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Comparison of Single and Combination Diuretics on Glucose Tolerance (PATHWAY-3): a randomised double-blind trial

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Keywords: Hypertension, Clinical Trials, Protocol

Abstract

Introduction

Thiazide diuretics are associated with increased risk of developing diabetes mellitus. This risk may arise from K^+-depletion. We hypothesized that a K^+-sparing diuretic has a beneficial influence on glucose tolerance, and that the use of low-dose thiazide combined with a K^+-sparing diuretic may achieve similar blood pressure reduction, but improved glucose tolerance, compared to a high-dose thiazide.

Methods and analysis

This is a parallel-group, randomised, double-blind, multi-centre trial, comparing 3 treatment strategies: hydrochlorothiazide 25-50 mg; amiloride 10-20 mg; combination of both diuretics at half these doses. A single-blind placebo run-in of 1 month is followed by 24 weeks of blinded active treatment. There is forced dose-doubling after 3 months. The **Primary Endpoint** is the blood glucose two hours after oral ingestion of a 75 G glucose drink (OGTT), following overnight fasting. The primary outcome is the difference between two hour glucose at weeks 0, 12 and 24. **Secondary outcomes** are the change in home systolic BP from the end of placebo run-in to 24 weeks, and change in 30 minute plasma insulin during OGTT, and HbA1C, between 0 and 24 weeks. Eligibility criteria are: age 18-80, diagnosis of hypertension, systolic BP on permitted background treatment ≥ 140 mmHg and home BP ≥ 130mmHg, and one component of the metabolic syndrome additional to hypertension. Principal exclusions are Diabetes, eGFR < 45 mls/min, abnormal plasma K^+, clinic SBP >200 mmHg or DBP >120mmHg. The sample size calculation indicates that 486 patients will give 80% power at α=0.01 to detect a difference in means of 1 mmol/L (SD=2.2) between 2 hr glucose on HCTZ and comparators.[1]

Ethics and dissemination:

PATHWAY-3 has been approved by the Cambridge South Ethics Committee, number 09/H035/19. The trial results will be published in a peer-reviewed scientific journal. Eudract number 2009-010068-41 and Clinical trials registration number: NCT02351973.

Strengths

This is a randomised, masked study adequately powered to detect a 1 mmol/L difference in 2 hour glucose, during oral glucose tolerance test, between strategies.

Weaknesses

Hydrochlorothiazide is not available in the United Kingdom, except as part of combination formulations.

The combination therapy is only available in the United Kingdom at present as fixed dose tablets of Amiloride 2.5mg/Hydrochlorothiazide 25mg and Amiloride 5mg/Hydrochlorothiazide 50mg.

Summary Box

Focus:

- PATHWAY 3 will answer an important question about the optimal type of diuretic treatment for essential hypertension, using widely available and inexpensive medication.

Key Messages:

- This study will determine whether substitution or addition of amiloride to hydrochlorothiazide will prevent deterioration in glucose tolerance, without poorer performance in controlling blood pressure.

Strengths and Limitations of this study:

- The strengths are that this is a randomised, masked study adequately powered to detect a 1 mmol/L difference in 2 hour glucose, during oral glucose tolerance test, between strategies.

INTRODUCTION

Thiazide and thiazide-like diuretics are widely used. However such diuretics are associated with increased risk of developing diabetes mellitus.[2] This risk may arise from K^+-depletion and be avoided by use of K^+-sparing diuretics. We therefore hypothesized that a K^+-sparing diuretic has a beneficial influence on glucose tolerance compared to a thiazide, and that the use of low-dose thiazide combined with a K^+-sparing diuretic may achieve similar blood pressure reduction, but improved glucose tolerance, compared to a high-dose thiazide.

Diuretics are no longer used at doses achieving maximum reduction in BP. This is because of the evidence that higher doses are associated with increased risk of diabetes mellitus (DM), and an extrapolation from small studies in the 1980's and 90's that maximal blood pressure reductions were achieved by low-dose thiazides.[3-6] But unpublished dose-titration data from INSIGHT (Figure 1a), where the average age was 60, shows as steep a dose-response for hydrochlorothiazide as for nifedipine in patients (right panel) whose dose was doubled after 2 weeks.[7] Amiloride has never been fully investigated at doses equi-effective with thiazides, and is used mainly in an ancillary K^+-sparing role.[8] A diuretic crossover study ('SALT') confirmed that in low-renin patients bendroflumethiazide 2.5 mg is not maximal, and showed either spironolactone or amiloride to be effective alternatives to the higher dose (Figure 1b).[9] Several indices in SALT indicated that even 5 mg of bendroflumethiazide was a less effective natriuretic than the K^+-sparing diuretics, perhaps because it lowers BP partly through vasodilatation.[10] The difference in mechanisms raised the possibility, to be explored by PATHWAY-3, that the diuretics will be found to have an additive effect on BP.

Diuretics and new-onset diabetes: A major attraction of K^+-sparing diuretics is the possibility that they will offset the diabetogenic potential of thiazides. Since they have not been compared in hypertension outcome trials, and diabetes (DM) has not been an endpoint in heart failure studies of spironolactone or eplerenone, we do not know for certain whether they are clean in this respect. Short-term studies suggest they are.[11] Interestingly in INSIGHT there was no excess of DM in patients receiving HCTZ 25 mg, which was combined with amiloride 2.5 mg, but increased by 30% in patients on HCTZ/amiloride 50/5 mg.[7] In PATHWAY-3, we use the oral glucose tolerance test (oGTT) to provide an endpoint for each subject. This strategy was previously used to demonstrate a difference after just 12 weeks of dosing with a thiazide diuretic.[1] In the STAR study, which compared 200 markedly obese patients randomly assigned to either ACE inhibitor + Ca^{++} blocker, or ARB + thiazide, the subjects had impaired glucose tolerance (IGT) at entry, allowing detection of changes on low-dose thiazide. Subsequently, two small crossover studies in about 40 patients showed a rise in 2-hour glucose within four weeks of treatment with bendroflumethiazide 5mg or HCTZ 50 mg, with a highly significant difference from the 2-hour glucose during four weeks of treatment with amiloride 20 mg (Figures 1-2).[12]

PATHWAY-3 will test whether the apparent superiority of amiloride, in protecting glucose tolerance, is maintained over six months of treatment, and translates into measurable differences in HbA1C. The study will be large enough for secondary estimates of mechanism, e.g. the 0 and 30 minute plasma insulin, to determine whether the main drug effects are on insulin secretion or sensitivity, and are influenced by the opposite effects of the two diuretics on plasma K^+. Because, however, of the lack of long-term study of amiloride other than in

combination with HCTZ, the study is also evaluating a group in which the two diuretics are used in combination. If we demonstrate that HCTZ 25 mg + amiloride 10 mg achieves the same (or greater) blood pressure reduction as HCTZ 50 mg, without an adverse effect on OGTT, this could become the recommended diuretic treatment for hypertension in the future.

In order to maximize recruitment, whilst also maximizing sensitivity to detect changes in OGTT, the trial is open to most of those patients with hypertension in whom diuretic is a reasonable next option, providing they have one feature of the metabolic syndrome – additional to hypertension. This broad eligibility allows us also to assess safety of amiloride in combination with all commonly used antihypertensive drugs.

Primary Objectives

The primary objective of the study is to determine whether a K^+-sparing diuretic can be safely substituted for, or combined with, a thiazide diuretic in order to maximize the long-term benefits of diuretic treatment.

Secondary Objectives

The secondary objectives of the study are

- To demonstrate whether half-dose combination of two classes of diuretic improve efficacy and tolerability of diuretics, compared to taking one class alone.
- To evaluate the mechanism of changes in glucose tolerance, particularly whether these are related to changes in K^+
- To determine whether a baseline measurement of plasma renin, measured on various background treatment permutations predicts whether patients' blood pressure is likely to be improved by addition of either low- or high-dose diuretic
- To determine the best predictors of patients whose glucose tolerance will be impaired by addition of thiazide diuretic.

A further secondary objective is to establish a repository of pharmacogenetic samples and investigate relationships between genetic factors and pharmacodynamic responses.

METHODS AND ANALYSIS

Trial design

Overall trial design

This is a parallel-group, randomised, double-blind, multi-centre trial, comparing three treatment strategies in patients with hypertension, an indication for diuretic treatment, and at least one other component (*i.e.* additional to hypertension) of the metabolic syndrome. Following a month's placebo run-in, patients receive their randomized treatment (diuretic) in addition to existing background therapy for six months, with an oGTT at the beginning, middle and end of this period. The dose of each diuretic is doubled after the second (3-month) oGTT. The trial design is outlined in the flow chart (figure 2).

