Protocol

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This trial protocol has been provided by the authors to give readers additional information about the work.

This supplement contains the following items:

Blood Pressure Control Target in Diabetes (BPROAD) Trial

Protocol Version 1.0

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Executive Summary

Cardiovascular disease and stroke are the leading causes of death in the world and in China (1-3). Over the past decades, type 2 diabetes mellitus and hypertension have reached epidemic proportions in China (4-8). Diabetes and hypertension are major preventable risk factors for cardiovascular disease (9-11). Previous clinical trials have demonstrated that blood pressure reduction lowers the risk of cardiovascular disease and all-cause mortality among patients with diabetes (12,13). However, the most appropriate target for blood pressure reduction in patients with diabetes is uncertain. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, no significant overall difference in cardiovascular events (hazard ratio 0.88, 95% confidence interval [CI] 0.73 to 1.06, P=0.20) or all-cause mortality (hazard ratio 1.07, 95% CI 0.85 to 1.35, P=0.55) between patients with diabetes assigned to a systolic blood pressure target of <120 mmHg and those assigned to a target of <140 mmHg was observed (14). In the recently published Systolic Blood Pressure Intervention Trial (SPRINT), the risks of cardiovascular events (hazard ratio 0.75, 95% CI 0.64 to 0.89, P<0.001) and all-cause mortality (hazard ratio 0.73, 95% CI 0.60 to 0.90, P=0.003) were significantly reduced in the intensive-treatment group (a systolic blood pressure target of <120 mmHg) compared to the standard-treatment group (a systolic blood pressure target of <140 mmHg) (15). In the SPRINT trial, however, patients with a history of diabetes were excluded.

This multicenter randomized controlled trial will test the primary hypothesis of whether an intensive treatment strategy (a systolic blood pressure target of <120 mmHg) is more effective than a standard treatment strategy (a systolic blood pressure target of <140 mmHg) in reducing the risk of major cardiovascular disease (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) over a follow-up period of up to 5 years among patients with a history of diabetes and elevated systolic blood pressure. The secondary hypotheses are to compare the intensive blood pressure treatment strategy with the standard treatment strategy on total stroke (ischemic and hemorrhagic stroke), major coronary heart disease events (fatal coronary heart disease, nonfatal myocardial infarction, and hospitalized unstable angina), treated or hospitalized heart failure, cardiovascular disease mortality, all-cause mortality, cognitive function, kidney outcomes, quality of life, and falls with serious injury.

The trial will recruit 12,702 patients from approximately 200 hospitals within the China

Diabetes Clinical Research Network. Eligible criteria include men and women aged ≥50 years; type 2 diabetes mellitus; elevated systolic blood pressure; and a history of clinical cardiovascular disease or increased risk for cardiovascular disease. Main exclusion criteria include known secondary cause of hypertension, symptomatic heart failure, end-stage renal disease, and other serious illness. The proposed trial has 90% statistical power to detect a 20% reduction (hazard ratio of 0.80) in major cardiovascular disease between intensive and standard treatment groups at a 2-sided significance level of 0.05. We further assume an event rate of major cardiovascular disease of 2.0% per year in the control arm based on 3.8-year follow-up data from the China Cardiometabolic Disease and Cancer Cohort (4C) study, 2-year uniform recruitment period, total study length of 5 years, and 2% per year rate of loss to follow-up.

To achieve the proposed study objectives, we plan to perform the following specific aims:

1. Recruit 12,702 study participants who meet the eligibility criteria and randomly assign 6,351 to the intensive blood pressure treatment and 6,351 to standard blood pressure treatment groups;

2. Achieve and maintain two-level targets of systolic blood pressure (<120 mmHg vs. <140 mmHg);

3. Employ a study-wide strategy to encourage standard of care for all participants for the treatment of type 2 diabetes and dyslipidemia other than blood pressure;

4. Obtain clinical data on study outcomes for up to 60 months of follow-up among all trial participants;

5. Perform strict quality control procedures for intervention and data collection;

6. Conduct data analysis according to the intention-to-treat principle; and

7. Disseminate the study findings to influence clinical practice and clinical guidelines.

Impact: The optimal blood pressure levels for reducing cardiovascular disease and all-cause mortality in patients with type 2 diabetes have not been well defined. The findings from this trial will provide evidence as to whether intensive blood pressure management to achieve a systolic blood pressure target of <120 mmHg has additional benefits over standard management of systolic blood pressure <140 mmHg. These findings will help in the development of clinical guidelines for blood pressure management among patients with type 2 diabetes and will have important clinical impact.

