Ultra-low-dose quadruple combination blood pressure lowering therapy in patients with hypertension: The QUARTET randomized controlled trial protocol

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Abstract

High blood pressure is the leading cause of preventable morbidity and mortality globally. Many patients remain on single-drug treatment with poor control although guidelines recognize that most require combination therapy for blood pressure control. Our hypothesis is that a single-pill combination of four blood pressure- lowering agents each at a quarter dose may provide a simple, safe and effective blood pressure lowering solution which may also improve long term-adherence. The QUARTET (Quadruple UltrA-low-dose tReaTment for hypErTension) double-blind, active controlled, randomized clinical trial will examine whether ultra-low-dose quadruple combination therapy is more effective than guideline recommended standard care, in lowering blood pressure. QUARTET will enroll 650 participants with high blood pressure, either on no treatment or on monotherapy. Participants will be randomized 1:1 and allocated to intervention therapy of a single pill (quadpill) containing irbesartan 37.5mg, amlodipine 1.25mg, indapamide 0.625mg and bisoprolol 2.5mg or to control therapy of a single identical appearing pill containing irbesartan 150mg. In both arms step up therapy of open-label amlodipine 5 mg will be provided if BP is > 140/90 at 6 weeks. The primary outcome is the difference between groups in the change from baseline in mean unattended automated office systolic blood pressure at 12 weeks follow-up. The primary outcome and some secondary outcomes will be assessed at 12 weeks, there is an optional 12 months extension phase to assess longer term efficacy and tolerability. Our secondary aims are to assess if this approach is safe, has fewer adverse effects and better tolerability compared to standard care control. QUARTET will therefore provide evidence for the effectiveness and safety of a new paradigm in the management of high blood pressure.

Keywords

Hypertension, primary care, ambulatory blood pressure monitoring, double-blinded, randomized

Strengths and limitations of this study

Strengths

- Large, multi-site randomized trial with up to 12 months follow-up
- Double-blind design
- Comparison with current guideline-based blood pressure management
- Objective measurement of the primary outcome
- Embedded economic and acceptability evaluations

Limitations

- Single country study. A sister trial, QUARTET USA, will provide further information on generalizability.
- Trial not powered for cardiovascular events.

Abbreviations

ABP/ABPM	ambulatory blood pressure /monitoring
ACE-I	angiotensin converting enzyme inhibitor
ARB	angiotensin II receptor blocker
BB	beta-blocker
CCB	calcium channel blocker
DALY	disability-adjusted life-year
DBP	diastolic blood pressure
DSMC	data safety and monitoring committee
eGFR	estimated Glomerular Filtration Rate
GP	general practitioner
QUARTET	Quadruple UltrA-low-dose tReatment for hypErTension
SBP	systolic blood pressure
SD	standard deviation
TZ	thiazide or thiazide-like diuretic

Introduction

Burden of high blood pressure and treatment gaps

High blood pressure is the leading cause of preventable morbidity and mortality globally.[1] The benefits of blood pressure lowering in reducing cardiovascular events are unequivocal[2] and there is clear evidence of greater benefits for combination-based therapy compared to monotherapy.[3] Furthermore, numerous studies have indicated the benefits of more rapid control of blood pressure, and have shown that this is more likely to occur with use of combination therapy.[4] Yet, control of high blood pressure is poor, with only 1 in 3 on treatment achieving blood pressure targets.[5-8]

Previous guidelines typically recommended initiating monotherapy, up-titration of dose, switching drugs if not tolerated, and adding other agents if needed.[7] This often takes multiple visits to achieve target blood pressure – and studies show that most individuals remain on monotherapy and with inadequate blood pressure control.[5] The largest global survey of hypertension practice showed only 34% of those treated for high blood pressure were controlled (SBP<140 and DBP<90mmHg), and 31% of treated patients were receiving combination therapy.[5] The 2017 May Measurement Month blood pressure screening campaign included a convenience sample of 1.2 million across 34 countries, and found 54% of those treated had adequate blood pressure control. A 2013 survey of 31 international hypertension guidelines showed that 27 (87%) now recommend use of combination for initial treatment, but typically only as an option for patients at >20/10mmHg from goal.[9] As 50 to 75% of patients require combination treatment for blood pressure control, there has been increasing interest in the initial use of combination therapy.[10] Most recently the ESC/ESH guidelines recommended initial combination therapy for most people, except those with low cardiovascular risk and SBP<150mmHg and frail older adults.[11]

There are multiple barriers to blood pressure control that are patient, healthcare system and physician related. Patient adherence is a major factor and is worsened by increased number of medications, complexity of dosing regimens and medication side effects.[12,13] 'Therapeutic inertia', the reluctance of physicians to treat mild hypertension and up-titrate medications, is also a barrier to blood pressure control. A large study conducted in Western Europe and the US of more than 20,000 people with hypertension found that blood pressure control rates ranged from 31 to 63%, and only 15 to 38% of instances of elevated blood pressure had up-titration during the visit.[14] There is a clear need for improved strategies that will: a) make the treatment of high blood pressure more effective and easier to implement for doctors and patients; b) quickly and safely bring blood pressure under control and; c) increase long term adherence with therapy. We hypothesize that a single-pill combination of four blood pressure lowering agents at quarter dose may achieve these goals.