Study population

Inclusion criteria are shown in Box 1. These are intended to enable recruitment of most patients in whom addition of diuretic might be part of usual practice, enriched for patients most likely to be at risk of develop type 2 DM during long-term treatment with thiazide diuretic.

The PATHWAY programme anticipated changes to the definition of Hypertension introduced by the NICE guidance of 2011. The trials use home blood pressure measurements as an outcome measure, and patients are required to exceed threshold levels of both clinic blood pressure (at screening and/or randomization) and home blood pressure (at randomization). Initially we set the clinic threshold at 145 mmHg, until we had enough experience within the trial of adding high-dose hydrochlorothiazide or amiloride to multiple background drugs. The threshold was then reduced, to 140 mmHg (see Box 1).

Recruitment and randomisation of participants

Potentially suitable patients are identified from hospital and general practice populations. Written informed consent is obtained from participants. The research nurse records baseline variables, takes blood and urine for baseline biochemistry and haematology and records the medical history. Blood samples are analysed at the local health service laboratory according to usual practice. Serum for future analyses and blood for future genetic analyses are stored by centres. Subjects who have given informed consent, and meet the inclusion and exclusion criteria at the end of a month's placebo run-in, are randomised to receive hydrochlorothiazide 25 mg daily, amiloride 10 mg daily, or a combination of hydrochlorothiazide 12.5 mg and amiloride 5 mg daily, each in addition to any other antihypertensive drug being taken at the time of randomization. Randomisation is performed by contacting a central randomisation facility based at the Robertson Centre for Biostatistics, University of Glasgow by telephone or via a web-based service.

Trial treatments

Initial treatment is the 3 groups described above. After 3 months, each of the groups are force-titrated to twice the starting dose, namely hydrochlorothiazide 50 mg daily, amiloride 20 mg daily, or a combination of hydrochlorothiazide 25 mg and amiloride 10 mg daily. These 3 groups are shown in the Flow Diagram (Figure 2). Blinding of medication is carried out by the

Royal Free Hospital Pharmacy, according to a randomization schedule provided by the Robertson Centre, University of Glasgow.

Tolerability

Adverse events are recorded in the electronic case record form at each visit. A two-week drug holiday is permitted at any point where the investigator considers this may allow subjects to remain in the trial without early withdrawal.

Trial procedures

These are shown for each visit in the Schedule of Assessments (Table 1). There are three principal visits, at 0, 12 and 24 weeks, at which subjects have an oral glucose tolerance test (oGTT). Blood glucose is measured at 0,30,60, 120 minutes, and insulin at 0 and 30 minutes. At these visits, blood is also collected for electrolytes and eGFR, plasma renin, HbA1c and plasma lipids. Electrolytes and eGFR are also checked at 2 and 14 weeks, namely 2 weeks after initiation and dose-doubling of trial diuretic medication. Seated home blood pressure readings are recorded (morning and evening, in triplicate) over four days prior to each of the 3 principal visits, using the Microlife WatchBP monitor. Clinic blood pressure is measured in triplicate at each visit, by the same monitor. For analyses of home blood pressure, we will use the average of the last 18 recordings prior to the visit – that is, from days -1, -2 and -3 if all recordings have been undertaken. For clinic blood pressure, we will analyse the average of readings 2 and 3.

Trial endpoints

Primary endpoint

The primary study endpoint is the difference in blood glucose, measured two hours after oral ingestion of a 75 g glucose drink, between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment.

Secondary endpoints

These are:

- Difference in area under the curve of the oGTT between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment
- Difference in plasma insulin at 30 minutes, between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment
- Difference in fasting serum lipids, between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment
- The change in home systolic BP from end of placebo run-in to the end of three months and six months of blinded treatment.
- The change in clinic systolic BP from end of placebo run-in to the end of three months and six months of blinded treatment.
- The natriuretic response, as assessed from the compensatory increase in plasma renin from end of placebo run-in to the end of three months and six months of blinded treatment.
- Prediction, by baseline plasma renin, of clinic and home SBP response to each treatment

Data Handling and Record Keeping

Study data is recorded by remote data entry into a web-based electronic case report form (eCRF) developed for the study. eCRF data is anonymous and will identify study subjects by their assigned study numbers only.

Data analysis

Sample size determination

Based on at least 80% power to detect a mean difference in glucose between any two of the treatment arms of 1mmol/L (SD= 2.2mmol/L) using two-sample t-tests with a 1% significance level, 414 patients are required. Adjusting for an anticipated dropout proportion of 15%, 486 patients are required overall – 162 in each treatment arm.

Analysis will be performed on the full analysis population – defined as all patients with at least one post baseline visit - on an Intention-To-Treat basis. For sensitivity, all analyses will also be performed on the per-protocol population – defined as all patients with at least one post baseline visit and excluding those with any form of major violation of the study.

Recruitment started in November 2009, and is expected to finish during 2015.

Statistical plan

In order to meet the primary objective of determining whether amiloride should be substituted for, or added to, hydrochlorothiazide, the study has a hierarchical co-primary endpoint. The first-tested comparison will be amiloride vs HCTZ. The second tested will be combination vs HCTZ. A mixed effects model will be used to compare the 2h glucose on oGTT between the three treatment groups (baseline, 12 and 24 weeks). This model will adjust for baseline covariates.

For secondary analyses, the primary analysis will be repeated but with the area under the curve (AUC) of the OGTT as the dependent variable. Mixed effects models will be used to estimate treatment effects for home and clinic systolic blood pressure, and for HbA1c. ANCOVA's will be used to compare: insulin (fasting, and rise at 30 minutes during oGTT), HbA1c, lipid profile, renin mass, and weight at the end of study between the three treatment groups adjusting for baseline measures. Logistic models will be used to compare the proportion of subjects to achieve target systolic blood pressure (defined as ≤ 140mmHg) at 24 weeks between the treatment groups. Logistic models will be used to compare the proportion of patients who develop diabetes (defined by fasting glucose≥ 7mmol/L or 2h glucose≥11.1mmol/L or HbA1c≥6.5%) by the end of the study between the three treatment groups. The covariates in analyses of blood pressure will include baseline plasma renin as a potential predictor of response.

Ethics and dissemination

PATHWAY-3 is approved by Cambridge South Ethics Committee and the MHRA. The results will be published in a peer-reviewed journal, and presented to national and international meetings.

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

The trial is sponsored by the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust. Trial investigators will permit authorized third parties access to the trial site and medical records relating to trial subjects. This will include, but not necessarily be restricted to, access for trial-related monitoring, audits, Ethics Committee review and regulatory inspections.

Associated Projects

This study (PATHWAY-3) is one of three complementary studies in a BHF-funded programme which will investigate optimal treatment for patients with hypertension. PATHWAY-1 will investigate whether initial treatment with a combination of drugs is more effective in achieving a sustained target pressure than starting with monotherapy and adding a second drug. PATHWAY-2 will recruit patients with more severe hypertension than either PATHWAY-1 or PATHWAY-3, and compare the blood pressure response to each of the three classes recommended by current guidelines.

Authors's contributions

TMM, MJB, BW, MC, JKC, GM, PS, DJW, IF designed the trial. TM, MJB, BW constituted the trial executive committee. MJB and JS drafted the protocol aided by TMM and BW. SM advised on stastical analysis. MJB drafted the paper aided by BW and TMM.

Funding statement

The study was funded by a special project grant from the British Heart Foundation (number SP/08/002), and support from National Institute of Health Research Comprehensive Local Research Networks.

Acknowledgements

BW, PS, MC and MJB are NIHR Senior Investigators. National Institute of Health Research Primary Care Research networks facilitate recruitment of patients. Blinded medication was packed by Alan Wong and colleagues at the Royal Free Hospital pharmacy.

Competing interest statement

MJB has received honoraria from Novartis.

BW None declared

MC None declared

JKC is Vice-President of the Artery Society, with no competing interest to declare.

GM has received honoraria from Novartis.

PS None declared

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.

IF None declared

SVM None declared

TMM is Chief investigator on two large investigator initiated, industry funded but University sponsored cardiovascular outcome studies (funded by Pfizer and Menarini / IPSEN / Teijin pharmaceuticals) but none with a focus on BP. His research unit also does industry funded

studies by Novartis and Amgen. He has provided consultancy or received honoraria for speaking from Novartis, Takeda, Daiichi Sankyo, Shire and Astellus. TMM is the current president of the British Hypertension Society.

