

1 Ultra-low-dose quadruple combination blood pressure lowering therapy in
2 patients with hypertension: The QUARTET randomized controlled trial protocol
3

4 Clara K. Chow, PhD ^{1,2}

5 Emily R. Atkins, PhD ^{1,2}

6 Laurent Billot, PhD ²

7 John Chalmers, PhD ²

8 Graham S. Hillis, PhD ³

9 Peter Hay, MBBS⁴

10 Bruce Neal, PhD ²

11 Mark Nelson, PhD ⁵

12 Anushka Patel, PhD ²

13 Christopher M. Reid, PhD ⁶

14 Markus Schlaich, PhD ⁷

15 Tim Usherwood, PhD ¹

16 Ruth Webster, PhD ^{2,8}

17 Anthony Rodgers, PhD ^{1,2}

18 Affiliations: 1 The Westmead Applied Research Centre, Faculty of Medicine and Health, University of Sydney, Australia

19 2. The George Institute for Global Health, UNSW, Australia

20 3. Department of Cardiology, Royal Perth Hospital and University of Western Australia, Australia

21 4. Castle Hill Medical Centre, NSW, Australia

22 5. Menzies Institute for Medical Research, University of Tasmania, Tasmania, Australia

23 6. School of Public Health, Curtin University, Perth, Australia

24 7. Dobney Hypertension Centre, School of Medicine, University of Western Australia and Royal Perth Hospital

25 8. Centre for Health Economics Research and Evaluation, University of Technology Sydney, Australia

26 Corresponding author:

27 Prof. Clara K Chow

28 Rm No 2041, Research & Education Network, Westmead Hospital | Westmead | NSW | 2145

29 Tel +61 2 8890 3125, 8890 6511, 8890 5555 | F +61 2 8890 8323

30 Clara.chow@sydney.edu.au

31

32

33

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.

66 Abbreviations

67	ABP/ABPM	ambulatory blood pressure /monitoring
68	ACE-I	angiotensin converting enzyme inhibitor
69	ARB	angiotensin II receptor blocker
70	BB	beta-blocker
71	CCB	calcium channel blocker
72	DALY	disability-adjusted life-year
73	DBP	diastolic blood pressure
74	DSMC	data safety and monitoring committee
75	eGFR	estimated Glomerular Filtration Rate
76	GP	general practitioner
77	QUARTET	Quadruple Ultra-low-dose tReatment for hypErTension
78	SBP	systolic blood pressure
79	SD	standard deviation
80	TZ	thiazide or thiazide-like diuretic

81

82

83 Introduction

84 Burden of high blood pressure and treatment gaps

85 High blood pressure is the leading cause of preventable morbidity and mortality globally.¹ The benefits of blood
86 pressure lowering in reducing cardiovascular events are unequivocal² and there is clear evidence of greater benefits
87 for combination-based therapy compared to monotherapy.³ Furthermore, numerous studies have indicated the
88 benefits of more rapid control of blood pressure, and have shown that this is more likely to occur with use of
89 combination therapy.⁴ Yet, control of high blood pressure is poor, with only 1 in 3 on treatment achieving blood
90 pressure targets.⁵⁻⁸

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

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

113 Rationale for very low-dose combination therapy

114 Dose response data on blood pressure reduction

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

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

126 There is strong evidence that the blood pressure lowering effects of different classes of drugs are independent and
127 fully additive.^{15, 18} The effects of adding a second blood pressure lowering agent are closely concordant with those
128 predicted by independent effects, occur across all pairs of medication classes, and are about five times more effective
129 than doubling the dose of the first agent.¹⁸ The additive effects across three classes of low-dose drugs were also

130 demonstrated in a placebo-controlled, crossover trial of three half-dose blood pressure drugs in 86 participants aged
131 over 50 years without a history of cardiovascular disease.¹⁹ Overall a 17.4/9.4 mmHg blood pressure reduction was
132 observed, compared to the anticipated 17.9/9.5 mmHg decline expected from the cumulative effects of the three
133 separate agents.