Rationale for very low-dose combination therapy

Dose response data on blood pressure reduction

Pharmacological dose response curves for blood pressure lowering drugs indicate that a quarter-dose has at least half the blood pressure-lowering effect of a standard dose (usual maintenance dose) but with much fewer side effects.[3]

A systematic review of all randomized trials of quarter dose blood pressure lowering identified a total of 42 trials, 38 of single quarter-dose comparisons, seven of dual quarter-dose comparisons and two of a quadruple quarter-dose combination.[15] Compared to placebo, single quarter dose therapy reduced blood pressure by 5/2 mmHg (p<0.0001) with no increase in adverse events. Dual quarter-dose therapy was similarly efficacious as standard-dose monotherapy. Two studies of quadruple quarter-dose therapy have been published. One unblinded pilot with four control groups of standard-dose monotherapies of the components showed a reduction of 13/8mmHg compared to the average reduction of all four controls after four weeks.[16] The other, our pilot, a double-blinded placebo-controlled cross-over trial in people with newly diagnosed hypertension showed a reduction of 22/13mmHg after four weeks active treatment versus placebo.[17]

There is strong evidence that the blood pressure lowering effects of different classes of drugs are independent and fully additive.[15,18] The effects of adding a second blood pressure lowering agent are closely concordant with those predicted by independent effects, occur across all pairs of medication classes, and are about five times more effective than doubling the dose of the first agent.[18] The additive effects across three classes of low-dose drugs were also demonstrated in a placebo-controlled, crossover trial of three half-dose blood pressure drugs in 86 participants aged

over 50 years without a history of cardiovascular disease.[19] Overall a 17.4/9.4 mmHg blood pressure reduction was observed, compared to the anticipated 17.9/9.5 mmHg decline expected from the cumulative effects of the three separate agents.

Dose response data on adverse effects

Avoiding or minimising adverse effects is critical to long-term adherence for blood pressure lowering, given that high blood pressure is typically symptomless. Blood pressure lowering medications rarely cause adverse effects when used at low dose but each doubling in dose typically leads to a steep increase in adverse effect rates.[20] This contrasts to the dose response for blood pressure reduction whereby significant effects are seen at quarter-dose, with only a moderate dose response thereafter. For thiazide or thiazide-like diuretics (TZs), beta-blockers (BBs) and calcium-channel blockers (CCBs) there is a relatively steep increase in adverse effects across all dose ranges.[20] Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) are usually well tolerated at low and standard doses but are associated with more adverse effects at higher doses, with the exception of ACE-I-cough which is not dose-dependent.[21]

Few direct data have been published on the adverse effects of ultra-low doses of anti-hypertensive medications. Bennett et al. reviewed 15 studies that had data on adverse effects.[15] Comparisons with placebo showed no difference in total adverse events for single quarter-dose (14 trials, n=1838), dual quarter-dose (6 trials, n=312), and quadruple quarter-dose (1 trial, n=19) therapy. Comparisons with standard-dose monotherapy showed significantly fewer adverse events overall for single quarter-dose (15 trials, n=1978) and dual quarter-dose (2 trials, n=290) therapy. Biochemical changes appear minimal with quarter-dose therapy compared to standard-dose monotherapy.[15] These data suggest that dose-dependent adverse effects will be minimal with this intervention, and idiosyncratic reactions are uncommon with these component medications.

Objective

The primary objective of the Quadruple UltrA-low-dose tReatment for hypErTension (QUARTET) trial is to examine whether ultra-low-dose quadruple combination therapy (quadpill) is more effective than guideline recommended therapy with an ARB plus a CCB if required in lowering blood pressure. Our secondary aim is to assess if this approach is safe and has fewer adverse effects compared to standard care.

Methods

Trial design

This is a 12-week double blind randomized controlled trial of 650 patients with high blood pressure. Participants are randomized in a 1:1 allocation ratio using a central computer-based service, to initial therapy with quadpill or to a standard dose of an ARB, with a CCB added as required, as per current guideline recommendations (Figure 1). The primary outcome is reduction in mean office systolic blood pressure (SBP) measured using Omron HEM-907 at 12 weeks. Secondary outcomes include: the proportion of participants with controlled blood pressure (SBP<140mmHg and diastolic blood pressure [DBP] <90mmHg) at 6 weeks and 12 weeks, ambulatory blood pressure (ABP) measures at 12 weeks, tolerability and the occurrence of adverse events. Learnings from the quadpill pilot informed the design and conduct of the present trial.[17]

Extension study

An extension study to 12 months follow-up involves two more visits, at 26 and 52 weeks after randomization to examine longer term efficacy and tolerability.