Chapter 1 – Introduction and Rationale

1.1 Epidemic of Type 2 diabetes mellitus

The global age-standardized prevalence of type 2 diabetes increased from 4.3% (95% CI 2.4 to 7.0%) in 1980 to 9.0% (7.2 to 11.1%) in 2014 in men, and from 5.0% (2.9 to 7.9%) to 7.9% (6.4 to 9.7%) in women (16). The number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014 (16). In the same period, the prevalence of diabetes in China has increased even more strikingly and has now reached epidemic proportions (5). For example, the prevalence of diabetes was less than 1% in the Chinese population in 1980 (17). In subsequent national surveys conducted in 1994, 2000-2001, and 2007, the prevalence of diabetes was 2.5%, 5.5%, and 9.7%, respectively (4,18,19). The recent national survey in 2010 reported that the overall prevalence of diabetes was estimated to be 11.6% (95% CI, 11.3 to 11.8%) in the Chinese adult population, representing an estimated 113.9 million adults in China with diabetes (5). Although different sampling methods, screening procedures, and diagnostic criteria were used, these data document a rapid increase in diabetes in the Chinese population.

1.2 Type 2 Diabetes, Hypertension and Risk of Cardiovascular Disease

Individuals with type 2 diabetes are at elevated risk for a number of serious health problems, including cardiovascular disease (CVD), kidney failure, dementia, and premature death (20-22). It was estimated that, worldwide, 1,490,000 deaths from coronary heart disease (CHD) and 709,000 from stroke were attributable to high blood glucose, in addition to 959,000 deaths directly assigned to diabetes (21).

Hypertension is common in patients with type 2 diabetes and confers an elevated risk of CVD (23). For example, the prevalence of hypertension was 66.3% in patients with a history of diabetes, compared to 21.9% in those with normal glucose regulation in Chinese adults (24). More troublesome, the hypertension control rate was only 4.7% in patients with a history of diabetes, compared to 19.6% in those with normal glucose regulation. Hypertension is an important and modifiable risk factor for CVD in patients with type 2 diabetes and the results of prospective cohort studies suggest that 35% to 75% of the cardiovascular risk in patients with diabetes can be attributed to hypertension (25,26).

1.3 Blood Pressure Lowering Clinical Trials

Randomized clinical trials have demonstrated the benefit (reduction in the risk of CVD and all-cause mortality) of lowering blood pressure (BP) to <140 mmHg systolic and <90 mmHg diastolic in patients with diabetes (12,13). For example, in a meta-analysis of 40 clinical trials (100,354 participants), each 10–mmHg lower systolic BP was associated with a significantly lower risk of mortality (relative risk [RR] 0.87, 95% CI 0.78-0.96) and

cardiovascular events (RR 0.89, 95% CI 0.83-0.95). The mean achieved systolic BP in the active treatment group at the end of intervention was 139 mmHg among the included trials (12). There are limited data from clinical trials on the benefit of more intensive BP control in patients with type 2 diabetes.

ACCORD (Action to Control Cardiovascular Risk in Diabetes): The ACCORD trial examined whether a lower systolic BP of <120 mmHg in patients with type 2 diabetes at high risk for CVD provided greater cardiovascular protection than a systolic BP of 130-140 mmHg (14). The ACCORD trial reported no significant difference in cardiovascular events (hazard ratio 0.88, 95% CI 0.73 to 1.06, P=0.20) or all-cause mortality (hazard ratio 1.07, 95% CI 0.85 to 1.35, P=0.55) comparing intensive BP treatment (goal <120 mmHg, average BP achieved = 119/64 mmHg) with standard treatment (average BP achieved = 143/70 mmHg). However, the incidence rate of the primary outcome in the control group was only half of the incidence rate used for sample size calculation (2.09% vs. 4% per year), leading to reduced statistical power to detect a true difference between intensive and standard blood pressure lowering groups. In addition, interaction may exist between glucose control and blood pressure control because subgroup analysis revealed a statistically significant reduction in cardiovascular risks for intensive blood pressure lowering in people assigned to standard glycemic control group whereas no significant difference in people assigned to intensive glycemic control group (p for interaction = 0.08).

ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation): The ADVANCE trial assessed the effects of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination compared to placebo on composites of major macrovascular and microvascular events (death from CVD, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease). Compared with the placebo group (141.6/75.2 mmHg), the patients treated with a single-pill, fixed-dose combination of perindopril and indapamide experienced an average reduction of 5.6 mmHg in systolic and 2.2 mmHg in diastolic BP with a final BP of 136/73 mmHg in the treated group (27). The primary outcome (major macrovascular or microvascular event) was significantly reduced by 9% (hazard ratio 0.91, 95% CI 0.83 to 1.00, p=0.04) but not CVD (hazard ratio 0.92, 95% CI 0.81 to 1.04, p=0.16). All-cause death was reduced by 14% (hazard ratio 0.86, 95% CI 0.75 to 0.98, p=0.03). ADVANCE trial tested intensive vs. standard blood pressure lowering strategies rather than different blood pressure lowering targets. In addition, there were no blood pressure criteria for inclusion.

SPRINT (Systolic Blood Pressure Intervention Trial): SPRINT was a multicenter, randomized controlled trial comparing a systolic BP target of <120 mmHg (intensive treatment) with a target of <140 mmHg (standard treatment) on a composite outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from

cardiovascular causes (15). The SPRINT trial showed that compared to standard treatment, intensive treatment significantly lowered cardiovascular events (hazard ratio 0.75, 95% CI 0.64 to 0.89, p<0.001) and all-cause mortality (hazard ratio 0.73, 95% CI 0.60 to 0.90, P=0.003) among 9,361 patients with a systolic BP of ≥130 mmHg and an increased CVD risk, but without diabetes (15). The risk of incident stroke was not significantly different (hazard ratio 0.89, 95% CI 0.63 to 1.25, p=0.50) between the intensive treatment and standard treatment groups. Patients with diabetes were excluded from participating in this trial, so the results have no direct implications for BP management in this population.

In summary, uncertainty remains about the optimal systolic BP levels for the prevention of CVD and all-cause mortality among patients with diabetes.

1.4 Clinical and Public Health Significance

CVD and stroke are the leading causes of death in the world and in China and have a huge public health impact on society as a whole (1-3). Over the past several decades, type 2 diabetes has reached epidemic proportions in China (4,5). Hypertension is the most common modifiable risk factor for CVD and stroke in patients with diabetes and contributes to 35% to 75% of the cardiovascular risk (25,26). Previous clinical trials have demonstrated that BP reduction lowers the risk of CVD and all-cause mortality among patients with diabetes (12,13). However, the most appropriate target for BP reduction in patients with diabetes is uncertain. In the ACCORD trial, no significant overall difference in cardiovascular events or all-cause mortality between patients with diabetes assigned to a systolic BP target of <120 mmHg and those assigned to a target of <140 mmHg was observed (14). In the recently published SPRINT trial, the risks of cardiovascular events and all-cause mortality were significantly reduced in patients randomized to the systolic BP target of <120 mmHg compared to the systolic BP target of <140 mm Hg) (15). In the SPRINT trial, however, patients with a history of diabetes were excluded.

This trial will test the hypotheses of whether intensive BP management to achieve a systolic BP target of <120 mmHg has additional benefits over standard management of systolic BP <140 mmHg in patients with diabetes. The findings from this trial will help in the development of clinical guidelines for BP management among patients with diabetes.

Chapter 2 – Objectives

The primary objective of the proposed randomized controlled trial is to determine whether randomization to an antihypertensive treatment strategy achieving systolic BP <120 mmHg is more effective than a treatment strategy achieving systolic BP <140 mmHg in reducing the risk of major CVD events (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) among patients with diabetes over a follow-up period of up to 5 years. Other important study objectives are to assess the impact of different systolic BP treatment goals on the risk of total stroke (ischemic and hemorrhagic stroke), coronary artery disease events (fatal CAD, nonfatal myocardial infarction, and hospitalized unstable angina), treated or hospitalized heart failure, CVD mortality, all-cause mortality, kidney outcomes, cognitive function, quality of life, and falls with serious injury. Target systolic BP goals will be <120 vs. <140 mmHg in the intensive vs. standard treatment group.