134 Dose response data on adverse effects

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

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

152 Objective

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

157 Methods

158 Trial design

159 This is a 12-week double blind randomized controlled trial of 650 patients with high blood pressure. Participants are
160 randomized in a 1:1 allocation ratio using a central computer-based service, to initial therapy with quadpill or to a
161 standard dose of an ARB, with a CCB added as required, as per current guideline recommendations (Figure 1). The
162 primary outcome is reduction in mean office systolic blood pressure (SBP) measured using Omron HEM-907 at 12
163 weeks. Secondary outcomes include: the proportion of participants with controlled blood pressure (SBP<140mmHg
164 and diastolic blood pressure [DBP] <90mmHg) at 6 weeks and 12 weeks, ambulatory blood pressure (ABP) measures at
165 12 weeks, tolerability and the occurrence of adverse events. Learnings from the quadpill pilot informed the design and
166 conduct of the present trial.¹⁷

167 Extension study

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

170 Participants

171 Eligibility criteria

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

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

177 Inclusion criteria

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

192 Exclusion criteria

- 193 • Contraindication to irbesartan, amlodipine, indapamide or bisoprolol
- 194 • Evidence of secondary cause of hypertension;
- 195 • Estimated Glomerular Filtration Rate [eGFR] <50 mL/min/1.73m²,
- 196 • Raised serum potassium (above local laboratory normal limit)
- 197 • Women who are pregnant, breast feeding and/ or of childbearing potential and not using medically
198 acceptable form of contraception throughout the study
- 199 • Concomitant illness, physical impairment or mental condition which in the opinion of the study team/
200 primary care physician could interfere with the conduct of the study including outcome assessments
- 201 • Participation in a concurrent interventional medical investigation or clinical trial. Patients in observational,
202 natural history and/or epidemiological studies not involving an intervention are eligible.
- 203 • Participant's primary care doctor or other responsible physician believes it is not appropriate for participant
204 to switch current monotherapy or initiate study drug.
- 205 • Inability or unwillingness to provide written informed consent
- 206 • Unable to complete study procedures including 24-hour ABPM
- 207 • Definite indication for one or more components of the quadpill

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

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

213 Changes to inclusion and exclusion criteria to facilitate recruitment

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

- 216 • Adults (≥ 18 years)
- 217 • Previous documentation of hypertension or high blood pressure (SBP 140-179mmHg and/or DBP 90-109
218 mmHg) from general practitioner (GP), pharmacist or other health care professional
- 219 • And either meeting criterion A or B:
 - 220 ○ Criterion A: In treatment naïve (i.e. never treated) or in patients currently not on treatment (not
221 taken in last 4 weeks) either:
 - 222 ■ A measure of Clinic SBP 140-179mmHg and/or DBP 90-109mmHg documented by study
223 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 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 ≥ 125 mmHg and/or DBP ≥ 80 mmHg 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 guidelines²³ 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.

271 Preparation of study treatment

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

278 Study procedures

279 Patients are assessed for eligibility and randomized if criteria are met. Follow-up clinical assessments are conducted at
280 6 and 12 weeks. The 6-week visit includes a clinic blood pressure measurement (3 unattended automated office
281 measures) and recording of any changes in concomitant medications, adverse events, and health service use. At 6
282 weeks if clinic blood pressure is >140/90mmHg the researcher will alert the study doctor who will assess participant
283 (BP and symptoms) and consider adding open-label amlodipine 5mg (consistent with current guidelines). The week 12
284 visit includes the above plus 24-hour ABPM, quality of life, and additional laboratory assessments sodium, potassium,
285 chloride, bicarbonate, serum creatinine, eGFR (CKD-EPI formula), uric acid, liver function tests, and urine
286 albumin/creatinine ratio. No central lab is used. Participants have an option to extend their involvement in the study
287 to 12 months after randomization, involving extra visits at weeks 26 and 52 (with comparable follow-up procedures to
288 weeks 6 and week 12 visits, respectively). Extension involves continuing to receive the randomly allocated treatment,
289 but with management through their general practitioner or site doctor. They may add additional drugs if clinically
290 necessary with open label treatment added without the need to unblind randomized therapy. Adherence to
291 medications is assessed by self-report and a pill count of returned study medications at end of study time points, that
292 is week 12 final visit and at 12 months the final visit of the extension study. Participants are asked how many days in
293 the last 30 days they have missed taking any of their regular medications, and similarly about missed medications in
294 the last 7 days.

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

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

308

309 Outcome measures and outcome assessment

310 The primary and secondary outcomes are listed in Table 1.

311 The blood pressure measurements are recorded using an Omron HEM907. An appropriate cuff size is selected for all
312 BP measurements. First a measure of clinic blood pressure is observed and recorded by research staff. Then,
313 automated office blood pressure is measured following the recommendations of the European Society of
314 Hypertension/European Society of Cardiology and Australian National Heart Foundation.^{22, 30} This requires the
315 research staff to set the automated device to take three separate BP measurements while the researcher steps out of
316 the room (unattended BP measurement). The Omron HEM907 is programmed to start the first measurement after
317 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 $\frac{1}{2}$ 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.