Participants

Eligibility criteria

The study enrolled the first participant on 8th June 2017, and the last participants are expected to complete follow-up by 30th November 2020. Currently 575 (88%) participants have been randomized and 421 have agreed to continue in the extension study. At the time of submission COVID-19 has impacted study recruitment as health services have paused

non-essential activities (from mid-March 2020) to minimise infection risk. This may increase the likelihood of stopping the trial before the recruitment target is reached

Inclusion criteria

- Adults (⩾18 years)
- Previous documentation of hypertension or high blood pressure (SBP 140-179mmHg and/or DBP 90-109 mmHg) from general practitioner (GP), pharmacist or other health care professional
- And either:
    - A measure of office SBP 140-179mmHg and/or DBP 90-109 mmHg documented by study staff in the last 12 weeks with a study automatic BP device or;
    - A recorded measure of daytime average SBP ⩾ 135 mmHg and/or DBP ⩾ 85 mmHg on a 24-hour ambulatory BP monitoring device in the last 12 weeks.
- And one of the following:
    - Treatment naïve (i.e. never treated);
    - Currently not on treatment (not taken in last 4 weeks);
    - Currently taking one BP lowering drug (that is any of the following drug classes: ACE-I, ARB, CCB, BB, aldosterone antagonist, alpha-blocker) at any dose.

Exclusion criteria

- Contraindication to irbesartan, amlodipine, indapamide or bisoprolol
- Evidence of secondary cause of hypertension;
- Estimated Glomerular Filtration Rate [eGFR]<50 mL/min/1.73m^2,
- Raised serum potassium (above local laboratory normal limit)
- Women who are pregnant, breast feeding and/ or of childbearing potential and not using medically acceptable form of contraception throughout the study
- Concomitant illness, physical impairment or mental condition which in the opinion of the study team/ primary care physician could interfere with the conduct of the study including outcome assessments
- Participation in a concurrent interventional medical investigation or clinical trial. Patients in observational, natural history and/or epidemiological studies not involving an intervention are eligible.
- Participant's primary care doctor or other responsible physician believes it is not appropriate for participant to switch current monotherapy or initiate study drug.
- Inability or unwillingness to provide written informed consent
- Unable to complete study procedures including 24-hour ABPM
- Definite indication for one or more components of the quadpill

We amended exclusion criteria in November 2017 to ensure participants in an influenza vaccination study were not precluded from participation in the trial.

- Participation in a concurrent clinical trial of an investigational medical product. Patients in trials of approved medical products, or in observational, natural history and/or epidemiological studies not involving an intervention are eligible.

Changes to inclusion and exclusion criteria to facilitate recruitment

In June 2018 we further amended inclusion criteria to allow lower BP entry for those on monotherapy, as these participants are considered not-at-target within Australian guidelines.[22]

- Adults (⩾18 years)
- Previous documentation of hypertension or high blood pressure (SBP 140-179mmHg and/or DBP 90-109 mmHg) from general practitioner (GP), pharmacist or other health care professional
- And either meeting criterion A or B:
    - Criterion A: In treatment naïve (i.e. never treated) or in patients currently not on treatment (not taken in last 4 weeks) either:
        - A measure of Clinic SBP 140-179mmHg and/or DBP 90-109mmHg documented by study staff in the last 12 weeks with a study automatic BP device OR

- A recorded measure of daytime average SBP ⩾135mmHg and/or DBP ⩾85mmHg on a 24-hour ambulatory blood pressure monitoring (ABPM) device in the last 12 weeks
- Criterion B: In patients currently taking one BP lowering drug 'monotherapy' either:
  - A measure of Clinic SBP 130-179mmHg and/or DBP 85-109mmHg documented by study staff in the last 12 weeks with a study automatic BP device OR
  - A recorded measure of daytime average SBP ⩾125mmHg and/or DBP ⩾80mmHg on a 24-hour ABPM device in the last 12 weeks.

Setting, locations and recruitment

Participants are recruited from community general practices and outpatient clinics. Current active sites are listed in the appendix. There is a total of 10 sites in 4 of the 8 states and territories of Australia (New South Wales, Victoria, Tasmania and Western Australia), with 3 of these based in primary care and the rest in hospital or university locations. We employ several methods to identify potentially eligible participants. This includes community advertising and awareness campaigns (using print and electronic media advertisements and radio), referral by clinicians aware of the study (advertising through clinical trial sites and communication media to health professionals) and screening of relevant patient lists by clinical investigators for potentially eligible patients. Participants are not paid for their participation. Participants may be reimbursed for travel.

Study treatment

Patients are randomized to a) an encapsulated single pill (quadpill) containing irbesartan 37.5mg, amlodipine 1.25mg, indapamide 0.625mg and bisoprolol 2.5mg; or to b) an identical capsule containing irbesartan 150mg. At 6 weeks, if the blood pressure is greater than 140/90 mmHg in either arm open label amlodipine 5mg is added: this is provided as an additional pill.

