Monotherapy versus dual therapy for the initial treatment of hypertension (PATHWAY-1): a randomised double-blind controlled trial

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ABSTRACT
Introduction: Previous studies have suggested that more intensive initial therapy for hypertension results in better long-term blood pressure (BP) control. We test this hypothesis comparing initial monotherapy with dual therapy in the management of essential hypertension.

Methods and analysis: The study is a prospective, multicentre, double-blind, active-controlled trial in patients with essential hypertension. Around 50% of patients studied will be newly diagnosed and the others will be known hypertensives who previously received only monotherapy. The trial is divided into three phases as follows: Phase 1 (Week 0–Week 16): Randomised, parallel-group, masked assignment to either combination or monotherapy. Phase 2 (Week 17–Week 32): Open-label combination therapy. Phase 3 (Week 33–Week 52): Open-label combination therapy plus open-label add-on (if BP is above 140/90 mm Hg). Hierarchical primary end points are: a comparison of home BP (home systolic blood pressure (HSBP)) averaged over the duration of phase 1 and 2 in the combination versus monotherapy arms. If combination is superior in this analysis, then the trial will end at the end of phase 2 in the combination versus monotherapy arms. Furthermore, a study of dual therapy versus monotherapy with amlodipine showed that participants started on initial dual therapy appeared always to have better BP control than the monotherapy group.4

Strengths and limitations of this study
- Randomised, double-blind, multicentre, controlled clinical trial.
- Uses home systolic blood pressure as the primary outcome.
- Powered to detect a 4 mm Hg difference in blood pressure; so a smaller but possibly important true difference may be missed.

INTRODUCTION
At least 20% of patients with essential hypertension do not have their blood pressure (BP) under control despite treatment with triple therapy. The hypothesis that aggressive early treatment of hypertension may prevent subsequent treatment resistance was generated by the results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE)2 and the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT)3 studies. In these studies, participants randomised to the less effective of two treatments early in the study ‘never caught up’ with the BP lowering achieved in the other group, despite eventually receiving more drug therapy. Furthermore, a study of dual therapy versus monotherapy with amlodipine showed that participants started on initial dual therapy appeared always to have better BP control than the monotherapy group.4

A plausible explanation of the ‘never catch up’ phenomenon is that one drug given alone initiates activation of homeostatic mechanisms, which minimises efficacy. Thus a diuretic or calcium antagonist given alone would lead to a rise in renin levels, effectively antagonising the effect of the initial drug. Given such a mechanism, one would expect that a drug that blocked the effects of a rise in renin would produce complementary effects. Support for this concept comes from
a study where measurements of thoracic fluid volume supported the occult volume expansion hypothesis as a mediator of antihypertensive drug resistance. This study guided increasing the diuretic dose and adjustment of antihypertensive treatment by using thoracic bioimpedance measurements, which was found to be an effective strategy.5

Historically, initial treatment of hypertension with combination therapy has been discouraged because of concern about excessive reduction in BP, increased side effects and the difficulty of attributing adverse events to one drug. However, the US Joint National Committee guideline 8 (JNC8) guidelines have listed that a two-drug initial treatment is an acceptable strategy in patients who are 20 mm Hg above systolic target BP or 10 mm Hg above diastolic BP target or whose systolic BP is >160 mm Hg or diastolic >100 mm Hg.6 These and previous guidelines that advocated similar strategies have not resulted in reports of problems with this approach. The European guidelines also include low-dose combination therapy as an initial treatment option.7

Despite the currently available evidence, in reality, initial combination therapy is not commonly used and formal prospective studies are required to catalyse change. A further study demonstrating improved BP control with initial combination therapy would provide further evidence that using widely available, inexpensive combinations is appropriate. Our trial here, PATHWAY 1, funded by the British Heart Foundation, aims to provide such evidence.

METHOD
Setting
British Hypertension Society Research Network of investigators recruiting participants from both primary care and secondary care.

Overall trial design
The study is a prospective, multicentre, active-controlled, three-phase trial in UK patients with essential hypertension. A study schematic is shown in figure 1.