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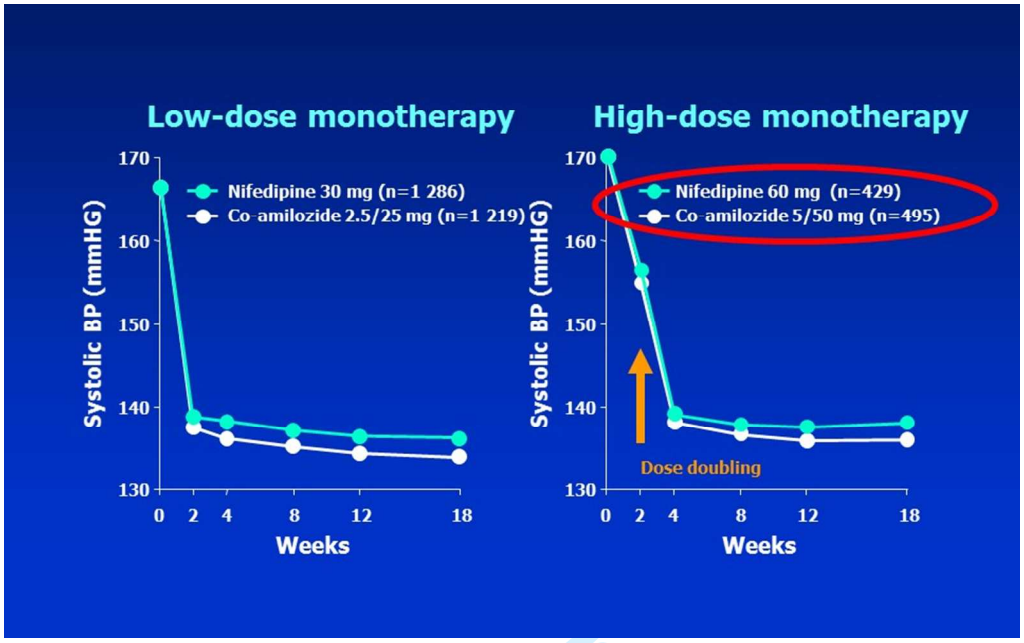
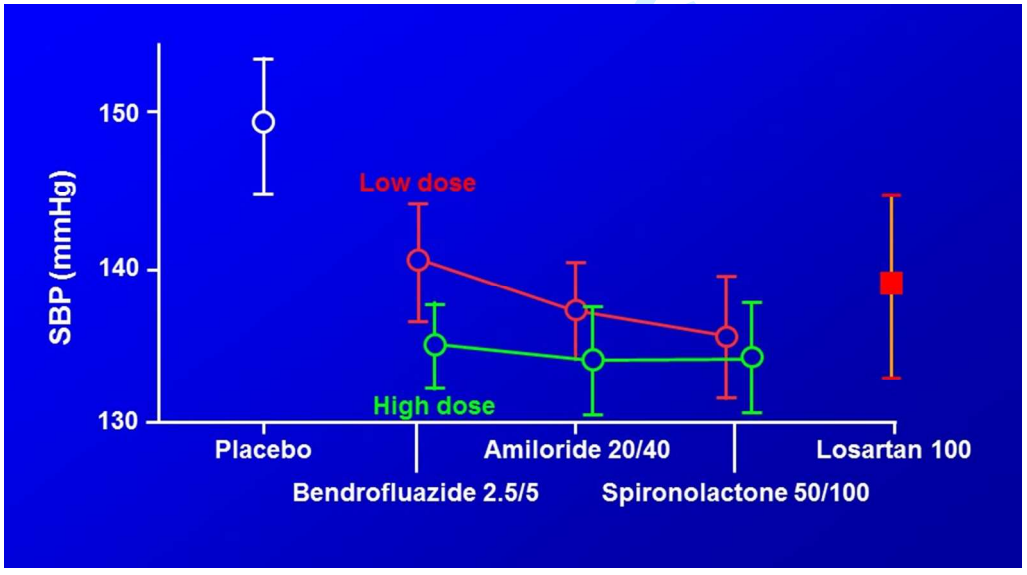
Figure 1

Evidence for dose-response to thiazide diuretics

(a)



(b)

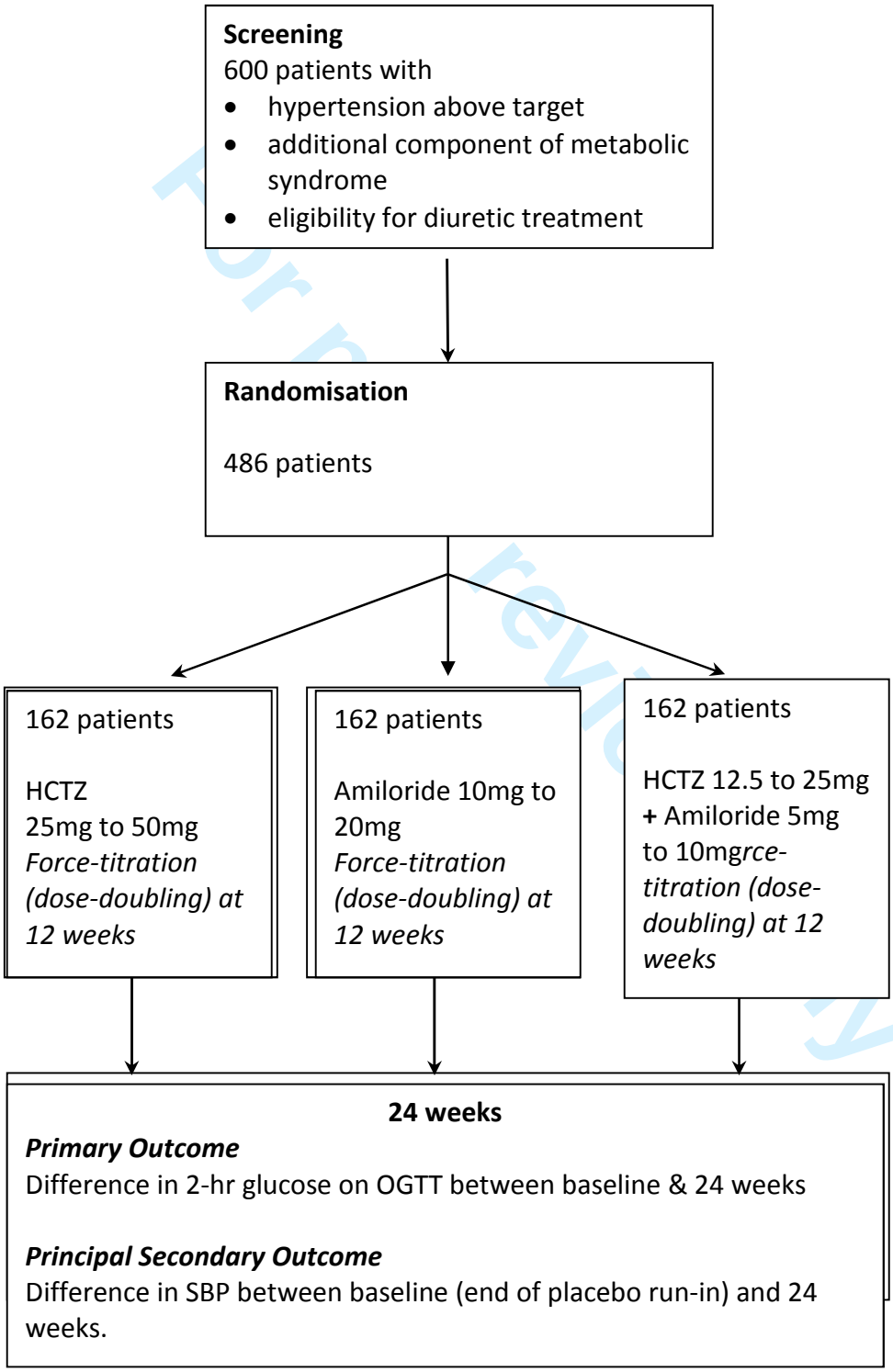


(a) Comparison of blood pressure response to dose-doubling of a calcium-channel blocker, nifedipine, and diuretic combination, hydrochlorothiazide and amiloride, in the INSIGHT study. The figure shows the response in patients achieving target blood pressure, 140/90 mmHg, on low-dose (left panel) or high-dose (right panel) monotherapy. (Unpublished data from reference 17).

(b) Comparison of blood pressure response to dose-doubling of three types of diuretic – bendroflumethiazide, amiloride, spironolactone. (Data re-drawn from reference 9).