363 Economic evaluation

364 Cost-effectiveness and cost-utility analysis

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

371 Acceptability evaluation

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

380 Trial management, funding, and sponsorship

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

388 Trial registration, human research ethics, and dissemination plan

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

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

399 Discussion

400 High blood pressure is the leading risk factor for lost healthy life years globally.¹ For women it is the leading risk factor,
401 with 90 million disability-adjusted life-years (DALYs), and the second leading risk factor in men with 124 million
402 DALYs.³⁶ Although the global age-standardized death rate attributable to high SBP declined by 1.35% over the last 30
403 years, the number of deaths attributable to high SBP has increased globally over this time, with 10.4 million deaths in
404 2016.³⁷ Achieving sustainable and affordable reductions in SBP is key to addressing this leading risk factor for lost
405 healthy life.

406 The QUARTET trial is the first large-scale trial to examine a quadruple, quarter-dose regimen. This approach has many
407 theoretical benefits, including greater efficacy and fewer side effects as well as pragmatic benefits that should
408 improve adherence and decrease costs. If this new intervention achieves its conservative additional 4mmHg of blood

409 pressure reduction compared to that conferred by optimal guideline-recommended care, such a difference could
410 translate into an additional 15 to 20% reduction in cardiovascular events.³

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

414 Benefits of combination therapy

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

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

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

435 Conclusion

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

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

444 Authors' contributions

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

450 Funding statement

451 The QUARTET trial received principal funding through a project grant from the National Health and Medical Research
452 Council Australia (APP1100377). The trial was also supported by funding from NHMRC program grants (APP1052555
453 and APP1092642). Individual investigators also received support to enable their time allocation to the trial: CC was

supported by NHMRC Career Development Fellowship Level 2 (APP1105447), ERA was supported by a National Heart Foundation Australia Postdoctoral Fellowship 2018-2019 (101884), CMR was supported through a NHMRC Principal Research Fellowship (APP1136372), MPS was supported through a NHMRC Senior Research Fellowship (APP1080404), RW was supported by an NHMRC Early Career Fellowship (APP1125044), AP was supported by NHMRC Principal Research Fellowship (APP1136898).

459

460 Competing interests

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

464 References

- 465 1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, AlMazroa MA, Amann M, Anderson HR,
466 Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A,
467 Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG,
468 Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J,
469 Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT-A, Child JC, Cohen A, Colson KE, Cowie BC, Darby
470 S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER,
471 Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM,
472 Flaxman S, Fowkes FGR, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K,
473 Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood Iii HD, Hoy D, Hu H,
474 Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N,
475 Kawakami N, Khang Y-H, Khatibzadeh S, Khoo J-P, Kok C, Laden F, Laloo R, Lan Q, Lathlean T, Leasher JL, Leigh
476 J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L,
477 Marks R, Martin R, McGale P, McGrath J, Mehta S, Memish ZA, Mensah GA, Merriman TR, Micha R, Michaud
478 C, Mishra V, Hanafiah KM, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK,
479 Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CDH,
480 Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope Iii CA, Powles J, Rao M,
481 Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I,
482 Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A,
483 Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJC, Steenland K,
484 Stöckl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL,
485 Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC,
486 Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJL, Ezzati M. A comparative risk
487 assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions,
488 1990–2010: A systematic analysis for the global burden of disease study 2010. *The Lancet*. 2012;380:2224-
489 2260
- 490 2. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of
491 prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527-1535
- 492 3. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease:
493 Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological
494 studies. *BMJ (Clinical research ed.)*. 2009;338:b1665-b1665
- 495 4. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat
496 F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with
497 regimens based on valsartan or amlodipine: The value randomised trial. *Lancet*. 2004;363:2022-2031
- 498 5. Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural
499 and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310:959-968
- 500 6. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U. Cardiovascular prevention guidelines in
501 daily practice: A comparison of euroaspire i, ii, and iii surveys in eight european countries. *The Lancet*.
502 2009;373:929-940
- 503 7. Peiris DP, Patel Aa, Cass A, Howard MP, Tchan ML, Brady JP, De Vries J, Rickards Ba, Yarnold DJ, Hayman NE,
504 Brown AD. Cardiovascular disease risk management for aboriginal and torres strait islander peoples in
505 primary health care settings: Findings from the kanyini audit. *The Medical journal of Australia*. 2009;191:304-
506 309