2.1 Primary Hypothesis

In patients with diabetes, aged ≥50 years, and with a systolic BP ≥140 mmHg (or systolic BP ≥130 mmHg if on ≥1 medication), does a treatment strategy that targets a systolic BP of <120 mmHg reduce the risk of major CVD events (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) compared to a strategy that targets a systolic BP of <140 mmHg over a follow-up period of up to 5 years?

2.2 Subgroup Hypotheses

Is the effect of an intervention achieving systolic BP <120 mmHg vs. systolic BP <140 mm Hg on the primary study outcome (major CVD) consistent in the following subgroups?

- Age <65 vs. ≥65 years at baseline
- Men vs. women
- Systolic BP levels at baseline (tertitles)
- Previous CVD
- Previous chronic kidney disease (CKD, eGFR<60 ml/min/1.73 m^2)
- HbA1c (tertiles)
- Diabetes duration (< vs. ≥ the median)

2.3 Secondary Hypotheses

2.3.1 Secondary outcomes

Does a treatment strategy that targets a systolic BP of <120 mm Hg reduce the risk of the

following secondary CVD outcomes compared to a strategy that targets a systolic BP of <140 mm Hg?

- An expanded outcome including the composite primary outcome and all-cause mortality
- Macrovascular outcome including the composite primary outcome, hospitalized unstable angina, and all cardiovascular revascularization procedures (defined in 'other outcomes')
- Major coronary artery diseases including non-fatal MI, hospitalized unstable angina, revascularization of coronary arteries, and deaths due to coronary artery diseases
- Total stroke including fatal and non-fatal stroke
- Hospitalized or treated heart failure, or heart failure death
- Cardiovascular death
- Total mortality
- Cognitive function
- Health related quality of life

2.3.2 Kidney outcomes

- Progression of CKD: In patients with CKD, we will determine whether a treatment strategy that targets a systolic BP of <120 mmHg slows CKD progression (a composite outcome of end-stage renal disease and 50% decline in eGFR from baseline) compared to a strategy that targets a systolic BP of <140 mmHg
- Development of CKD: In patients without CKD, we will determine whether a treatment strategy that targets a systolic BP of <120 mmHg reduces the risk of CKD (eGFR <60 ml/min/1.73 m^2 and 30% decrease from baseline eGFR) compared to a strategy that targets a systolic BP of <140 mmHg
- Incident albuminuria: In all patients with or without CKD, we will determine whether a treatment strategy that targets a systolic BP of <120 mmHg reduces the risk of albuminuria (a doubling of urinary albumin-to-creatinine ratio [ACR] from a value <10 mg/g to a value of >10 mg/g) compared to a strategy that targets a systolic BP of <140 mmHg

2.3.3 Other outcomes

- All cardiovascular revascularization procedures including percutaneous transluminal coronary angioplasty (PTCA) with balloon or stent, CABG, carotid angioplasty with stent, carotid endarterectomy, peripheral angioplasty with or without stent, peripheral vascular surgery (including aortic aneurysm repair) and limb amputation including partial or digit amputation due to vascular disease
- Hospitalized unstable angina
- Transient ischemic attack (TIA)
- Left ventricular hypertrophy (LVH) diagnosed by ECG

- Atrial fibrillation or flutter
- All cancers
- Cost-effectiveness

2.3.4 Adverse effects

- Symptomatic hypotension
- Arrhythmia
- Acute renal failure
- Electrolyte abnormalities
- Injurious falls
- Syncope

Chapter 3 – Participant Selection and Recruitment

3.1 Eligibility Criteria

The proposed trial will compare the intensive and standard BP treatment strategies on the risk of CVD. Thus, the trial will be conducted among diabetes patients aged ≥50 years with elevated systolic BP and increased risk of CVD.

a) Inclusion Criteria

1. Men and women aged ≥50 years
2. Diabetes defined as (28):

- A self-reported previous diagnosis by health care professionals and taking anti-diabetic medications;
- Fasting plasma glucose level of ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours;
- 2-hour plasma glucose level of ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; or
- HbA1c concentration of ≥6.5% (48 mmol/mol)

- The diagnosis of diabetes must be confirmed on a subsequent day by repeat measurement, repeating the same test for confirmation. However, if two different tests are available and are concordant for the diagnosis of diabetes, additional testing is not needed. If two different tests are discordant, the test that is diagnostic of diabetes should be repeated to confirm the diagnosis.