A 4-week single-blinded placebo run-in period precedes the first active phase. This run-in determines final patient eligibility based on BP readings recorded during this period. Following the placebo run-in, phase 1 randomises patients to either combination therapy or monotherapy. Phase 2 is open-label combination therapy for all patients with forced dose titration. Phase 3 is open-label combination therapy for all patients with the option of additional open-label add-on therapy to achieve BP target (<140/90 mm Hg).

Trial medication
The two medications used alone or in combination in the trial are losartan and hydrochlorothiazide (HCTZ). Each patient receives active trial medication for 52 weeks following the 4-week placebo run-in phase. Phase 1 medication is double blinded. Combination therapy used in phase 2 and phase 3 was initially Cozaar-Comp (100/12.5 mg and 100/25 mg); however, this was changed to generic losartan/HCTZ in 2013.

Phase 1: Medication—weeks 0–16
Intervention: Initial combination therapy with losartan/HCTZ. Dose titrations occur every 4 weeks (losartan/HCTZ 50/12.5 then losartan/HCTZ 50/25 then losartan/HCTZ 100/12.5 then losartan/HCTZ 100/25).

Active comparator: Initial monotherapy with randomisation to either HCTZ 12.5 mg titrated to 25 mg after 4 weeks or losartan 50 mg titrated to 100 mg after 4 weeks with crossover of HCTZ and losartan drugs at week 8.

Phase 2: Medication—weeks 17–32
All patients receive open-label combination therapy with losartan/HCTZ 100/12.5 initially, titrated to losartan/HCTZ 100/25 at week 24.

Phase 3: Medication—weeks 33–52
All patients receive losartan/HCTZ 100/25 with open label add-on therapy as required. Requirement for add-on therapy is assessed at the week 32 visit, and if clinic systolic BP >140 mm Hg or diastolic BP >90 mm Hg is recorded, the first-line add-on therapy is amlodipine 5 mg. At week 38 this may be titrated to amlodipine 10 mg if BP remains uncontrolled with addition of modified release doxazosin 4 mg or 8 mg, if required, at week 44 visit.

Figure 1
Study schematic.
Recruitment and randomisation
Patient recruitment is taking place at multiple sites across the UK. Consent will be obtained by study doctors at each study site (see online supplementary appendix 1 for consent form). Each participant will be in the study for 56 weeks (4-week placebo run-in followed by 52-week active treatment). Potential participants are identified by their general practitioner or via hypertension clinics.

Trial inclusion criteria are: (patients must meet all inclusion criteria to be eligible)
1. Clinic BP ≥150 mm Hg (systolic) OR ≥95 mm Hg (diastolic) after placebo run-in. Patients may be included if the investigator anticipates BP criteria for inclusion will be met at randomisation (ie, if BP is likely to meet criteria after withdrawal of previous monotherapy during placebo run-in phase).
2. Aged 18–79 years.
3. Either never-treated hypertension or received a maximum of one antihypertensive drug class in the previous year.
4. Male participants or female participants taking adequate contraception such as the contraceptive pill, an intrauterine device or who are surgically sterilised, or postmenopausal females.

Exclusion criteria are shown in box 1.

TRIAL PROCEDURES
BP measurements
Home BP and pulse rate will be measured using the Microlife WatchBP Home monitor. We believe this is one of the first trials to use home BP as the primary outcome measure, offering similar advantages to ambulatory monitoring (multiple measurements in the absence of white-coat stimuli) without the disadvantage of patient resistance to repeated use. Patients will be instructed to take BP readings on the past four consecutive days before each clinic visit (baseline and at weeks 4, 8, 12, 16, 24, 32, 38, 44 and 52). Patients will be asked to measure their BP as close as possible to 8:00 and 20:00, and to take readings in triplicate, after 10 min seated rest. The second and third readings are recorded on a pro forma provided to each patient. The 12 readings thus obtained for analysis confer near-maximal precision. All readings will also be captured automatically by the monitor. Study medication should be taken after morning BP readings are completed.