- 507 8. Webster RJ, Heeley EL, Peiris DP, Bayram C, Cass A, Patel AA. Gaps in cardiovascular disease risk management
508 in australian general practice. *Medical Journal of Australia*. 2009;191:324-329
- 509 9. Chalmers J, Arima H, Harrap S, Touyz RM, Park JB. Global survey of current practice in management of
510 hypertension as reported by societies affiliated with the international society of hypertension. *Journal of*
511 *hypertension*. 2013;31:1043-1048
- 512 10. Byrd JB, Zeng C, Tavel HM, Magid DJ, O'Connor PJ, Margolis KL, Selby JV, Ho PM. Combination therapy as
513 initial treatment for newly diagnosed hypertension. *American Heart Journal*. 2011;162:340-346
- 514 11. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G,
515 Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S,
516 Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais
517 I, Group ESCSD. 2018 esc/esh guidelines for the management of arterial hypertension. *European Heart*
518 *Journal*. 2018:ehy339-ehy339
- 519 12. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug
520 treatments: Longitudinal study of electronically compiled dosing histories. *BMJ (Clinical research ed.)*.
521 2008;336:1114-1117
- 522 13. Osterberg L, Blaschke T. Adherence to medication. *New England Journal of Medicine*. 2005;353:487-497
- 523 14. Wang Y, Alexander G, Stafford R. Outpatient hypertension treatment, treatment intensification, and control
524 in western europe and the united states. *Arch Intern Med*. 2007;167:141 - 147
- 525 15. Bennett A, Chow CK, Chou M, Dehbi H-M, Webster R, Salam A, Patel A, Neal B, Peiris D, Thakkar J, Chalmers J,
526 Nelson M, Reid C, Hillis GS, Woodward M, Hilmer S, Usherwood T, Thom S, Rodgers A. Efficacy and safety of
527 quarter-dose blood pressure-lowering agents. *Hypertension*. 2017;70:85-93
- 528 16. Mahmud A, Feely J. Low-dose quadruple antihypertensive combination: More efficacious than individual
529 agents - a preliminary report. *Hypertension*. 2007;49:272-275
- 530 17. Chow CK, Thakkar J, Bennett A, Hillis G, Burke M, Usherwood T, Vo K, Rogers K, Atkins E, Webster R, Chou M,
531 Dehbi HM, Salam A, Patel A, Neal B, Peiris D, Krum H, Chalmers J, Nelson M, Reid CM, Woodward M, Hilmer S,
532 Thom S, Rodgers A. Quarter-dose quadruple combination therapy for initial treatment of hypertension:
533 Placebo-controlled, crossover, randomised trial and systematic review. *The Lancet*. 2017;389:1035-1042
- 534 18. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing
535 blood pressure: Meta-analysis on 11,000 participants from 42 trials. *American Journal of Medicine*.
536 2009;122:290-300
- 537 19. Wald DS, Morris JK, Wald NJ. Randomized polypill crossover trial in people aged 50 and over. *PloS one*.
538 2012;7:e41297
- 539 20. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure
540 lowering drugs: Analysis of 354 randomised trials. *BMJ (Clinical Research Ed.)*. 2003;326:1427-1427
- 541 21. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez Fa, Riegger GA, Malbecq W, Smith RD,
542 Guptha S, Poole-Wilson Pa. Effects of high-dose versus low-dose losartan on clinical outcomes in patients
543 with heart failure (heal study): A randomised, double-blind trial. *The Lancet*. 2009;374:1840-1848
- 544 22. National Heart Foundation Australia. *Guideline for the diagnosis and management of hypertension in adults*.
545 2016.
- 546 23. National Institute for Health and Clinical Excellence. The clinical management of primary hypertension in
547 adults. *Clinical guideline 127*; 2011
- 548 24. Chalmers J, Arima H, Woodward M, Mancia G, Poulter N, Hirakawa Y, Zoungas S, Patel A, Williams B, Harrap S.
549 Effects of combination of perindopril, indapamide, and calcium channel blockers in patients with type 2
550 diabetes mellitus: Results from the action in diabetes and vascular disease: Preterax and diamicron controlled
551 evaluation (advance) trial. *Hypertension*. 2014;63:259-264
- 552 25. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen
553 among 6105 individuals with previous stroke or transient ischaemic attack. *The Lancet*. 2001;358:1033-1041
- 554 26. Hripcsak G, Suchard MA, Shea S, Chen R, You SC, Pratt N, Madigan D, Krumholz HM, Ryan PB, Schuemie MJ.
555 Comparison of cardiovascular and safety outcomes of chlorthalidone vs hydrochlorothiazide to treat
556 hypertension. *JAMA Internal Medicine*. 2020;180:542-551
- 557 27. Williams B, Mancia G. 2018 european society of cardiology (esc) and european society of hypertension (esh)
558 joint guidelines for the management of arterial hypertension. *Journal of Hypertension*. 2018;in press
- 559 28. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S,
560 Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Oviagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ,
561 Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017
562 acc/aha/aapa/abc/acpm/ags/apha/ash/aspc/nma/pcna guideline for the prevention, detection, evaluation,
563 and management of high blood pressure in adults. *Hypertension*. 2017
- 564 29. National Heart Foundation Australia (National Blood Pressure and Vascular Disease Advisory Committee).
565 Guide to management of hypertension 2008. Updated december 2010. 2010

