (29%)
Alcohol once or more per week- no. (%)	202 (67%)	174 (60%)
Diabetes- no. (%)	21 (7%)	24 (8%)
Chronic kidney disease- no. (%)	0 (0%)	1 (0.3%)
Coronary artery disease- no. (%)	14 (5%)	12 (4%)
Creatinine, mean $\pm$ SD (μ mol/L)	76.1 $\pm$ 15.1	74.7 $\pm$ 13.0
Estimated glomerular filtration rate, mean $\pm$ SD (ml/min/1.73m ²)**	77.0 $\pm$ 10.2	79.1 $\pm$ 9.0
Sodium, mean $\pm$ SD (mmol/L)	140.2 $\pm$ 2.2	140.3 $\pm$ 2.4
Potassium, mean $\pm$ SD (mmol/L)	4.4 $\pm$ 0.4	4.4 $\pm$ 0.4
Total cholesterol, mean $\pm$ SD (mmol/L)	5.3 $\pm$ 1.1	5.3 $\pm$ 1.1
HDL-cholesterol, mean $\pm$ SD (mmol/L)	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4
Fasting glucose, mean $\pm$ SD (mmol/L)	5.6 $\pm$ 1.6	5.4 $\pm$ 0.9

* Not treated - not taking blood pressure-lowering medications, or not currently taking treatment for at least 4 weeks

**eGFR estimated according to the CKD-EPI equation

Table 2a: Blood pressure by measurement method at 6 and 12 weeks

	Intervention (95% CI)	Control (95% CI)	Mean difference (mmHg), 95% CI	p-value
Unattended automated SBP Wk 12*	121 (118; 123)	127 (124; 129)	-7 (-9; -5)	<.0001
Other blood pressure measurements				
Unattended SBP Wk 6	121 (118; 123)	131 (128; 133)	-9 (-11; -7)	<.0001
Unattended DBP Wk 6	71 (69; 72)	78 (77; 80)	-8 (-9; -6)	<.0001
Unattended DBP Wk 12	71 (70; 73)	77 (75; 78)	-6 (-7; -4)	<.0001
Office SBP Wk 6	130 (126; 133)	139 (135; 142)	-8 (-11; -6)	<.0001
Office SBP Wk 12	129 (126; 132)	133 (130; 137)	-5 (-8; -3)	<.0001
Office DBP Wk 6	75 (73; 76)	82 (80; 84)	-8 (-9; -6)	<.0001
Office DBP Wk 12	76 (74; 77)	79 (77; 81)	-4 (-6; -3)	<.0001
24-hour ambulatory SBP at 12 wks				
SBP overall	121 (119; 123)	128 (126; 130)	-7 (-9; -6)	<.0001
DBP overall	69 (68; 70)	73 (72; 75)	-5 (-6; -4)	<.0001
Daytime SBP	127 (124; 128)	134 (132; 136)	-8 (-9; -6)	<.0001
Nighttime SBP	110 (109; 112)	116 (115; 119)	-7 (-8; -5)	<.0001
Daytime DBP	73 (72; 74)	78 (76; 79)	-5 (-6; -4)	<.0001
Daytime DBP	73 (72; 74)	78 (76; 79)	-5 (-6; -4)	<.0001

Table 2b Hypertension control at 6 and 12 weeks

	Intervention	Control	Absolute difference (95% CI)	Relative Risk (95% CI)	P-value
BP target** achieved (unattended office BP)					
Week 6	256/276 (92.8%)	203/272 (74.6%)	18.1 (12.1; 24.2)	1.24 (1.15; 1.34)	<.0001
Week 12	244/267 (91.4%)	221/270 (81.9%)	9.5 (3.8; 15.3)	1.11 (1.04; 1.19)	0.0016
Tight BP target*** achieved (unattended office BP)					
Week 6	196/276 (71.0%)	96/272 (35.3%)	35.7 (27.6; 43.1)	2.01 (1.68; 2.40)	<.0001
Week 12	188/267 (70.4%)	119/270 (44.1%)	26.3 (18.1; 34.1)	1.59 (1.36; 1.86)	0.0016
BP target** achieved (attended office BP)					
Week 6	200/274 (73.0%)	141/273 (51.6%)	21.3 (13.3; 29.0)	1.41 (1.24; 1.61)	<.0001
Week 12	205/269 (76.2%)	158/271 (58.3%)	17.9 (10.0; 25.5)	1.30 (1.15; 1.47)	<.0001
Tight BP target*** achieved (attended office BP)					
Week 6	116/274 (42.3%)	54/273 (19.8%)	22.6 (14.9; 29.9)	2.12 (1.61; 2.79)	<.0001
Week 12	124/269 (46.1%)	71/271 (26.2%)	19.9 (11.8; 27.6)	1.75 (1.38; 2.22)	<.0001

* primary outcome

** <140/90mmHg

*** <120/80 mmHg

Table 3a: Blood pressure by measurement method at 6, 12, 26 and 52 weeks in participants in the extended study