Clinic BP measurements are taken at each study visit, on the patient’s Microlife monitor, and patients will have their BP and pulse rate recorded in triplicate after 10 min seated rest. The first reading will be discarded and the mean clinic readings will be the average of the last 2 readings.

Additional procedures
A 12-lead ECG is captured at the start and end of the study. Haemodynamic measures (cardiac output, peripheral resistance and bioimpedance) and pulse wave analysis are captured at baseline and at weeks 8, 16, 32 and 52 in centres that have the appropriate Cardiodynamics equipment. Plasma renin is measured at baseline and a full biochemical series is taken at regular intervals for safety.

COMPLIANCE, EFFICACY AND TOLERABILITY
Compliance with study medication will be assessed at the end of the placebo run-in and at each scheduled clinic visit postrandomisation. Assessment is by counting capsules/tablets returned at each visit. To be evaluable as a compliant participant ≥80% compliance with therapy is required.

Patients may be withdrawn from the study if the investigator feels it would be in the patient’s best interest, if the patient demonstrates intolerance to study drug, if plasma potassium levels are sustained at <3.0 mmol/L or >5.9 mmol/L, if BP is uncontrolled (>200/120 mm Hg) or if the patient develops symptomatic hypotension with systolic BP <110 mm Hg. Investigators may advance patients with uncontrolled BP to the next study visit where dose titration will occur. There is no option for down titration of combination therapy during phase 2. Therefore, patients unable to tolerate losartan/HCTZ 100/25 mg will be withdrawn.

FOLLOW-UP
Primary end point
The first primary end point for PATHWAY 1 is the mean of all HSBP readings taken during phase 1 and 2 comparing the combination therapy versus the monotherapy arms. If (and only if) the mean systolic BP in phase 1 and 2 is significantly better in the combination therapy arm then the second primary end point will be the change in mean HSBP for the group treated initially with monotherapy compared to the group treated initially with combination therapy at the end of phase 2. Readings used for this calculation will be from the past 3 days of placebo run-in compared to the past 3 days of phase 2 (week 32).

Secondary end points and substudy
Secondary end points are detailed in box 2. In addition there will be a substudy in three sites using cardiac MRI to compare the change in left ventricular mass and aortic pulse wave velocity (arterial stiffness) between initial combination and initial monotherapy groups for which consent is sought separately.

Data handling and record keeping
Study data is recorded and stored via remote data entry into a web-based electronic case report form (eCRF) developed and maintained for the study by the Robertson Centre for Biostatistics, University of Glasgow, Level 11, Boyd Orr Building, University Avenue, Glasgow, G12 8QQ. eCRF data are anonymous and identify study participants by their assigned study numbers only.
Box 1  Exclusion criteria