- 566 30. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G,
567 Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM,
568 Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Burnier M, Ambrosioni E,
569 Caulfield M, Coca A, Olsen MH, Tsoufis C, Van De Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ,
570 Bueno H, Dean V, Deaton C, Erol C, Ferrari R, Hasdai D, Hoes AW, Knuuti J, Kolh P, Lancellotti P, Linhart A,
571 Nihoyannopoulos P, Piepoli MF, Ponikowski P, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S,
572 Clement DL, Gillebert TC, Rosei EA, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S,
573 Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Jordan J,
574 Kahan T, Komajda M, Lovic D, Mahrholdt H, Ostergren J, Parati G, Perk J, Polonia J, Popescu Ba, Reiner Ž,
575 Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Vlachopoulos C, Volpe M, Wood Da. 2013 esh/esc
576 guidelines for the management of arterial hypertension: The task force for the management of arterial
577 hypertension of the european society of hypertension (esh) and of the european society of cardiology (esc).
578 *European Heart Journal*. 2013;34:2159-2219
- 579 31. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML,
580 MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014
581 evidence-based guideline for the management of high blood pressure in adults. *JAMA*. 2014;311:507-520
- 582 32. Head GA, McGrath BP, Mihailidou AS, Nelson MR, Schlaich MP, Stowasser M, Mangoni Aa, Cowley D, Brown
583 Ma, Ruta L-A, Wilson A. Ambulatory blood pressure monitoring in australia: 2011 consensus position
584 statement. *Journal of hypertension*. 2012;30:253-266
- 585 33. O'Brien E, Parati G, Stergiou G. Ambulatory blood pressure measurement: What is the international
586 consensus? *Hypertension*. 2013;62:988-994
- 587 34. Farsang C. Efficacy and tolerability of fixed-dose combination of perindopril/indapamide in type 2 diabetes
588 mellitus: Picasso trial. *Advances in therapy*. 2014;31:333-344
- 589 35. Bobrie G, Investigators I-AS. I-add study: Assessment of efficacy and safety profile of irbesartan/amlodipine
590 fixed-dose combination therapy compared with irbesartan monotherapy in hypertensive patients
591 uncontrolled with irbesartan 150 mg monotherapy: A multicenter, phase iii, prospective, randomized, open-
592 label with blinded-end point evaluation study. *Clinical therapeutics*. 2012;34:1720-1734. e1723
- 593 36. Gakidou E, Afshin A, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulle AM, Abera SF,
594 Aboyans V, Abu-Raddad LJ, Abu-Rmeileh NME, Abyu GY, Adedeji IA, Adetokunboh O, Afarideh M, Agrawal A,
595 Agrawal S, Ahmadi H, Ahmed MB, Aichour MTE, Aichour AN, Aichour I, Akinyemi RO, Akseer N, Alahdab F,
596 Al-Aly Z, Alam K, Alam N, Alam T, Alasfoor D, Alene KA, Ali K, Alizadeh-Navaei R, Alkerwi Aa, Alla F, Allebeck P,
597 Al-Raddadi R, Alsharif U, Altirkawi KA, Alvis-Guzman N, Amare AT, Amini E, Ammar W, Amoako YA, Ansari H,