3. Systolic blood pressure

- ≥140 mmHg on 0 medication;
- 130-180 mmHg on 1 medication;
- 130-170 mmHg on up to 2 medications;
- 130-160 mmHg on up to 3 medications; or
- 130-150 mmHg on up to 4 medications

- There are no diastolic BP inclusion criteria. If a screenee is otherwise eligible for the proposed trial but presents with a treated BP and/or number of medications that fall outside the inclusion criteria, BP-lowering medications may be adjusted prior to the randomization visit to determine whether, with such adjustments, the screenee will meet

eligibility criteria. A screenee who presents on no BP medications should have documentation of systolic BP ≥140 mmHg on 2 visits within 3 months prior to the randomization visit in order to be eligible for the trial.

4. Increased risk of cardiovascular disease (one or more of the following):

- Previous history of clinical CVD (≥ 3 months)
  - Stroke
  - Myocardial infarction
  - Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)
  - Carotid endarterectomy or carotid stenting
  - Peripheral artery disease (PAD) with revascularization
  - Acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test, or positive cardiac imaging study
- Subclinical CVD within 3 years
  - Microalbuminuria
  - ≥50% stenosis of a coronary, carotid, or lower extremity artery
  - Coronary artery calcium score ≥400 Agatston units
  - Ankle brachial index (ABI) ≤0.90
  - Left ventricular hypertrophy
- 2 or more CVD risk factors
  - Current cigarette smoking
  - Body-mass index (BMI) ≥28 kg/m^2 or waist circumference ≥90 cm (in men) or ≥85 cm (in women)
  - Current lipid-lowering medications or LDL-cholesterol ≥130 mg/dl (3.38 mmol/l)
  - Current lipid-lowering medications or HDL-cholesterol <40 mg/dl (1.04 mmol/l)
  - Current lipid-lowering medications or triglycerides ≥150 mg/dl (1.69 mmol/l)
- Estimated glomerular filtration rate (eGFR) 30-59 ml/min/1.73 m^2

b) Exclusion Criteria

1. History consistent with type 1 diabetes
2. Known secondary cause of hypertension
3. Orthostatic hypotension

4. Cardiovascular event or procedure (as defined above as clinical CVD for study entry) or hospitalization for unstable angina within the past 3 months
5. Symptomatic heart failure within the past 6 months or left ventricular ejection fraction (by any method) <35%
6. ALT or AST levels more than twice the upper limit of the normal range or active liver diseases
7. Dialysis or eGFR <30 ml/min/1.73 m^2 or serum creatinine >2.0 mg/dl
8. Proteinuria
    - 24-hour urinary protein excretion ≥1 g/d, or
    - 24-hour urinary albumin excretion ≥600 mg/d, or
    - Spot urine protein/creatinine ratio ≥1 g/g, or
    - Albumin/creatinine ratio ≥600 mg/g
9. Previous diagnosis of polycystic kidney disease or glomerulonephritis
10. A cancer diagnosed and treated within the past two years
11. Any organ transplant
12. A medical condition likely to limit survival to less than 5 years
13. Any factors judged by the clinic team to be likely to limit adherence to interventions:
    - Active alcohol or substance abuse within the last 12 months
    - Significant history of poor compliance with medications or attendance at clinic visits
    - Residence too far from the study clinic site, or plans to move outside the clinic catchment area in the next 5 years
    - Clinical diagnosis of dementia, treatment with medications for dementia, or in the judgment of the clinician cognitively unable to follow the protocol
    - Other medical, psychiatric, or behavioral factors that in the judgment of the research staff may interfere with study participation or the ability to follow the intervention protocol
14. Failure to obtain informed consent from participant
15. Currently participating in another intervention study
16. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not using birth control

3.2 Participant recruitment

Participants will be recruited from hospital visits at outpatient and inpatient department of Endocrine and Metabolic Diseases at each study sites. Retrospective review of medical records for potential participants can also be conducted at study sites where electronical medical record system is accessible. A brief screening form with simple questions such as age, history of diabetes and hypertension, and the willingness to participate will be completed at outpatient and inpatient departments. Potential participants will be contacted by study staff and a screening visit will be arranged, during which the written informed consent will be obtained, and a detailed inquisition of medical history, physical examination, and biochemical evaluation if necessary, will be conducted to assess eligibility according to study inclusion and exclusion criteria.