Figure 2

Flow Chart



Box 1: Inclusion Criteria

1. Age 18-80
2. Diagnosis of hypertension according to BHS criteria
3. Systolic BP on permitted background treatment ≥ 140 mmHg and home BP ≥ 130mmHg.
4. Indication for diuretic treatment as a treatment option for the patient's uncontrolled hypertension :

   (a) Untreated + (age>55 AND/OR Black AND/OR renin<12mU/L)

   OR (b) receiving one or any permutation of the following:

   ACEi, ARB, β-blocker, CCB, direct renin inhibitor

5. At least one other component (i.e. additional to hypertension) of the metabolic syndrome (reduced HDL, raised triglycerides, glucose, waist circumference)*

* Definition of Metabolic Syndrome according to the International Diabetes Federation, 2006:
Central obesity (waist circumference > 94cm male (>90 if Asian), > 80 female
plus two of:

- SBP ≥ 130 or DBP ≥ 85 mmHg
- Fasting glucose >5.6mmol/l
- Fasting Triglycerides > 1.7 mmol/l (or on treatment)
- HDL < 1.03 mmol/l males, < 1.29 mmol/l females (or on treatment)

Box 2: Exclusion Criteria

1. Diabetes (types 1 or 2)
2. Secondary hypertension
3. eGFR < 45 mls/min
4. Plasma K^+ outside normal range on two successive measurements during screening
5. Clinic SBP >200 mmHg or DBP >120mmHg, with PI discretion to override if home BP measurements are lower
6. Requirement for diuretic therapy (other than for hypertension)
7. Absolute contra-indications to any of the study drugs (listed on their data-sheet)
8. Current therapy for cancer
9. Anticipation of change in medical status during course of trial (e.g. planned surgical intervention requiring >2 weeks convalescence, actual or planned pregnancy)
10. Inability to give informed consent
11. Not on stable doses of all hypertensive medications to be continued throughout the study for a minimum of 4 weeks prior to randomisation, or not normally less than 2 weeks if early randomisation is required at the discretion of the PI.
12. Participation in a clinical study involving an investigational drug or device within 4 weeks of screening.
13. 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 subject's lifespan or ability to complete the study (eg, alcohol or drug abuse, disabling or terminal illness, mental disorders).
14. Treatment with any of the following prohibited medications:

a. Oral corticosteroids within 3 months of Screening.

b. Chronic use (defined as $\geq$3 days of treatment per week) of non-steroidal anti-inflammatory drugs (NSAIDs) other than acetylsalicylic acid.

c. The use of short-acting oral nitrates within 4 hours of screening or any subsequent study visit; long-acting oral nitrates (eg, Isordil) is permitted, but the dose must be stable for at least 2 weeks prior to screening and randomisation

15. A pill count will be made at the end of the 4 week run-in period and those with adherence <70% will be excluded from randomization

Assessment	Screening	Placebo Run-in D-3, D-2, D-1	Week 0	Week 2	Week 11 D-3, D-2, D-1	Week 12	Week 14	Week 23 D-3, D-2, D-1	Week 24
Informed Consent	x								
Demography	x								
Medical history	x		x						
Medical examination	x								
Concomitant medications	x		x	x		x	x		x
Inclusion/exclusion checks	x		x						
Height and weight[1]	x		x			x			x
Clinic BP[2]	x		x			x			x
Home BP[3]		x			x			x	
ECG	x								
Waist and hip circumference	x								x
Urinalysis	x		x						x
Blood Tests:									
Electrolytes (incl bicarbonate)	x		x	x		x	x		x
Glucose (non fasting)	x								
Full blood count	x					x			x
Lipid profile	x		x			x			x
Uric acid	x					x			x
Ca++	x					x			x
renin			x			x			x
Pharmacogenetics[4]			x						
HbA1C			x			x			x
Glucose(fast)*			x			x			x
Insulin*			x			x			x
OGTT**			x			x			x
Pregnancy serum[5]	x								
A/E's						x			x
Randomisation			x						
Study medication dispensed	x		x			x			
Compliance check			x			x			x
Dose force titrated						x			

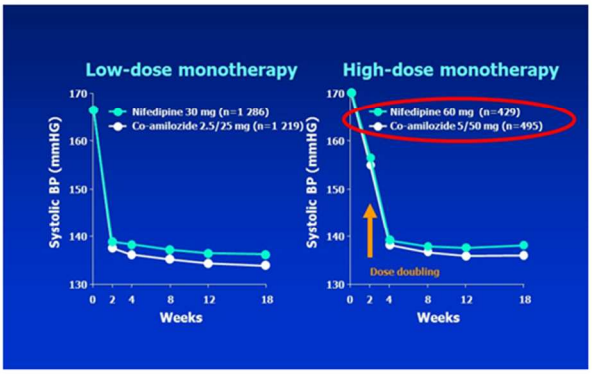
TABLE 1 – SCHEDULE OF MEASUREMENTS

1 Height recorded at first visit only.
2 Clinic BP will be measured following 10 mins rest and recorded in triplicate.
3 Home BP will be measured using the BP device given by clinic at approximately 08.00am and 08.00pm on the 4 days before the clinic visit. Patients will be asked to take triplicate reading after 10 mins rest and to record the second and third on the proforma provided.
4 Pharmacogenetics sample to be taken where specific informed consent has been given. Sampling will typically be at baseline (Day 0), but may be at any time later in the study.
5 Serum HcG may be replaced by EMU specimen for HcG testing.
* i.e. baseline sample for OGTT
** glucose at 0, 30, 60, 120 mins; insulin at 0, 30 mins

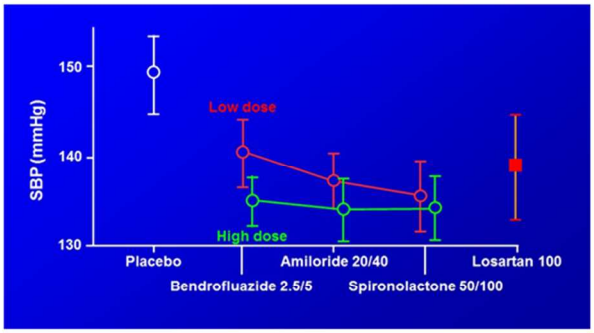
Figure 1

- Evidence for dose-response to thiazide diuretics

(a)



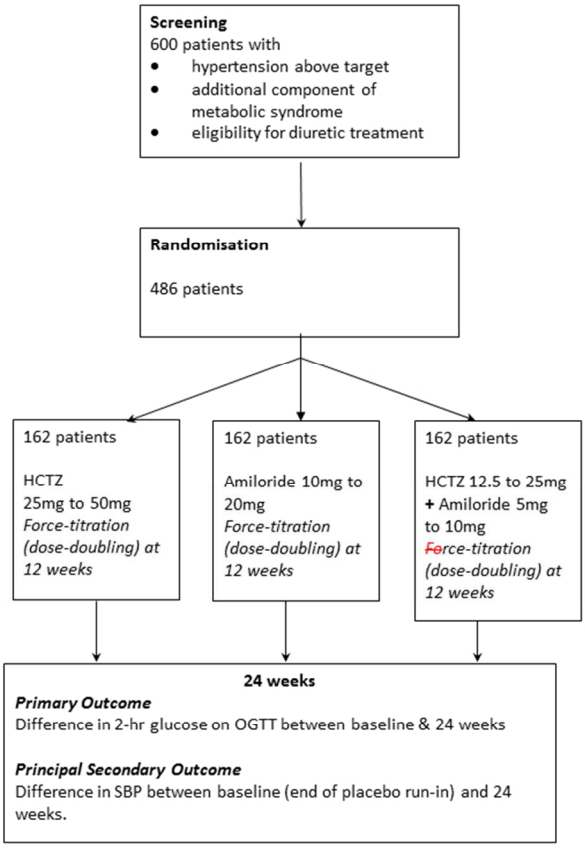
(b)



a) Comparison of blood pressure response to dose-doubling of a calcium-channel blocker, nifedipine, and diuretic combination, hydrochlorothiazide and amiloride, in the INSIGHT study. The figure shows the response in patients achieving target blood pressure, 140/90 mmHg, on low-dose (left panel) or high-dose (right panel) monotherapy. (Unpublished data from reference 17).

b) Comparison of blood pressure response to dose-doubling of three types of diuretic–bendroflumethiazide, amiloride, spironolactone. (Data re-drawn from reference 9).