598 Antó JM, Antonio CAT, Anwari P, Arian N, Ärnlöv J, Artaman A, Aryal KK, Asayesh H, Asgedom SW, Atey TM,
599 Avila-Burgos L, Avokpaho EFGA, Awasthi A, Azzopardi P, Bacha U, Badawi A, Balakrishnan K, Ballew SH, Barac
600 A, Barber RM, Barker-Collo SL, Bärnighausen T, Barquera S, Barregard L, Barrero LH, Batis C, Battle KE,
601 Baumgarner BR, Baune BT, Beardsley J, Bedi N, Beghi E, Bell ML, Bennett DA, Bennett JR, Bensenor IM,
602 Berhane A, Berhe DF, Bernabé E, Betsu BD, Beuran M, Beyene AS, Bhansali A, Bhutta ZA, Bicer BK, Bikbov B,
603 Birungi C, Biryukov S, Blosser CD, Boneya DJ, Bou-Orm IR, Brauer M, Breitborde NJK, Brenner H, Brugha TS,
604 Bulto LNB, Butt ZA, Cahuana-Hurtado L, Cárdenas R, Carrero JJ, Castañeda-Orjuela CA, Catalá-López F, Cerci K,
605 Chang H-Y, Charlson FJ, Chimed-Ochir O, Chisumpa VH, Chitheer AA, Christensen H, Christopher DJ, Cirillo M,
606 Cohen AJ, Comfort H, Cooper C, Coresh J, Cornaby L, Cortesi PA, Criqui MH, Crump JA, Dandona L, Dandona R,
607 das Neves J, Davey G, Davitoiu DV, Davletov K, de Courten B, Defo BK, Degenhardt L, Deiparine S, Dellavalle
608 RP, Deribe K, Deshpande A, Dharmaratne SD, Ding EL, Djalalinia S, Do HP, Dokova K, Doku DT, Donkelaar Av,
609 Dorsey ER, Driscoll TR, Dubey M, Duncan BB, Duncan S, Ebrahimi H, El-Khatib ZZ, Enayati A, Endries AY,
610 Ermakov SP, Erskine HE, Eshrati B, Eskandarieh S, Esteghamati A, Estep K, Faraon EJA, Farinha CSeS, Faro A,
611 Farzadfar F, Fay K, Feigin VL, Fereshtehnejad S-M, Fernandes JC, Ferrari AJ, Feyissa TR, Filip I, Fischer F,
612 Fitzmaurice C, Flaxman AD, Foigt N, Foreman KJ, Frostad JJ, Fullman N, Fürst T, Furtado JM, Ganji M, Garcia-
613 Basteiro AL, Gebrehiwot TT, Geleijnse JM, Geleto A, Gemechu BL, Gesesew HA, Gething PW, Ghajar A, Gibney
614 KB, Gill PS, Gillum RF, Giref AZ, Gishu MD, Giussani G, Godwin WW, Gona PN, Goodridge A, Gopalani SV,
615 Goryakin Y, Goulart AC, Graetz N, Gughani HC, Guo J, Gupta R, Gupta T, Gupta V, Gutiérrez RA, Hachinski V,
616 Hafezi-Nejad N, Hailu GB, Hamadeh RR, Hamidi S, Hammami M, Handal AJ, Hankey GJ, Hanson SW, Harb HL,
617 Hareri HA, Hassanvand MS, Havmoeller R, Hawley C, Hay SI, Hedayati MT, Hendrie D, Heredia-Pi IB,
618 Hernandez JCM, Hoek HW, Horita N, Hosgood HD, Hostiuc S, Hoy DG, Hsairi M, Hu G, Huang JJ, Huang H,
619 Ibrahim NM, Iburg KM, Ikeda C, Inoue M, Irvine CMS, Jackson MD, Jacobsen KH, Jahanmehr N, Jakovljevic MB,
620 Jauregui A, Javanbakht M, Jeemon P, Johansson LRK, Johnson CO, Jonas JB, Jürisson M, Kabir Z, Kadel R,
621 Kahsay A, Kamal R, Karch A, Karema CK, Kasaeian A, Kassebaum NJ, Kastor A, Katikireddi SV, Kawakami N,
622 Keiyoro PN, Kelbore SG, Kemmer L, Kengne AP, Kesavachandran CN, Khader YS, Khalil IA, Khan EA, Khang Y-H,
623 Khosravi A, Khubchandani J, Kiadaliri AA, Kieling C, Kim JY, Kim YJ, Kim D, Kimokoti RW, Kinfu Y, Kisa A,
624 Kissimova-Skarbek KA, Kivimaki M, Knibbs LD, Knudsen AK, Kopeck JA, Kosen S, Koul PA, Koyanagi A,