Patients will be excluded for ANY ONE of the following reasons
1. Clinic systolic blood pressure >200 mm Hg or diastolic blood pressure >120 mm Hg, with principal investigator discretion to over-ride if home blood pressure (HBP) measurements are lower.
2. Secondary or accelerated phase hypertension.
3. Estimated-glomerular filtration rate <45 mLs/min.
4. Contraindication or previous intolerance to any trial therapy.
5. Failure to record required HBP readings during placebo run-in.
6. Significant comorbidity (investigator opinion but to include alcoholism, terminal illness, documented non-attendance at clinics etc).
8. Plasma K+ outside normal range on two successive measurements during screening.
9. Requirement for treatment with ≥2 drugs (which can be a CCB and/or (ACEi OR ARB OR direct renin inhibitor OR β-blocker) in order to reduce blood pressure to ≤180/120 mm Hg.
10. Requirement for diuretic therapy (other than for hypertension).
11. Requirement for ACE inhibitor (or angiotensin II receptor blocker) therapy (other than for hypertension).
12. Absolute contraindications to any of the study drugs (listed on their data-sheet).
14. Anticipation of change in medical status during course of trial (eg, planned surgical intervention requiring >2 weeks convalescence, actual or planned pregnancy).
15. Inability to give informed consent.
16. Participation in a clinical study involving an investigational drug or device within 4 weeks of screening.
17. Any concomitant condition that, in the opinion of the investigator, may adversely affect the safety and/or efficacy of the study drug or severely limit the participant’s lifespan or ability to complete the study (eg, alcohol or drug abuse, disabling or terminal illness, mental disorders).
18. Treatment with any of the following prohibited medications
   A. Oral corticosteroids within 3 months of screening. Treatment with systemic corticosteroids is also prohibited during study participation.
   B. Chronic stable or unstable use of non-steroidal anti-inflammatory drugs (NSAIDs) other than acetylsalicylic acid is prohibited. Chronic use is defined as >3 consecutive or non-consecutive days of treatment per week. In addition, the intermittent use of NSAIDs is strongly discouraged throughout the duration of this study. If intermittent treatment is required, NSAIDs must not be used for more than a total of 2 days. For all participants requiring analgesic or antipyretic agents, the use of paracetamol is recommended during study participation.
   C. The use of short-acting oral nitrates (eg, sublingual nitroglycerin) is permitted; however, participants should not take short-acting oral nitrates within 4 h of screening or any subsequent study visit.
   D. The use of long-acting oral nitrates (eg, Isordil) is permitted; however, the dose must be stable for at least 2 weeks prior to screening and randomisation.
   E. The use of sympathomimetic decongestants is permitted; however, not within 1 day prior to any clinic visit/BP assessment.
   F. The use of theophylline is permitted; however, the dose must be stable for at least 4 weeks prior to screening and throughout study participation.
   G. The use of phosphodiesterase (PDE) type V inhibitors is permitted; however, participants must refrain from taking these medications within 1 day of screening or any subsequent study visit.
   H. The use of α-blockers is not permitted—with the exception of alfuzosin and tamsulosin for prostatic symptoms.

Investigator training
All investigators were trained in good clinical practice and received trial-specific training. The trial was monitored by the sponsor. Regular meetings were held to discuss trial quality issues and progress. A full list of study sites is available at: https://www.clinicaltrials.gov/ct2/show/NCT00994617?term=pathway-1&rank=1

Adverse events and serious adverse events
All observed or volunteered adverse events considered related to treatment will be recorded on the adverse events page of the eCRF. Study staff will pursue and obtain information adequate to confirm whether the event meets the criteria for classification as a serious adverse event. An event will be deemed serious if it results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability/ incapacity, is a congenital anomaly or birth defect or is another medically important event. Adverse events will be classified according to seriousness, severity (mild, moderate or severe), causal relationship (certain, probably, possible, unlikely, unrelated) and expectedness. Suspected unexpected serious adverse drug reactions (SUSARs) are not considered likely in this trial as there have been many years of experience with each of the trial drugs. All potential SUSARs are subject to expedited reporting.

DATA ANALYSIS AND STATISTICAL METHODS
Sample size
A sample size of 268 in each group will have 90% power to detect a difference in means of 4 mm Hg HSBP, assuming a common SD of 12 mm Hg using a two group t test with α=0.01.
Box 2  Secondary end points

1. A comparison of the proportion of patients who drop out of the trial at any stage after randomisation or who require additional antihypertensive drug therapy in phase 3 of the trial between the initial monotherapy and combination therapy limbs. (Note a separate count of those who drop out because blood pressure (BP) is reduced too avidly will be noted).

2. A comparison of the change in BP from baseline to the end of phase 3 between the initial monotherapy and combination therapy limbs.

3. A comparison of the change in thoracic bioimpedance and arterial stiffness from baseline to the end of phase 1 and then separately to the end of phase 2 between the initial monotherapy and combination therapy limbs and how this predicts the primary end point.

4. An analysis of how the baseline covariates of age, gender, renin mass, weight, height, thoracic bioimpedance and arterial stiffness prior treatment of BP etc. predict the differences in \( \Delta \)systolic BP between the initial monotherapy and combination therapy limbs.

5. A comparison of the predictors of BP fall with each initial monotherapy in phase 1 is predicted by age (particularly ≤55 or >55 years), gender, renin mass, weight, height, thoracic bioimpedance and arterial stiffness, prior treatment of BP, etc.