	Intervention (95% CI)	Control (95% CI)	Mean difference (95% CI)	p-value
Unattended automated SBP, mmHg				
Week 6	121 (118; 123)	131 (128; 133)	-10 (-12; -8)	<.0001
Week 12	121 (118; 123)	127 (124; 129)	-6 (-8; -4)	<.0001
Week 26	122 (120; 125)	126 (123; 129)	-4 (-6; -1)	0.0035
Week 52	121 (118; 123)	128 (126; 131)	-8 (-10; -5)	<.0001
Overall			-7 (-9; -5)	<.0001
Unattended automated DBP, mmHg				
Week 6	71 (69; 72)	78 (77; 80)	-8 (-9; -6)	<.0001
Week 12	71 (70; 73)	77 (75; 78)	-5 (-7; -4)	<.0001
Week 26	72 (70; 74)	76 (75; 78)	-4 (-6; -2)	<.0001
Week 52	71 (69; 73)	77 (75; 79)	-6 (-8; -4)	<.0001
Overall			-6 (-7; -5)	<.0001
Office SBP, mmHg				
Week 6	130 (126; 133)	139 (135; 142)	-9 (-12; -6)	<.0001
Week 12	129 (126; 132)	134 (130; 137)	-4 (-7; -2)	0.0015
Week 26	130 (127; 133)	134 (131; 137)	-4 (-7; -1)	0.0031
Week 52	128 (125; 131)	136 (133; 139)	-8 (-10; -5)	<.0001
Overall			-6 (-8; -4)	<.0001
Office DBP, mmHg				
Week 6	75 (73; 76)	82 (80; 84)	-7 (-9; -5)	<.0001
Week 12	76 (74; 77)	79 (77; 81)	-4 (-5; -2)	<.0001
Week 26	75 (74; 77)	79 (78; 81)	-4 (-6; -2)	<.0001
Week 52	75 (73; 77)	79 (78; 81)	-4 (-6; -3)	<.0001
Overall			-5 (-6; -4)	<.0001

Table 3b Hypertension control at 6, 12, 26 and 52 weeks in extended cohort

	Intervention	Control	Absolute rate difference (95% CI)	Relative Rate (95% CI)	P-value
BP target achieved (office BP <140/90 mmHg)					
Week 6	154/201 (77%)	109/208 (52%)	24.2 (15.0; 32.8)	1.47 (1.26; 1.71)	<.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)	<.0001
Tight BP target achieved (office BP <120/80 mmHg)					
Week 6	85/201 (42%)	44/208 (21%)	21.1 (12.2; 29.7)	1.98 (1.45; 2.70)	<.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)	<.0001

Table 4: Tolerability at 12 weeks

Variable	Intervention n=300	Control n=291		P- value
Side effects, n (%)			Relative risk (95% CI)	
Dizziness	93 (31.0%)	74 (25.4%)	1.27 (0.98; 1.64)	0.07
Pedal oedema	21 (7.0%)	22 (7.6%)	0.96 (0.54; 1.69)	0.88
Muscle cramps	66 (22.0%)	61 (21.0%)	1.09 (0.80; 1.47)	0.60
Hypersensitivity	28 (9.3%)	30 (10.3%)	0.93 (0.57; 1.52)	0.79
Gastrointestinal complaints	37 (12.3%)	36 (12.4%)	1.03 (0.67; 1.59)	0.89
Musculoskeletal complaints	38 (12.7%)	45 (15.5%)	0.85 (0.57; 1.27)	0.41
Headache	43 (14.3%)	43 (14.8%)	1.00 (0.68; 1.47)	0.99
Other side effects	109 (36.3%)	104 (35.7%)	1.05 (0.85; 1.30)	0.64
Laboratory measures, mean $\pm$ SD			Mean difference (95% CI)	
Sodium, (mmol/L)	139.8 $\pm$ 2.5	140.2 $\pm$ 2.2	-0.4 (-0.8, 0.0)	0.06
Potassium, (mmol/L)	4.3 $\pm$ 0.4	4.4 $\pm$ 0.4	-0.2 (-0.2, -0.1)	<.0001
Uric acid, (mmol/L)	0.4 $\pm$ 0.08	2.0 $\pm$ 26.2	-1.6 (-5.0, 1.7)	0.34
Fasting glucose, (mmol/L)	5.8 $\pm$ 1.7	5.4 $\pm$ 1.1	0.4 (0.1, 0.7)	0.018
Total cholesterol, (mmol/L)	5.2 $\pm$ 1.0	5.3 $\pm$ 1.0	-0.04 (-0.24, 0.17)	0.72
HDL cholesterol, (mmol/L)	1.3 $\pm$ 0.4	1.4 $\pm$ 0.4	-0.06 (-0.1, 0.0)	0.14
ALT, (U/L)	30.0 $\pm$ 17.9	28.9 $\pm$ 14.6	1.1 (-1.8, 4.0)	0.45
AST, (U/L)	25.2 $\pm$ 9.4	25.6 $\pm$ 8.9	-0.4 (-2.0, 1.3)	0.67
Urea, (mmol/L))	6.1 $\pm$ 1.8	5.7 $\pm$ 1.4	0.5 (0.2, 0.8)	0.001
Creatinine, (μ mol/L)	79.3 $\pm$ 17.7	75.3 $\pm$ 14.9	4.0 (1.1, 6.8)	0.006
UACR, (mg/mmol)	1.1 $\pm$ 1.8	1.6 $\pm$ 6.7	-0.4 (-1.3, 0.5)	0.35
eGFR, (ml/min/1.73m ²)	76.2 $\pm$ 12.1	77.4 $\pm$ 10.5	-2.9 (-5.6, -0.2)	0.04

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