Kravchenko M, Krohn KJ, Kromhout H, Kumar GA, Kutz M, Kyu HH, Lal DK, Lalloo R, Lallukka T, Lan Q, Lansingh VC, Larsson A, Lee PH, Lee A, Leigh J, Leung J, Levi M, Levy TS, Li Y, Li Y, Liang X, Liben ML, Linn S, Liu P, Lodha R, Logroscino G, Looker KJ, Lopez AD, Lorkowski S, Lotufo PA, Lozano R, Lunevicius R, Macarayan ERK, Magdy Abd El Razek H, Magdy Abd El Razek M, Majdan M, Majdzadeh R, Majeed A, Malekzadeh R, Malhotra R, Malta DC, Mamun AA, Manguerra H, Mantovani LG, Mapoma CC, Martin RV, Martinez-Raga J, Martins-Melo FR, Mathur MR, Matsushita K, Matzopoulos R, Mazidi M, McAlinden C, McGrath JJ, Mehata S, Mehndiratta MM, Meier T, Melaku YA, Memiah P, Memish ZA, Mendoza W, Mengesha MM, Mensah GA, Mensink GBM, Mereta ST, Meretoja TJ, Meretoja A, Mezgebe HB, Micha R, Millear A, Miller TR, Minnig S, Mirarefin M, Mirrahimov EM, Misganaw A, Mishra SR, Mohammad KA, Mohammed KE, Mohammed S, Mohan MBV, Mokdad AH, Monasta L, Montico M, Moradi-Lakeh M, Moraga P, Morawska L, Morrison SD, Mountjoy-Venning C, Mueller UO, Mullany EC, Muller K, Murthy GVS, Musa KI, Naghavi M, Naheed A, Nangia V, Natarajan G, Negoi RI, Negoi I, Nguyen CT, Nguyen QL, Nguyen TH, Nguyen G, Nguyen M, Nichols E, Ningrum DNA, Nomura M, Nong VM, Norheim OF, Norrving B, Noubiap JJN, Obermeyer CM, Ogbo FA, Oh I-H, Oladimeji O, Olagunju AT, Olagunju TO, Olivares PR, Olsen HE, Olusanya BO, Olusanya JO, Opio JN, Oren E, Ortiz A, Ota E, Owolabi MO, Pa M, Pacella RE, Pana A, Panda BK, Panda-Jonas S, Pandian JD, Papachristou C, Park E-K, Parry CD, Patten SB, Patton GC, Pereira DM, Perico N, Pesudovs K, Petzold M, Phillips MR, Pillay JD, Piradov MA, Pishgar F, Plass D, Pletcher MA, Polinder S, Popova S, Poulton RG, Pourmalek F, Prasad N, Purcell C, Qorbani M, Radfar A, Rafay A, Rahimi-Movaghar A, Rahimi-Movaghar V, Rahman MHU, Rahman MA, Rahman M, Rai RK, Rajsic S, Ram U, Rawaf S, Rehm CD, Rehm J, Reiner RC, Reitsma MB, Remuzzi G, Renzaho AMN, Resnikoff S, Reynales-Shigematsu LM, Rezaei S, Ribeiro AL, Rivera JA, Roba KT, Rojas-Rueda D, Roman Y, Room R, Roshandel G, Roth GA, Rothenbacher D, Rubagotti E, Rushton L, Sadat N, Safdarian M, Safi S, Safiri S, Sahathevan R, Salama J, Salomon JA, Samy AM, Sanabria JR, Sanchez-Niño MD, Sánchez-Pimienta TG, Santomauro D, Santos IS, Santric Milicevic MM, Sartorius B, Satpathy M, Sawhney M, Saxena S, Schmidt MI, Schneider IJC, Schutte AE, Schwebel DC, Schwendicke F, Seedat S, Sepanlou SG, Serdar B, Servan-Mori EE, Shaddick G, Shaheen A, Shahraz S, Shaikh MA, Shamsipour M, Shamsizadeh M, Shariful Islam SM, Sharma J, Sharma R, She J, Shen J, Shi P, Shibuya K, Shields C, Shiferaw MS, Shigematsu M, Shin M-J, Shiri R, Shirkoobi R, Shishani K, Shoman H, Shrimme MG, Sigfusdottir ID, Silva DAS, Silva JP, Silveira DGA, Singh JA, Singh V, Sinha DN, Skiadaresi E, Slepak EL, Smith DL, Smith M, Sobaih BHA, Sobngwi E, Soneji S, Sorensen RJD, Sposato LA, Sreeramareddy CT, Srinivasan V, Steel N, Stein DJ, Steiner C, Steinke S, Stokes MA, Strub B, Subart M, Sufiyan MB, Suliankatchi RA, Sur PJ, Swaminathan S, Sykes BL, Szoeki CEI, Tabarés-Seisdedos R, Tadakamadla SK, Takahashi K, Takala JS, Tandon N, Tanner M, Tarekegn YL, Tavakkoli M, Tegegne TK, Tehrani-Banihashemi A, Terkawi AS, Tessaema B, Thakur JS, Thamsuwan O, Thankappan KR, Theis AM, Thomas ML, Thomson AJ, Thrift AG, Tillmann T, Tobe-Gai R, Tobollik M, Tollanes MC, Tonelli M, Topor-Madry R, Torre A, Tortajada M, Touvier M, Tran BX, Truelsen T, Tuem KB, Tuzcu EM, Tyrovolas S, Ukwaja KN, Uneke CJ, Updike R, Uthman OA, van Boven JFM, Varughese S, Vasankari T, Veerman LJ, Venkateswaran V, Venketasubramanian N, Violante FS, Vladimirov SK, Vlassov VV, Vollset SE, Vos T, Wadilo F, Wakayo T, Wallin MT, Wang Y-P, Weichenthal S, Weiderpass E, Weintraub RG, Weiss DJ, Werdecker A, Westerman R, Whiteford HA, Wiysonge CS, Woldeyes BG, Wolfe CDA, Woodbrook R, Workicho A, Xavier D, Xu G, Yadgir S, Yakob B, Yan LL, Yaseri M, Yimam HH, Yip P, Yonemoto N, Yoon S-J, Yotebieng M, Younis MZ, Zaidi Z, Zaki MES, Zavala-Arciniega L, Zhang X, Zimsen SRM, Zipkin B, Zodpey S, Lim SS, Murray CJL. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: A systematic analysis for the global burden of disease study 2016. *The Lancet*. 2017;390:1345-1422
 37. Marczak L, Williams J, Loeffler M, for the For the Institute for Health M, Evaluation. Global deaths attributable to high systolic blood pressure, 1990-2016. *JAMA*. 2018;319:2163-2163
 38. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: A cluster randomized, controlled trial. *Hypertension*. 2009;53:646-653
 39. Dickerson JC, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *The Lancet*. 1999;353:2008-2013
 40. Keenan K, Hayen A, Neal BC, Irwig L. Long term monitoring in patients receiving treatment to lower blood pressure: Analysis of data from placebo controlled randomised controlled trial. *BMJ*. 2009;338:b1492
 41. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: A meta-analysis. *Hypertension*. 2010;55:399-407
 42. Kizilirmak P, Uresin Y, Yildiz OB. The efficacy and safety of triple vs dual combination of angiotensin ii receptor blocker and calcium channel blocker and diuretic: A systematic review and meta-analysis. *The Journal of Clinical Hypertension*. 2013;15:193-200
 43. de la Sierra A, Barrios V. Blood pressure control with angiotensin receptor blocker-based three-drug combinations: Key trials. *Advances in therapy*. 2012;29:401-415