6. Analyses of relationships between genetic factors and pharmacodynamic responses. (Pharmacogenetic research is likely to continue following completion of this study, and will not be reported as part of the main study report).

7. A comparison of the change in left ventricular mass (cardiac hypertrophy) and aortic pulse wave velocity (arterial stiffness) from baseline to the end of phase 3 between the initial monotherapy and combination therapy groups.

Randomisation

Study participants are randomised 1:1 to either initial combination or initial monotherapy using an Interactive Voice Recognition System located at the Robertson Centre for Biostatistics at Glasgow University. The aim is to achieve a 50:50 balance between never treated and previously treated patients. Therefore, recruitment to one of these groups (never treated, or previously treated) may be stopped temporarily, or permanently, if the chief investigator and data management centre consider it necessary in order to achieve a final recruitment that does not exceed a 60:40 proportion of either group. Randomisation will continue until 600 participants have been recruited (to allow for dropouts) or until 536 evaluable participants have completed the study.

Database lock

Since the study is double-blind, all investigators remain blinded until database lock. Un-blinding is only permissible if required for an urgent patient-safety issue.

Analysis

There will be hierarchical coprimary end points. An analysis will be performed first to compare the mean HSBP readings in phase 1 and 2 between combination therapy and monotherapy. If averaged combination therapy is superior to monotherapy, a second primary analysis will compare the mean HSBP at the end of phase 2 (namely visit 8 at week 32) between initial combination and monotherapy. The analyses will adjust for baseline covariates (demographics, baseline HSBP and never vs previously treated). Last reading carried forward will be used in the intention to treat analysis in those participants who fail to complete the full study for whatever reason.

Secondary analyses will compare: change in HSBP at 8, 16 (end of phase 1) and 52 weeks (end of phase 3); change in clinic SBP at these times and end of phase 2; responder rates at the end of phase 1, 2 and 3 (defined as HSBP <135/<85, and/or clinic <140/<90, and/or fall in SBP ≥10 mm Hg); withdrawals due to adverse events; the number of drugs being prescribed at the end of phase 3; a Kaplan-Meier analysis for events, namely either addition of third drug or withdrawal due to an adverse event; haemodynamic variables and pulse wave analysis—these will be analysed in the same way as BP, with and without correction for BP. The extent to which plasma renin and haemodynamic variables explain variation in response between and within treatment groups will be investigated for both primary and secondary outcomes.

A full statistical analysis plan is available from the chief investigator MJB.

ETHICAL AND OTHER APPROVALS

The trial has been approved by the Cambridgeshire 2 Research Ethics Committee of the NHS National Research Ethics Service (number 09/1/H0308/1132), and the Medicines and Healthcare products Regulatory Agency (EudraCT number: 2008-007749-29). The trial is performed in line with Good Clinical Practice guidelines. A trial steering committee composed of the investigators and authors of this protocol were responsible for designing the study and are responsible for setting up, evaluating and reporting results of the trial and will consider requests for access to trial data and analyses if requested.

Protocol amendments

All protocol amendments will be approved by the sponsor, research ethics committees and the Medicines Healthcare Regulatory Agency Clinical Trials Unit.

Study sponsorship: monitoring, audit, quality control and quality assurance

The trial is sponsored by the University of Cambridge and Cambridge University Hospitals National Health Service (NHS) Foundation Trust. Trial investigators will permit authorised third parties access to the trial site and medical records relating to trial participants. This will include, but not necessarily be restricted to, access for trial-related monitoring, audits, Ethics Committee review and regulatory inspections.
Dissemination
The results of the trial will be published in a peer-reviewed scientific journal. All participants will be informed about the trial results and the treatment allocation arm they were allocated.

ASSOCIATED PROJECTS
This study (PATHWAY-1) is one of three complementary studies in a BHF-funded programme which will investigate optimal treatment for patients with drug-resistant hypertension. PATHWAY-2 will recruit patients with more severe hypertension than either PATHWAY-1 or PATHWAY-3, which is a comparison of a potassium retaining plus a thiazide diuretic with either alone, for their effects on BP and glucose tolerance.