190x275mm (96 x 96 DPI)



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•Box 1: Inclusion Criteria

1. Age 18-80
2. Diagnosis of hypertension according to BHS criteria
3. Systolic BP on permitted background treatment ≥ 140 mmHg and home BP ≥ 130mmHg.
4. Indication for diuretic treatment as a treatment option for the patient's uncontrolled hypertension :

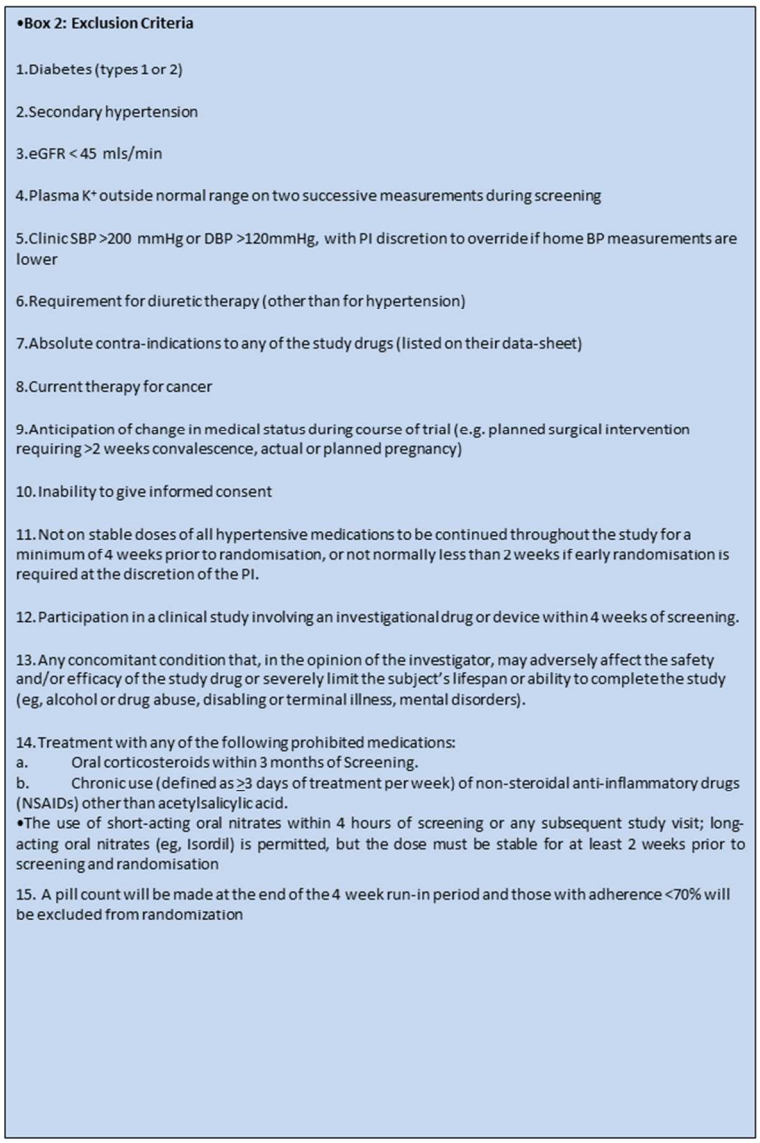
   (a) Untreated + (age>55 AND/OR Black AND/OR renin<12mU/L)

   OR (b) receiving one or any permutation of the following:
   ACEi, ARB, β-blocker, CCB, direct renin inhibitor
5. At least one other component (i.e. additional to hypertension) of the metabolic syndrome (reduced HDL, raised triglycerides, glucose, waist circumference)*

* Definition of Metabolic Syndrome according to the International Diabetes Federation, 2006:
Central obesity (waist circumference >94cm male (>90 if Asian), >80 female
plus two of:

- SBP ≥ 130 or DBP ≥ 85 mmHg
- Fasting glucose >5.6mmol/l
- Fasting Triglycerides >1.7 mmol/l (or on treatment)
- HDL < 1.03 mmol/l males, < 1.29 mmol/l females (or on treatment)

190x275mm (96 x 96 DPI)



•Box 2: Exclusion Criteria

1. Diabetes (types 1 or 2)

2. Secondary hypertension

3. eGFR < 45 mls/min

4. Plasma K^+ outside normal range on two successive measurements during screening

5. Clinic SBP >200 mmHg or DBP >120mmHg, with PI discretion to override if home BP measurements are lower

6. Requirement for diuretic therapy (other than for hypertension)

7. Absolute contra-indications to any of the study drugs (listed on their data-sheet)

8. Current therapy for cancer

9. Anticipation of change in medical status during course of trial (e.g. planned surgical intervention requiring >2 weeks convalescence, actual or planned pregnancy)

10. Inability to give informed consent

11. Not on stable doses of all hypertensive medications to be continued throughout the study for a minimum of 4 weeks prior to randomisation, or not normally less than 2 weeks if early randomisation is required at the discretion of the PI.

12. Participation in a clinical study involving an investigational drug or device within 4 weeks of screening.

13. 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 subject's lifespan or ability to complete the study (eg, alcohol or drug abuse, disabling or terminal illness, mental disorders).

14. Treatment with any of the following prohibited medications:
a. Oral corticosteroids within 3 months of Screening.
b. Chronic use (defined as ≥3 days of treatment per week) of non-steroidal anti-inflammatory drugs (NSAIDs) other than acetylsalicylic acid.
•The use of short-acting oral nitrates within 4 hours of screening or any subsequent study visit; long-acting oral nitrates (eg, Isordil) is permitted, but the dose must be stable for at least 2 weeks prior to screening and randomisation

15. A pill count will be made at the end of the 4 week run-in period and those with adherence <70% will be excluded from randomization

190x275mm (96 x 96 DPI)

Assessment	Screening	Placebo Run-in D-3, D-2, D-1	Week 0	Week 2	Week 11 D-3, D-2, D-1	Week 12	Week 14	Week 23 D-3, D-2, D-1	Week 24
Informed Consent	x								
Demography	x								
Medical history	x		x						
Medical examination	x								
Concomitant medications	x		x	x		x	x		x
Inclusion/exclusion checks	x		x						
Height and weight	x		x			x			x
Clinic BP	x		x			x			x
Home BP		x			x			x	
ECG	x								
Waist and hip circumference	x								x
Urinalysis	x		x						x
Blood Tests:									
Electrolytes (incl bicarbonate)	x		x	x		x	x		x
Glucose (non fasting)	x								
Full blood count	x					x			x
Lipid profile	x		x			x			x
Uric acid	x					x			x
Ca++	x					x			x
renin			x			x			x
Pharmacogenetics			x						
HbA1C			x			x			x
Glucose(fast)*			x			x			x
Insulin*			x			x			x
OGTT**			x			x			x
Pregnancy serum	x								
A/E's						x			x
Randomisation			x						
Study medication dispensed	x		x			x			
Compliance check			x			x			x
Dose force titrated						x			

1. TABLE 1 – SCHEDULE OF MEASUREMENTS

[1] Height recorded at first visit only.
[2] Clinic BP will be measured following 10 mins rest and recorded in triplicate.
[3] Home BP will be measured using the BP device given by clinic at approximately 08.00am and 08.00pm on the 4 days before the clinic visit. Patients will be asked to take triplicate reading after 10 mins rest and to record the second and third on the proforma provided.
[4] Pharmacogenetics sample to be taken where specific informed consent has been given. Sampling will typically be at baseline (Day 0), but may be at any time later in the study.
[5] Serum HcG may be replaced by EMU specimen for HcG testing.
* i.e. baseline sample for OGTT
** glucose at 0, 30, 60, 120 mins; insulin at 0, 30 mins

254x190mm (96 x 96 DPI)

TCONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title Page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	14
	4b	Settings and locations where the data were collected	Title Page
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Table 1
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	blocking
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Robertson Centre page 6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Page6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results (protocol only being published at this stage)			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 3
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	4
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a protocol only
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a protocol only
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	EU Clinical Trials Register/Clinical Trials.Gov
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Comparison of Single and Combination Diuretics on Glucose Tolerance (PATHWAY-3): Protocol for a randomised double-blind trial in patients with Essential Hypertension

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Secondary Subject Heading:	Pharmacology and therapeutics, Cardiovascular medicine
Keywords:	Hypertension < CARDIOLOGY, CLINICAL PHARMACOLOGY, Clinical trials < THERAPEUTICS

Comparison of Single and Combination Diuretics on Glucose Tolerance (PATHWAY-3): Protocol for a randomised double-blind trial in patients with Essential Hypertension

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Keywords: Hypertension, Clinical Trials, Protocol

Abstract

Introduction

Thiazide diuretics are associated with increased risk of diabetes mellitus. This risk may arise from K^+-depletion. We hypothesized that a K^+-sparing diuretic will improve glucose tolerance, and that combination of low-dose thiazide with K^+-sparing diuretic will improve both blood pressure reduction and glucose tolerance, compared to a high-dose thiazide.