We selected quarter standard doses of irbesartan, amlodipine, indapamide, and bisoprolol. The first three were chosen as the most commonly prescribed ARB, CCB, and TZ in Australia (PBS Information Management Section Pharmaceutical Policy Branch, 2013). Standard dose was determined following the method of Bennett et al.[15] While hydrochlorothiazide is included in a number of fixed dose combinations, some recent guidelines[23] and literature recommend indapamide or chlorthalidone, principally on the basis that some data suggest more cardiovascular event reduction with these agents,[24,25] though a recent paper suggests no difference.[26] The additional blood pressure reduction expected from including a quarter-dose of a different class of drug is about three times as great as would be achieved by doubling the dose of any other component.[15] We chose the 4th agent to be a BB, due to its long duration of action, relatively minimal side effects at a quarter dose. The choice of a beta-blocker as a 4th agent of choice is also consistent with a number of international hypertension guidelines which specify Beta-blocker use after renin angiotensin system blockers, CCBs and thiazide type diuretics.[22,27,28] We chose bisoprolol over atenolol due to its longer duration of action. The other major consideration was use of off-patent components to minimize costs.

The control group follows the recommendations of the current Australian guidelines,[22,29] i.e. initiating with an ACE-I or ARB, and if blood pressure is not controlled adding a CCB. This approach is also consistent with the 2011 NICE Hypertension Guidelines, and among the preferred treatment options in the 2013 JNC-8 Guidelines and the 2013 ESC/ESH Guidelines, which were current at the inception of this study.[23,30,31] We chose irbesartan as it is the most commonly prescribed ARB in Australia and amlodipine because it is the most commonly prescribed CCB.

Patients who are on monotherapy at time of recruitment will be asked to stop their treatment while they are taking the study treatment. The drug is provided to both intervention and control arms at no cost to the participant. Medications are provided in quantities of 99 tablets at 3 monthly intervals. That is a medication kit is given to patients at baseline, week 12 and at 6 months and 9 months in participants participating in the extension study. Each kit consists of 3 bottles comprising 33 tablets in each bottle. Most sites provide in-person pick-up of medications, and in selected sites in New South Wales (Westmead Hospital, Royal North Shore Hospital) and Western Australia (Sir Charles Gardiner Hospital, Royal Perth Hospital) medication is mailed to participants.

Preparation of study treatment

The study drug has been made up by PCI Clinical Services (formerly Pharmaceutical Packaging Professionals), a Therapeutic Goods Administration Code of Good Manufacturing Practice audited facility approved for all stages of finished product manufacture for clinical trials. This company encapsulated the drugs listed for intervention and control arms into a single capsule, with additional placebos in the control capsule. Thus, both the intervention and control participants receive a single capsule that appears identical, inside and out, to all participants, their health care providers and trial personnel.

Study procedures

Patients are assessed for eligibility and randomized if criteria are met. Follow-up clinical assessments are conducted at 6 and 12 weeks. The 6-week visit includes a clinic blood pressure measurement (3 unattended automated office measures) and recording of any changes in concomitant medications, adverse events, and health service use. At 6 weeks if clinic blood pressure is >140/90mmHg the researcher will alert the study doctor who will assess participant (BP and symptoms) and consider adding open-label amlodipine 5mg (consistent with current guidelines). The week 12 visit includes the above plus 24-hour ABPM, quality of life, and additional laboratory assessments sodium, potassium, chloride, bicarbonate, serum creatinine, eGFR (CKD-EPI formula), uric acid, liver function tests, and urine albumin/creatinine ratio. No central lab is used. Participants have an option to extend their involvement in the study to 12 months after randomization, involving extra visits at weeks 26 and 52 (with comparable follow-up procedures to weeks 6 and week 12 visits, respectively). Extension involves continuing to receive the randomly allocated treatment, but with management through their general practitioner or site doctor. They may add additional drugs if clinically necessary with open label treatment added without the need to unblind randomized therapy. Adherence to medications is assessed by self-report and a pill count of returned study medications at end of study time points, that is week 12 final visit and at 12 months the final visit of the extension study. Participants are asked how many days in the last 30 days they have missed taking any of their regular medications, and similarly about missed medications in the last 7 days.

During the study we will obtain information on self-reported health service utilization, and specifically ask if patients have seen and how frequently they have seen the following health providers – Practice nurse, General Practitioner, Doctor in public hospital emergency department (not admitted), Doctor in public outpatients clinic for any reason and Doctor in private specialist clinic for any reason. We also request consent to link data to MBS (Medical Benefits Schedule – listing of Medicare services subsidized by the Australian Government) and PBS (Pharmaceutical Benefits Scheme – listing of medicines subsidised by the Australian Government).