- 683 44. Webster R, Salam A, de Silva H, et al. Fixed low-dose triple combination antihypertensive medication vs usual
684 care for blood pressure control in patients with mild to moderate hypertension in sri lanka: A randomized
685 clinical trial. *JAMA*. 2018;320:566-579
- 686 45. Lung T, Jan S, de Silva HA, Guggilla R, Maulik PK, Naik N, Patel A, de Silva AP, Rajapakse S, Ranasinghe G,
687 Prabhakaran D, Rodgers A, Salam A, Selak V, Stepien S, Thom S, Webster R, Lea-Laba T. Fixed-combination,
688 low-dose, triple-pill antihypertensive medication versus usual care in patients with mild-to-moderate
689 hypertension in sri lanka: A within-trial and modelled economic evaluation of the triumph trial. *The Lancet*
690 *Global Health*. 2019;7:e1359-e1366

691

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

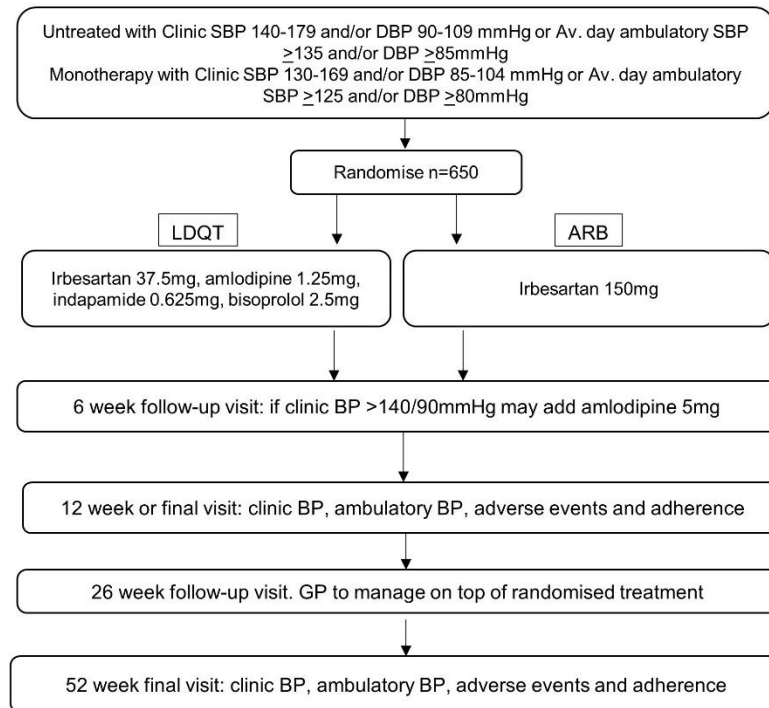


Figure 1 Trial Schema

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?