Methods and analysis

This is a parallel-group, randomised, double-blind, multi-centre trial, comparing hydrochlorothiazide 25-50 mg, amiloride 10-20 mg and combination of both diuretics at half these doses. A single-blind placebo run-in of 1 month is followed by 24 weeks of blinded active treatment. There is forced dose-doubling after 3 months. The **Primary Endpoint** is the blood glucose two hours after oral ingestion of a 75 G glucose drink (OGTT), following overnight fasting. The primary outcome is the difference between two hour glucose at weeks 0, 12 and 24. **Secondary outcomes** include the changes in home systolic BP and HbA1c and prediction of response by baseline plasma renin. Eligibility criteria are: age 18-79, systolic BP on permitted background treatment ≥ 140 mmHg and home BP ≥ 130mmHg, and one component of the metabolic syndrome additional to hypertension. Principal exclusions are Diabetes, eGFR < 45 mls/min, abnormal plasma K^+, clinic SBP >200 mmHg or DBP >120mmHg. The sample size calculation indicates that 486 patients will give 80% power at α=0.01 to detect a difference in means of 1 mmol/L (SD=2.2) between 2 hr glucose on HCTZ and comparators.

Ethics and dissemination:

PATHWAY-3 was approved by Cambridge South Ethics Committee, number 09/H035/19. The trial results will be published in a peer-reviewed scientific journal. Eudract number 2009-010068-41 and Clinical trials registration number: NCT02351973.

Strengths

This is a randomised, masked adequately powered study.

Weaknesses

Two of the randomized treatments are available in the UK only in combination formulations containing different doses from those under study.

INTRODUCTION

Thiazide and thiazide-like diuretics are widely used. However such diuretics are associated with increased risk of developing diabetes mellitus.[1] This risk may arise from K^+-depletion and be avoided by use of K^+-sparing diuretics. We therefore hypothesized that a K^+-sparing diuretic has a beneficial influence on glucose tolerance compared to a thiazide, and that the use of low-dose thiazide combined with a K^+-sparing diuretic may achieve similar blood pressure reduction, but improved glucose tolerance, compared to a high-dose thiazide.

Diuretics are no longer used at doses achieving maximum reduction in BP. This is because of the evidence that higher doses are associated with increased risk of diabetes mellitus (DM), and an extrapolation from small studies in the 1980's and 90's that maximal blood pressure reductions were achieved by low-dose thiazides.[2-5] But unpublished dose-titration data from INSIGHT (Figure 1a), where the average age was 60, shows as steep a dose-response for hydrochlorothiazide as for nifedipine in patients (right panel) whose dose was doubled after 2 weeks.[6] Amiloride has never been fully investigated at doses equi-effective with thiazides, and is used mainly in an ancillary K^+-sparing role.[7] A diuretic crossover study ('SALT') confirmed that in low-renin patients bendroflumethiazide 2.5 mg is not maximal, and showed either spironolactone or amiloride to be effective alternatives to the higher dose (Figure 1b).[8] Several indices in SALT indicated that even 5 mg of bendroflumethiazide was a less effective natriuretic than the K^+-sparing diuretics, perhaps because it lowers BP partly through vasodilatation.[9] The difference in mechanisms raised the possibility, to be explored by PATHWAY-3, that the diuretics will be found to have an additive effect on BP.

Diuretics and new-onset diabetes: A major attraction of K^+-sparing diuretics is the possibility that they will offset the diabetogenic potential of thiazides. Since they have not been compared in hypertension outcome trials, and diabetes (DM) has not been an endpoint in heart failure studies of spironolactone or eplerenone, we do not know for certain whether they are clean in this respect. Short-term studies suggest they are.[10] Interestingly in INSIGHT there was no excess of DM in patients receiving HCTZ 25 mg, which was combined with amiloride 2.5 mg, but increased by 30% in patients on HCTZ/amiloride 50/5 mg.[6] In PATHWAY-3, we use the oral glucose tolerance test (oGTT) to provide an endpoint for each subject. This strategy was previously used to demonstrate a difference after just 12 weeks of dosing with a thiazide diuretic.[11] In the STAR study, which compared 200 markedly obese patients randomly assigned to either ACE inhibitor + Ca^{++} blocker, or ARB + thiazide, the subjects had impaired glucose tolerance (IGT) at entry, allowing detection of changes on low-dose thiazide. Subsequently, two small crossover studies in about 40 patients showed a rise in 2-hour glucose within four weeks of treatment with bendroflumethiazide 5mg or HCTZ 50 mg, with a highly significant difference from the 2-hour glucose during four weeks of treatment with amiloride 20 mg (Figures 1-2).[12]

PATHWAY-3 will test whether the apparent superiority of amiloride, in protecting glucose tolerance, is maintained over six months of treatment, and translates into measurable differences in HbA1C. The study will be large enough for secondary estimates of mechanism, e.g. the 0 and 30 minute plasma insulin, to determine whether the main drug effects are on insulin secretion or sensitivity, and are influenced by the opposite effects of the two diuretics on plasma K^+. Because, however, of the lack of long-term study of amiloride other than in

combination with HCTZ, the study is also evaluating a group in which the two diuretics are used in combination. If we demonstrate that HCTZ 25 mg + amiloride 10 mg achieves the same (or greater) blood pressure reduction as HCTZ 50 mg, without an adverse effect on OGTT, this could become the recommended diuretic treatment for hypertension in the future.

In order to maximize recruitment, whilst also maximizing sensitivity to detect changes in OGTT, the trial is open to most of those patients with hypertension in whom diuretic is a reasonable next option, providing they have one feature of the metabolic syndrome – additional to hypertension. This broad eligibility allows us also to assess safety of amiloride in combination with all commonly used antihypertensive drugs.

The initial protocol was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 8th May 2009, and is visible at https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-010068-41/GB#A. This was not registered until 2015, because of the prior registrations with MHRA and UKCRN, and local advice that these sufficed. The current protocol is version 8, as approved on 13th February 2013. Any further amendments will be approved by Research Ethics and MHRA and registered also with clinicaltrials.gov.

Primary Objectives

The primary objective of the study is to determine whether a K^+-sparing diuretic can be safely substituted for, or combined with, a thiazide diuretic in order to maximize the long-term benefits of diuretic treatment.

Secondary Objectives

The secondary objectives of the study are

- To demonstrate whether half-dose combination of two classes of diuretic improve efficacy and tolerability of diuretics, compared to taking one class alone.
- To evaluate the mechanism of changes in glucose tolerance, particularly whether these are related to changes in K^+
- To determine whether a baseline measurement of plasma renin, measured on various background treatment permutations predicts whether patients' blood pressure is likely to be improved by addition of either low- or high-dose diuretic
- To determine the best predictors of patients whose glucose tolerance will be impaired by addition of thiazide diuretic.

A further secondary objective is to establish a repository of pharmacogenetic samples and investigate relationships between genetic factors and pharmacodynamic responses.

METHODS AND ANALYSIS

Trial design

Overall trial design

This is a parallel-group, randomised, double-blind, multi-centre trial, comparing three treatment strategies in patients with hypertension, an indication for diuretic treatment, and at least one other component (*i.e.* additional to hypertension) of the metabolic syndrome. Following a month's placebo run-in, patients receive their randomized treatment (diuretic) in addition to existing background therapy for six months, with an oGTT at the beginning, middle and end of this period. The dose of each diuretic is doubled after the second (3-month) oGTT. The trial design is outlined in the flow chart (figure 2).

Study population

Inclusion criteria are shown in Box 1. These are intended to enable recruitment of most patients in whom addition of diuretic might be part of usual practice, enriched for patients most likely to be at risk of develop type 2 DM during long-term treatment with thiazide diuretic.

The PATHWAY programme anticipated changes to the definition of Hypertension introduced by the NICE guidance of 2011. The trials use home blood pressure measurements as an outcome measure, and patients are required to exceed threshold levels of both clinic blood pressure (at screening and/or randomization) and home blood pressure (at randomization). Initially we set the clinic threshold at 145 mmHg, until we had enough experience within the trial of adding high-dose hydrochlorothiazide or amiloride to multiple background drugs. The threshold was then reduced, to 140 mmHg (see Box 1).

Recruitment and randomisation of participants

Potentially suitable patients are identified from hospital and general practice populations. Written informed consent is obtained from participants by a medical investigator. The research nurse records baseline variables, takes blood and urine for baseline biochemistry and haematology and records the medical history. Blood samples are analysed at the local health service laboratory according to usual practice. Serum for future analyses and blood for future genetic analyses are stored by centres. Subjects who have given informed consent, and meet the inclusion and exclusion criteria at the end of a month's placebo run-in, are randomised to receive hydrochlorothiazide 25 mg daily, amiloride 10 mg daily, or a combination of hydrochlorothiazide 12.5 mg and amiloride 5 mg daily, each in addition to any other antihypertensive drug being taken at the time of randomization. Randomisation is performed by contacting a central computerized randomisation facility based at the Robertson Centre for Biostatistics, University of Glasgow by telephone or via a web-based service.