Information is collected on serious adverse events and adverse events of special interest (see list in appendix). We specifically query participants about adverse events of special interest at each visit (6 week, 12 weeks and additional visits for extension participants 6 months and 12 months). Adverse events of special interest include: dizziness, hypotension, pedal oedema, muscle cramps, bradycardia, heart failure, hypersensitivity reactions (skin rashes, itching), gastrointestinal complaints (nausea, vomiting, diarrhea), musculoskeletal complaints, headaches. Adverse events are not adjudicated. The EuroQol Group (EQ-5D-3L) Quality of Life questionnaire is completed by participants at their baseline, 12 week and final visits.

Outcome measures and outcome assessment

The primary and secondary outcomes are listed in Table 1.

The blood pressure measurements are recorded using an Omron HEM907. An appropriate cuff size is selected for all BP measurements. First a measure of clinic blood pressure is observed and recorded by research staff. Then, automated office blood pressure is measured following the recommendations of the European Society of Hypertension/European Society of Cardiology and Australian National Heart Foundation.[22,30] This requires the research staff to set the automated device to take three separate BP measurements while the researcher steps out of the room (unattended BP measurement). The Omron HEM907 is programmed to start the first measurement after five minutes of rest, then at one-minute intervals. The primary outcome “mean SBP” will be calculated using the average of these three unattended

measures. In addition, 24-hour ABPM is conducted at baseline, 12 and 52 week follow-up visits using a Suntech Oscar-2 programmed to measure every 30 minutes while participant is awake, and hourly during sleep.[32,33]

Sample size

A sample size of 650 patients provides 90% power at p=0.05 to detect a difference between randomized groups of 4 mmHg in the primary outcome, assuming a standard deviation (SD) of 15mmHg.[34] A sample of 650 also has 85% power to detect a 3mmHg difference in average 24hr SBP (SD 12 mmHg)[34] and 85% power to detect a 25% increase in the proportion with controlled blood pressure assuming 50% are controlled in the comparator group. All calculations allow for a 10% dropout or data loss rate. It is assumed that irbesartan 150 mg and up-titration with the addition of amlodipine in 75% of participants in the control group will give an average reduction of 12mmHg from an average baseline SBP of 150mmHg.[35] Based on the information presented in the background, quadruple combination therapy will reduce SBP by at least 16mmHg.[16,20]

The rate of all adverse events is predicted to be around 15% in the control group,[35] and this study will have 90% power to rule out an increase of 5 percentage points (i.e. a non-inferiority margin of 20%) assuming the true incidence of adverse events in the quadpill group is 10% and a one-sided test with alpha=2.5%. The 10% incidence of adverse events is a conservative estimate from adding up the incidence of side effects from each treatment class at ½ standard dose described in a previous systematic review: BB 5.5%, TZ 2.0%, CCB 1.6% and ARB 0%.[3]

Interim analyses, monitoring, and stopping guidelines

The trial data safety and monitoring committee (DSMC) monitors safety data on an ongoing basis, with the analyses performed by an independent statistician from the George Institute for Global Health. The DSMC can recommend the Steering Committee of the QUARTET Study should continue the study unchanged, adjust the duration of follow-up, or terminate the study early if there is clear and substantial evidence of benefit, if the data suggests the risk of adverse events substantially outweighs the potential benefits, or for futility. The first DSMC meeting was held after 25% of participants completed 12 weeks follow up and recommended continuation of the study without modification.

Randomization

The unblinded statistician prepared a computer-generated randomization schedule stratified by site and using permuted blocks of variable size. This was loaded into the web-based data management system (IBM Clinical Development, Morrisville USA). Allocation concealment is maintained as only the unblinded statistician and unblinded data manager have access to the randomization list and allocation within the database.

Participants are enrolled at sites by blinded staff, with participant randomization and study drug allocation conducted through the database with blinding maintained. The study drug kit numbering is separate to the randomization sequence to prevent the kit allocation potentially unblinding site staff. The investigators, project management, site staff, and participants are blinded to the randomization sequence and treatment allocation.

Statistical methods

The main analyses of study outcomes will be conducted according to the principle of intention-to-treat. The primary analysis of change in SBP at 12 weeks will be performed using an analysis of covariance including the treatment arm and baseline SBP as a covariate. Continuous secondary outcomes will be analyzed similarly. Additional analyses will include all follow-up measurements in a longitudinal model including treatment arm, visit, and a treatment by visit interaction term as well as the baseline measurement. Within-patient correlations will be modelled using generalized estimating equations or random effects. A similar approach will be applied to binary endpoints (e.g. blood pressure control) with log-binomial regression used in place of linear regression. A per-protocol analysis will be performed to provide information on the difference in efficacy between the two study treatments. There will also be pre-defined subgroup analyses, including by baseline blood pressure, gender, age, diabetes, education and by BP lowering treatment at baseline (no treatment versus monotherapy). A detailed analysis plan will be finalized prior to unblinding.

Economic evaluation

Cost-effectiveness and cost-utility analysis

An incremental cost-effectiveness analysis will be used to compare the costs and outcomes of the treatment arms from a health system perspective. This will consider the cost per mmHg reduction in systolic blood pressure and the cost per quality adjusted life-year gained for quadpill versus monotherapy to facilitate comparison with other interventions. Costs will be determined through the collection of resource use during the study period and estimates of commercial costs for the quadpill. Information on hospital admissions, doctors' visits and medications is collected at follow-up visits.