DISCUSSION
Current practice in hypertension management uses a stepped care approach with initial monotherapy that is added on to, according to the results of subsequent blood pressure measurement. The concern is that lowering blood pressure by one drug triggers adaptive responses in the patient that, if triggered in the early stages of hypertension management, will impair further attempts to achieve target blood pressure. This study tests whether initial combination therapy with two drugs that are complementary in action is superior to the current stepped-care approach; we are using widely available, generic drugs at optimal doses. The primary end point uses home BP monitoring which will give a more accurate representation of the patients’ true BP compared to using clinics readings alone. In phase one, half the patients go through a crossover trial-within-a trial; so we will have excellent prospective data to evaluate whether angiotensin II receptor blocker (ARB) or diuretic is more effective, respectively, in the younger and older patients and whether baseline renin is more or less predictive than age. We also have haemodynamic indices, including peripheral resistance, cardiac output, thoracic impedance and arterial function, in order to determine whether increases in any parameter underpin the postulated compensatory responses to monotherapy. These measurements will also help to establish whether—for instance—peripheral resistance is higher in patients responding better to ARB than diuretic, and whether thoracic impedance (a measure of body fluid) a better predictor of response to diuretic. The relatively long duration of the study also allows for assessment of those patients who are deemed to have resistant hypertension in phase 3.

Confirmation that patients starting with monotherapy ‘never catch up’ with patients starting on combination therapy would have a major impact on hypertension treatment practice; possibly more than any previous study in hypertension.

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TM, BW, IF, MJB: Trial Executives for the British Hypertension Society’s PATHWAY programme of trials.

TM, BW, MC, PS, DJW, ISM, IF, MJB: Steering Committee for the British Hypertension Society’s PATHWAY programme of trials.

Contributors TM, MJB, BW, MC, JKC, GM, PS, DJW, IF and ISM designed the trial. TM, MJB and BW constituted the trial executive committee. MJB and JS drafted the protocol aided by TM and BW. TM designed the paper aided by BW, MJB and ISM.

Funding The study is funded by a special project grant from the British Heart Foundation (number SP/08/002). Further funding is provided by Comprehensive Local Research Networks and National Institute of Health Research (in front of Comprehensive Local Research Networks). The losartan and losartan-HCTZ were a generous gift from Dr Paul Robinson, Merck Sharpe Dohme, UK. BW is an NIHR Senior Investigator and PS is an NIHR Senior Investigator and recipient of Biomedical Research Centre Award to Imperial College NHS Health Care Trust.

Competing interests MJB has received honoraria from Novartis, MC received honoraria from Medtronic and Quantum Genomics during the life of the trial. This work was directly enabled by funds from the National Institute for Health Research Cardiovascular Biomedical Research Unit at St Bartholomew’s Hospital, London. JKC is Vice-President of the Artery Society. GM has received honoraria from Novartis. DJW has received funding for membership of Independent Data Monitoring Committees for Abbvie in relation to clinical trials in diabetic nephropathy. DJW is President-elect of the British Pharmacological Society and a Board Member of MHRA. TM is Chief investigator on two large investigator initiated, industry funded but University sponsored, cardiovascular outcome studies (funded by Pfizer and Menarini/IPSEn/Tejin pharmaceuticals). His research unit also does industry funded studies by Novartis and Agen but none of these studies focus on BP. He has provided consultancy or received honoraria for speaking for Novartis, Takeda, Daiichi Sanky, Shire and Astellas. TM is the current president of the British Hypertension Society. ISM is a member of the executive committee of the British Hypertension Society.

Patient consent Obtained.

Ethics approval Cambridge.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement The steering committee will be happy to share data from this trial with bona fide researchers.

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Monotherapy versus dual therapy for the initial treatment of hypertension (PATHWAY-1): a randomised double-blind controlled trial


BMJ Open 2015 5:
doi: 10.1136/bmjopen-2015-007645

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