Trial treatments

Initial treatment is the 3 groups described above. After 3 months, each of the groups are force-titrated to twice the starting dose, namely hydrochlorothiazide 50 mg daily, amiloride 20 mg daily, or a combination of hydrochlorothiazide 25 mg and amiloride 10 mg daily. These 3 groups are shown in the Flow Diagram (Figure 2). Trial medication is provided in identical-looking containers for each of the three assignments by the Royal Free Hospital Pharmacy, and

labelled without use of the drug name, according to a randomization schedule provided by the Robertson Centre, University of Glasgow. None of the investigators, patients or laboratory staff undertaking the primary outcome measures are informed of the assignment. A 24-hour telephone unblinding service is provided by the Data Management Centre for instances where principal investigators believe that treatment of an adverse event may be compromised by their not knowing treatment assignment. Compliance has been assessed by returned tablet counts.

Tolerability

Adverse events are recorded in the electronic case record form at each visit. A two-week drug holiday is permitted at any point where the investigator considers this may allow subjects to remain in the trial without early withdrawal.

Trial procedures

These are shown for each visit in the Schedule of Assessments (Table 1). There are three principal visits, at 0, 12 and 24 weeks, at which subjects have an oral glucose tolerance test (oGTT). Blood glucose is measured at 0,30,60, 120 minutes, and insulin at 0 and 30 minutes. At these visits, blood is also collected for electrolytes and eGFR, plasma renin, HbA1c and plasma lipids. Electrolytes and eGFR are also checked at 2 and 14 weeks, namely 2 weeks after initiation and dose-doubling of trial diuretic medication. Seated home blood pressure readings are recorded (morning and evening, in triplicate) over four days prior to each of the 3 principal visits, using the Microlife WatchBP monitor. Clinic blood pressure is measured in triplicate at each visit, by the same monitor. For analyses of home blood pressure, we will use the average of the last 18 recordings prior to the visit – that is, from days -1, -2 and -3 if all recordings have been undertaken. For clinic blood pressure, we will analyse the average of readings 2 and 3.

Trial endpoints

Primary endpoint

The primary study endpoint is the difference in blood glucose, measured two hours after oral ingestion of a 75 g glucose drink, between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment.

Secondary endpoints

These are:

- Difference in area under the curve of the oGTT between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment
- Difference in plasma insulin at 30 minutes, between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment
- Difference in fasting serum lipids, between the final day of the placebo run-in, and at the end of three months and six months of blinded treatment
- The change in home systolic BP from end of placebo run-in to the end of three months and six months of blinded treatment.
- The change in clinic systolic BP from end of placebo run-in to the end of three months and six months of blinded treatment.

- The natriuretic response, as assessed from the compensatory increase in plasma renin from end of placebo run-in to the end of three months and six months of blinded treatment.
- Prediction, by baseline plasma renin, of clinic and home SBP response to each treatment

Data Handling and Record Keeping

Study data is recorded by remote data entry into a web-based electronic case report form (eCRF) developed for the study by the Robertson Centre, Glasgow. eCRF data is anonymous and will identify study subjects by their assigned study numbers only. All missing data, possible duplication, and data outside pre-set limits for each parameter, is queried by the Management Centre, and will be internally validated before database lock.

Data analysis

Sample size determination

Based on at least 80% power to detect a mean difference in glucose between any two of the treatment arms of 1mmol/L (SD= 2.2mmol/L) using two-sample t-tests with a 1% significance level, 414 patients are required. This is the observed difference in 2 hour glucose in the largest previous trial of glucose intolerance caused by HCTZ.[11] Adjusting for an anticipated dropout proportion of 15%, 486 patients are required overall – 162 in each treatment arm.

Analysis will be performed on the full analysis population – defined as all patients with at least one post baseline visit - on an Intention-To-Treat basis. For sensitivity, all analyses will also be performed on the per-protocol population – defined as all patients with at least one post baseline visit and excluding those with any form of major violation of the study.

Recruitment started in November 2009, and is expected to finish during 2015.

Statistical plan

In order to meet the primary objective of determining whether amiloride should be substituted for, or added to, hydrochlorothiazide, the study has a hierarchical co-primary endpoint. The first-tested comparison will be amiloride vs HCTZ. The second tested will be combination vs HCTZ. A mixed effects model will be used to compare the 2h glucose on oGTT between the three treatment groups (baseline, 12 and 24 weeks). This model will adjust for baseline covariates.

For secondary analyses, the primary analysis will be repeated but with the area under the curve (AUC) of the OGTT as the dependent variable. Mixed effects models will be used to estimate treatment effects for home and clinic systolic blood pressure, and for HbA1c. ANCOVA's will be used to compare: insulin (fasting, and rise at 30 minutes during oGTT), HbA1c, lipid profile, renin mass, and weight at the end of study between the three treatment groups adjusting for baseline measures. Logistic models will be used to compare the proportion of subjects to achieve target systolic blood pressure (defined as ≤ 140mmHg) at 24 weeks between the treatment groups. Logistic models will be used to compare the proportion of patients who develop diabetes (defined by fasting glucose≥ 7mmol/L or 2h glucose≥11.1mmol/L or HbA1c≥6.5%) by the end of the study between the three treatment

groups. The covariates in analyses of blood pressure will include baseline plasma renin as a potential predictor of response.

Patients who withdraw from the study before final visit will be included in the primary analysis if they have at least one post-randomisation glucose tolerance test, and missing data imputed by application of last observation carried forwards. Patients with data missing from any timepoint required for analysis, and patients in whom major violation of the protocol is documented by investigators, or detected by the data management centre, will be excluded from per-protocol analysis.

There will be no interim analysis, no stopping rules, and no data monitoring committee. This is because all treatments are being used for licensed indications, and have been so used for several decades. We do not therefore anticipate any unexpected hazard that has eluded detection during many hundreds of thousands of person-years exposure; and the study is not powered to detect any significant differences in serious morbidity or mortality between treatment groups.

Ethics and dissemination

PATHWAY-3 is approved by Cambridge South Ethics Committee and the MHRA. The results will be published in a peer-reviewed journal, and presented to national and international meetings. All authors of this article will have full access to the complete dataset, subject only to agreement by co-authors to uses of the data. Authorship of future articles reporting outcomes will represent multidisciplinary input at each site, with the articles being written by a subset of the current authorship. There are no current plans to make anonymized participant-level data publicly available. However lay-friendly summaries of our findings will be sent to all our patients, and we expect to work with the British Heart Foundation to maximize patient and public access to the findings.

Ancillary and post-trial care

During the trial all patients are covered by the NHS indemnity. We expect most patients to continue diuretic treatment in addition to other pre-trial background therapy that has been continued during the trial.

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

The trial is sponsored by the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, contact stephen.kelleher@addenbrookes.nhs.uk. Trial investigators will permit authorized third parties access to the trial site and medical records relating to trial subjects. This will include, but not necessarily be restricted to, access for trial-related monitoring, audits, Ethics Committee review and regulatory inspections. We do not expect funders or sponsors to be involved in data analysis or reporting.

Associated Projects

This study (PATHWAY-3) is one of three complementary studies in a BHF-funded programme which will investigate optimal treatment for patients with hypertension. PATHWAY-1 will investigate whether initial treatment with a combination of drugs is more effective in achieving a sustained target pressure than starting with monotherapy and adding a second

drug. PATHWAY-2 will recruit patients with more severe hypertension than either PATHWAY-1 or PATHWAY-3, and compare the blood pressure response to each of the three classes recommended by current guidelines.

Authors's contributions

TMM, MJB, BW, MC, JKC, GM, PS, DJW, IF designed the trial. TM, MJB, BW constituted the trial executive committee. MJB and JS drafted the protocol aided by TMM and BW. SM advised on stastical analysis. MJB drafted the paper aided by BW and TMM.

Funding statement

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Acknowledgements

BW, PS, MC and MJB are NIHR Senior Investigators. National Institute of Health Research Primary Care Research networks facilitate recruitment of patients. Blinded medication was packed by Alan Wong and colleagues at the Royal Free Hospital pharmacy.

Competing interest statement

MJB has received honoraria from Novartis.

BW None declared

MC None declared

JKC is Vice-President of the Artery Society, with no competing interest to declare.

GM has received honoraria from Novartis.

PS None declared

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.

IF None declared

SVM None declared

TMM is Chief investigator on two large investigator initiated, industry funded but University sponsored cardiovascular outcome studies (funded by Pfizer and Menarini / IPSEN / Teijin pharmaceuticals) but none with a focus on BP. His research unit also does industry funded

studies by Novartis and Amgen. He has provided consultancy or received honoraria for speaking from Novartis, Takeda, Daiichi Sankyo, Shire and Astellus. TMM is the current president of the British Hypertension Society.