Acceptability evaluation

A semi-quantitative survey and in-depth interviews will be conducted to assess the acceptability of quadpill, and to identify which factors are important to participants and health providers in blood pressure reduction. Patient acceptability is a critical component of healthcare innovation. Patients and health providers in the study will be invited to answer questions assessing their perceptions, experience and the degree of engagement with the intervention at the completion of the trial. Patients and health providers will be invited to participate in semi-structured interviews on perceptions of the utility and acceptability of the intervention program. Examples of questions are included in the appendix. Interviews will be recorded and transcribed, then coded using NVivo. From the coded data key themes will be identified.

Trial management, funding, and sponsorship

The trial conduct is overseen by a steering committee (list in Appendix). The central coordinating center ensures implementation of the study according to the protocol, timelines and recruitment targets. We use an electronic data management system incorporating study checks and omissions. An independent data and safety monitoring committee meets regularly to assess emerging evidence on safety and efficacy. The QUARTET trial received primary funding from the National Health and Medical Research Council Australia (APP1100377). Investigators also received support from NHMRC program and investigator fellowships to enable the study (see Funding statement). The University of Sydney is the current study sponsor.

Trial registration, human research ethics, and dissemination plan

The QUARTET trial is registered on the Australian New Zealand Clinical Trial Registry (ACTRN12616001144404). The Western Sydney Local Health District Human Research Ethics Committee provides lead ethics approval (HREC/15/WMEAD/422).

The main trial results will be published in the name of the QUARTET Investigators with credit assigned to the collaborating investigators and other research staff. Publication authors must meet the International Committee of Medical Journal Editors guidelines for authorship. Presentations of the study findings will be made at national and international meetings concerned with the management of cardiovascular disease, and high blood pressure. Trial data will be made available through data access agreements established following approval through the Quartet Steering Committee. Trial data will not be publicly released or placed into an open-access repository. Trial data will be held by the University of Sydney for a minimum period of 15 years (or longer if required by applicable regulatory authorities).

Discussion

High blood pressure is the leading risk factor for lost healthy life years globally.[1] For women it is the leading risk factor, with 90 million disability-adjusted life-years (DALYs), and the second leading risk factor in men with 124 million DALYs.[36] Although the global age-standardized death rate attributable to high SBP declined by 1.35% over the last 30 years, the number of deaths attributable to high SBP has increased globally over this time, with 10.4 million deaths in 2016.[37] Achieving sustainable and affordable reductions in SBP is key to addressing this leading risk factor for lost healthy life.

The QUARTET trial is the first large-scale trial to examine a quadruple, quarter-dose regimen. This approach has many theoretical benefits, including greater efficacy and fewer side effects as well as pragmatic benefits that should improve adherence and decrease costs. If this new intervention achieves its conservative additional 4mmHg of blood pressure reduction compared to that conferred by optimal guideline-recommended care, such a difference could translate into an additional 15 to 20% reduction in cardiovascular events.[3]

There has been increasing acceptance of the role of dual anti-hypertensive combinations in blood pressure management both due to the observation that most patients require more than one agent to achieve BP control, and by trials showing early use of combination is beneficial.[38]

Benefits of combination therapy

It is apparent that people respond differently to different blood pressure classes,[23,39] however it is difficult to determine which drug is most effective for each individual.[40] A trial and error approach to finding an effective monotherapy regimen may contribute to low adherence. Combination therapy is more likely to provide a genuine good response more quickly and with less variability.

Fewer medications, and single-pill combination therapy improve adherence. A recent meta-analysis of trials comparing combination pills containing two antihypertensive agents to separate pills demonstrated a significant improvement in adherence with combination therapy.[41] Triple combinations are commercially available,[42,43] however they have not included an entirely low-dose option. These products are targeted to the relatively small subpopulation of patients with severe or resistant hypertension not controlled on full doses of dual combination therapy, or those already on the three medications.[43]

Some recent trials of low-dose combination therapy have demonstrated the potential of this strategy in other settings. The TRIUMPH trial evaluated a half-strength triple pill, but with several points of difference, most importantly the comparison against a variety of usual care options in Sri Lankan outpatient hospital care, with a focus on improving the access and affordability of blood pressure lowering medications in this setting.[44] This study found 70% of participants in the triple pill group achieved their target blood pressure versus 55% in the usual care group,[44] and the triple pill was cost-effective compared to usual care.[45] The Quadpill Pilot trial was a placebo-controlled pilot study was conducted in treatment-naïve people with newly diagnosed high blood pressure in primary care.[17] The ultra-low dose quadruple combination was very effective at lowering blood pressure in the short-term single center pilot study, hence the current study is needed. A sister trial, QUARTET USA (Clinicaltrials.gov NCT03640312), is currently underway in Chicago USA and an individual patient data meta-analysis is planned once both trials are completed.

Conclusion

If the intervention tested here is proven to be safe and effective, the trial results could be rapidly implemented, with immediate benefits in routine clinical practice. Similar therapy could be provided to patients using available medications, including existing dual combinations and the use of dose administration aids. Ultimately, most advantage will be gained from single pill formulations. The results of the current trial would stimulate the development of such products if the results were favorable.

In summary, ultra-low-dose combination therapy has the potential to have a major impact on current poor rates of blood pressure control globally. The critical next step is direct evidence on effectiveness and safety in a large-scale randomized controlled trial, which the QUARTET trial aims to provide.

Authors' contributions

CKC wrote the first draft of the Quartet protocol that was subsequently funded by NHMRC with critical review from AR as the senior author and all CIs of the NHMRC protocol including GH, MS, TU, RW, LB. ERA has been the postdoctoral fellow on Quartet, prepared the first draft of the manuscript and revised the manuscript. All authors have reviewed the final manuscript. We also acknowledge Henry Krum (deceased) who provided critical review of the Quartet protocol submitted to NHMRC.

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Competing interests

George Health Enterprises, the social enterprise arm of The George Institute for Global Health, has applied for patents in this research area, on which CKC and AR are named as inventors; George Health Enterprises has also received investment to develop fixed-dose combinations containing aspirin, statins, and blood pressure-lowering drugs.

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Table

TABLE 1 PRIMARY AND SECONDARY OUTCOMES FOR THE QUARTET TRIAL

Primary outcome	
Difference between groups in change in mean office systolic blood pressure from baseline to 12 weeks	
Secondary outcomes	
24-hour ambulatory blood pressure	**a) Difference between groups in mean 24-hour SBP and DBP at 12 and 52 weeks** b) Difference between groups in mean change in 24-hour SBP and DBP from 0 to 12 weeks, 0 to 52 weeks and 12 to 52 weeks c) Difference between groups in mean daytime SBP and DBP at 12 and 52 weeks d) Difference between groups in mean night-time SBP and DBP at 12 and 52 weeks e) Difference between groups in daytime, night-time, and 24-hour BP load (percentage area under the blood pressure curve above normal day, night, and 24-hour values as per National Heart Foundation guidelines f) Difference between groups in the proportion of non-dippers (night-time BP is not more than 10% lower than average daytime BP as per National Heart Foundation guidelines) and coefficient of variability of BP [33]
Other blood pressure measures	**a) Difference between groups in mean automated office systolic (52 weeks) and diastolic blood pressure (12 and 52 weeks).** **b) Difference between groups in standard clinic SBP/ DBP at 12 and 52 weeks** **c) Hypertension control (% with SBP <140 mmHg and DBP <90 mmHg) at 6, 12, 26 and 52 weeks,** d) Percentage requiring step-up treatment at 6 weeks e) Percentage requiring step-up blood pressure lowering treatment over 52 weeks f) Percentage with both BP control (as defined above) and no adverse events. g) Difference between groups in SBP and DBP variability
Tolerability	a) Difference between groups in potentially related side-effects (dizziness, blurred vision, syncope/ collapse/ fall, chest pain/ angina, shortness of breath, cough, wheeze, ankle edema, skin rash, itching, gout, hyperkalemia, hypokalemia, hyponatremia, other) b) Difference between groups in mean potassium, uric acid, blood glucose, cholesterol and fractions, ALT, AST, UACR (Urine albumin-to-creatinine ratio) and creatinine levels. c) Difference between groups in participant withdrawals from treatment
Safety	Percentage with any severe adverse event
Medication adherence	Self-reported measures and pill counts
Cost-effectiveness	The ratio of the difference in costs and outcomes between treatment arms
Patient and prescriber acceptability	End of study feedback questionnaires