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Box 1: Inclusion Criteria

1. Age 18-80
2. Diagnosis of hypertension according to BHS criteria
3. Systolic BP on permitted background treatment ≥ 140 mmHg and home BP ≥ 130mmHg.
4. Indication for diuretic treatment as a treatment option for the patient's uncontrolled hypertension :

   (a) Untreated + (age>55 AND/OR Black AND/OR renin<12mU/L)

   OR (b) receiving one or any permutation of the following:

   ACEi, ARB, β-blocker, CCB, direct renin inhibitor

5. At least one other component (i.e. additional to hypertension) of the metabolic syndrome (reduced HDL, raised triglycerides, glucose, waist circumference)*

* Definition of Metabolic Syndrome according to the International Diabetes Federation, 2006:
Central obesity (waist circumference > 94cm male (>90 if Asian), > 80 female
plus two of:

- SBP ≥ 130 or DBP ≥ 85 mmHg
- Fasting glucose >5.6mmol/l
- Fasting Triglycerides > 1.7 mmol/l (or on treatment)
- HDL < 1.03 mmol/l males, < 1.29 mmol/l females (or on treatment)

Box 2: Exclusion Criteria

1. Diabetes (types 1 or 2)
2. Secondary hypertension
3. eGFR < 45 mls/min
4. Plasma K^+ outside normal range on two successive measurements during screening
5. Clinic SBP >200 mmHg or DBP >120mmHg, with PI discretion to override if home BP measurements are lower
6. Requirement for diuretic therapy (other than for hypertension)
7. Absolute contra-indications to any of the study drugs (listed on their data-sheet)
8. Current therapy for cancer
9. Anticipation of change in medical status during course of trial (e.g. planned surgical intervention requiring >2 weeks convalescence, actual or planned pregnancy)
10. Inability to give informed consent
11. Not on stable doses of all hypertensive medications to be continued throughout the study for a minimum of 4 weeks prior to randomisation, or not normally less than 2 weeks if early randomisation is required at the discretion of the PI.
12. Participation in a clinical study involving an investigational drug or device within 4 weeks of screening.
13. 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 subject's lifespan or ability to complete the study (eg, alcohol or drug abuse, disabling or terminal illness, mental disorders).
14. Treatment with any of the following prohibited medications:

a. Oral corticosteroids within 3 months of Screening.

b. Chronic use (defined as $\geq$3 days of treatment per week) of non-steroidal anti-inflammatory drugs (NSAIDs) other than acetylsalicylic acid.

c. The use of short-acting oral nitrates within 4 hours of screening or any subsequent study visit; long-acting oral nitrates (eg, Isordil) is permitted, but the dose must be stable for at least 2 weeks prior to screening and randomisation

15. A pill count will be made at the end of the 4 week run-in period and those with adherence <70% will be excluded from randomization

Assessment	Screening	Placebo Run-in D-3, D-2, D-1	Week 0	Week 2	Week 11 D-3, D-2, D-1	Week 12	Week 14	Week 23 D-3, D-2, D-1	Week 24
Informed Consent	x								
Demography	x								
Medical history	x		x						
Medical examination	x								
Concomitant medications	x		x	x		x	x		x
Inclusion/exclusion checks	x		x						
Height and weight[1]	x		x			x			x
Clinic BP[2]	x		x			x			x
Home BP[3]		x			x			x	
ECG	x								
Waist and hip circumference	x								x
Urinalysis	x		x						x
Blood Tests:									
Electrolytes (incl bicarbonate)	x		x	x		x	x		x
Glucose (non fasting)	x								
Full blood count	x					x			x
Lipid profile	x		x			x			x
Uric acid	x					x			x
Ca++	x					x			x
renin			x			x			x
Pharmacogenetics[4]			x						
HbA1C			x			x			x
Glucose(fast)*			x			x			x
Insulin*			x			x			x
OGTT**			x			x			x
Pregnancy serum[5]	x								
A/E's						x			x
Randomisation			x						
Study medication dispensed	x		x			x			
Compliance check			x			x			x
Dose force titrated						x			

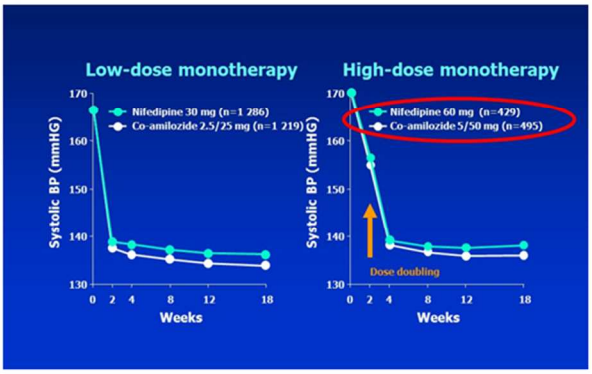
TABLE 1 – SCHEDULE OF MEASUREMENTS

1 Height recorded at first visit only.
2 Clinic BP will be measured following 10 mins rest and recorded in triplicate.
3 Home BP will be measured using the BP device given by clinic at approximately 08.00am and 08.00pm on the 4 days before the clinic visit. Patients will be asked to take triplicate reading after 10 mins rest and to record the second and third on the proforma provided.
4 Pharmacogenetics sample to be taken where specific informed consent has been given. Sampling will typically be at baseline (Day 0), but may be at any time later in the study.
5 Serum HcG may be replaced by EMU specimen for HcG testing.
* i.e. baseline sample for OGTT
** glucose at 0, 30, 60, 120 mins; insulin at 0, 30 mins

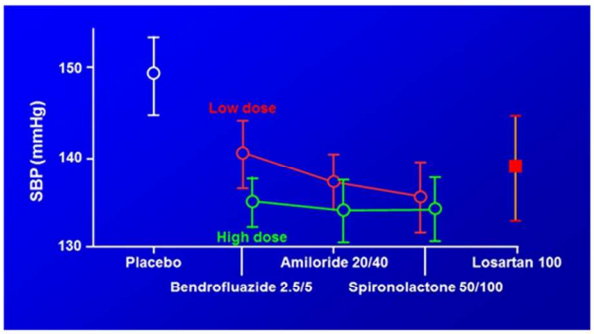
Figure 1

- Evidence for dose-response to thiazide diuretics

(a)



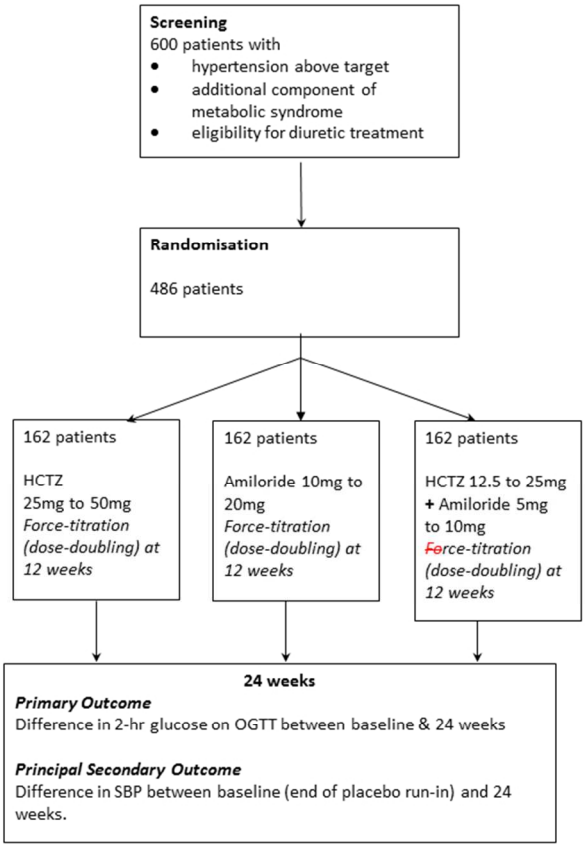
(b)



a) Comparison of blood pressure response to dose-doubling of a calcium-channel blocker, nifedipine, and diuretic combination, hydrochlorothiazide and amiloride, in the INSIGHT study. The figure shows the response in patients achieving target blood pressure, 140/90 mmHg, on low-dose (left panel) or high-dose (right panel) monotherapy. (Unpublished data from reference 17).

b) Comparison of blood pressure response to dose-doubling of three types of diuretic–bendroflumethiazide, amiloride, spironolactone. (Data re-drawn from reference 9).

190x275mm (96 x 96 DPI)



190x275mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 10
	5b	Name and contact information for the trial sponsor	9
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, 17

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	2
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	appended
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	17

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.