Note: Key secondary outcomes have been put in bold

Figure

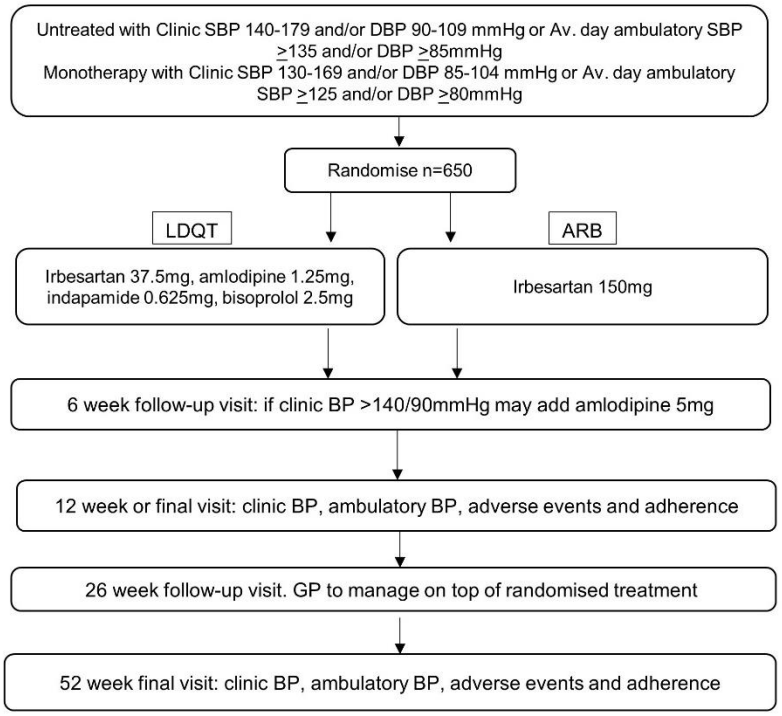

Figure 1 Trial Schema

Appendix

QUARTET Trial Steering Committee

- Prof Clara Chow (Chair)
- Dr Emily Atkins
- Prof Laurent Billot
- Prof John Chalmers
- Prof Graham Hillis
- Prof Bruce Neal
- Prof Mark Nelson
- Prof Anushka Patel
- Prof Chris Reid
- Prof Anthony Rodgers
- Prof Markus Schlaich
- Prof Tim Usherwood
- A/Prof Ruth Webster

Site investigators (alphabetical order, excluding above): Michael Bloch, Michael Burke, Gemma Figtree, Peter Hay, Shirley Jansen

Current sites

New South Wales

- Westmead hospital, Westmead
- Royal North Shore Hospital, St Leonards
- Holdsworth House Medical Centre, Darlinghurst
- Castle Hill Medical Centre, Castle Hill
- Kildare Road Medical Centre, Blacktown

Tasmania

- University of Tasmania, Hobart

Victoria

- Monash University, Caulfield

Western Australia

- Curtin University, Bentley
- Royal Perth Hospital, Perth
- Sir Charles Gairdner Hospital, Nedlands

Harms

All serious adverse events (SAEs) and adverse events of special interest (AESI) experienced by a participant after the informed consent document is signed and until the end of the study at week 12 or 52 will be collected and reported to the CCC as per applicable ICH GCP and applicable regulatory guidelines. If an SAE is unresolved at the conclusion of the study, a clinical assessment will be made by the medical monitor as to whether continued follow up of the SAE is warranted. SAE criteria, definitions and guidance for reporting are outlined in section 1 to 4

1. Adverse event (AE)

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

2 Adverse Events of Special Interest (AESI)

The expected adverse reactions to the BP lowering medications that will be used in QUARTET are well known (Appendix 2). To better assess participants' tolerability to the study medications the following AESI's and whether they are new or ongoing from baseline will be reported to the CCC regardless of severity and seriousness:

- Dizziness
- Hypotension
- Pedal Oedema
- Headache
- Muscle cramps
- Bradycardia
- Worsening of heart failure
- Hypersensitivity reactions (skin rashes, itching)
- Gastrointestinal complaints
- Musculoskeletal trauma

3 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose:

- results in death
- is life threatening in the opinion of the attending clinician (i.e. the patient was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation (Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria)
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defect (Note that the females in the study population are likely to be post-menopausal)
- is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalisation but which may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above

An adverse event that meets the above categories between when the informed consent form is signed, the end of study visit at week 12 or at 26 and 52 weeks if patient is participating in the study extension and until the 28 days after the study drug discontinued will be reported as an SAE. All SAEs are required to be reported to the sponsor team within 24 hours of the study team first becoming aware of the event. The SAE will also be required to be reported to the relevant HREC/ IRBs within the timeframe specified in the relevant committee guidelines. If irbesartan or the LDQT is discontinued as a result of an AE, the study team will document all events leading to the discontinuation of treatment. Adverse events which do not fall into these categories are defined as **non-serious**.

4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An unexpected adverse reaction (UAR) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. Refer to (Quartet protocol, Appendix 2) for a list of expected adverse reactions for the interventions used in this protocol.

A Suspected Unexpected Serious Adverse Reaction is any UAR that at any dose meets the definition of an SAE (refer to section 3). Any event that meets the definition of a SUSAR between when the informed consent form is signed and the end of study visit at week 12 or week 52 will be reported to the local HREC/ IRB and the relevant regulatory authorities as per local requirements and *ICH Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

Examples of questions asked of providers and participants to assess acceptability of the quadpill intervention

Examples of questions asked of participants include:

- During the trial, how easy did the participant find it to take the trial medications?
- If the LDQT is available to be prescribed by participant's usual doctor, how likely would the participant be to request it?
- Are there any other comments the participant had about the LDQT?

Examples of questions addressed to healthcare providers about the quad pill include:

- What do you think are the potential benefits of LDQT or your concerns about LDQT?
- If LDQT was available, in what circumstances would you prescribe it or what evidence would you require to start prescribing LDQT?
- What do you consider to be important factors in patients' decisions to take blood-pressure lowering medications?