3.3 Randomization and blindness

Information of eligible patients such as medical records and measurement results will be entered into the electronic data capture system and reviewed by staff at the Coordinating Center, who will review item-by-item inclusion and exclusion criteria and queries will be sent to study staff at study sites if confirmations are needed regarding participant eligibility. After eligibility is confirmed at the Coordinating Center, the electronic data capture system will generate a randomization number and the participant will be assigned to either treatment groups. The randomization will be conducted on stratification of study sites. At each study site, block randomization will be used with randomly selected block sizes of 2, 4, and 6. Study investigators at each study sites will be informed of the assignment of specific participants via the electronic data capture system.

Because BPROAD is a trial comparing 2 different levels of systolic BP control in patients with diabetes, blindness is not possible for study participants and study physician. However, study staff collecting information on study outcomes will be blinded to treatment assignment. In addition, adjudicators of study outcomes as well as statisticians will also be blinded to treatment assignment.

Chapter 4 – Interventions

4.1 Blood pressure goals

Participants eligible for the trial will be randomized to one of two goals:

- Systolic BP <120 mmHg for the intensive treatment group
- Systolic BP <140 mmHg for the standard treatment group

Although there are no diastolic BP inclusion criteria, participants in both groups with diastolic BP ≥90 mmHg will be treated to a diastolic BP goal of <90 mmHg if needed after meeting the systolic BP goal based on clinical guidelines.

4.2 Antihypertensive agents

Use of once-daily preparations of antihypertensive agents will be encouraged unless alternative dosing frequency (e.g., BID) is indicated/necessary.

- Angiotension converting enzyme-inhibitors (ACEIs)
- Angiotension receptor blockers (ARBs)
- Calcium channel blockers (CCBs)
- Thiazide-type diuretics
- Loop diuretics
- Potassium-sparing diuretics
- Beta-blockers
- Alpha1-receptor blockers
- Sympatholytics
- Direct vasodilators

Combination products of different classes will also be used.

4.3 Selection of antihypertensive medications

The proposed trial will test a treatment strategy question regarding different systolic BP goals and not test specific medications. Therefore, the BP treatment protocol is flexible in terms of the choice and doses of antihypertensive medications, but there should be preferences among the drug classes, based on CVD outcome trial results and current clinical guidelines. The 2010 Chinese Guidelines for the Prevention and Management of Hypertension will be recommended to guide drug choices. In addition, the update of hypertension recommendations in Chinese adults, should be available early in the recruitment

phase of BPROAD. These updates, along with any new scientific developments, will be considered during and following BPROAD protocol development and throughout the trial.

The study physician may select among the available antihypertensive medications for initiation of therapy. Other drugs may also be used as the study physician determines appropriate. However, all antihypertensive regimens should include one or more drug classes with strong CVD outcome data from large randomized controlled hypertension trials, i.e., a thiazide-type diuretic, CCB, ACEI, or ARB. All major antihypertensive drug classes (i.e., ACE inhibitors, ARBs, CCBs, and diuretics) are useful in the treatment of hypertension in diabetes. ACEIs and ARBs have the best efficacy among the drug classes on urinary albumin excretion. Therefore, an ACEI or ARB may be considered as part of the combination. A meta-analysis of RCTs of primary prevention of albuminuria in patients with diabetes demonstrated a significant reduction in progression of moderately to severely increased albuminuria with the use of ACEIs or ARBs. However, the combination of an ACEI and an ARB should be avoided. The preference for the order in which these agents are selected is left to the study physician as long as the systolic BP goals are achieved.

Since more than three drugs will be necessary in many participants to reach the intensive systolic BP goal, other classes of antihypertensive agents will also be used in the proposed study. These include the potassium-sparing diuretics, spironolactone and/or amiloride, which are very effective as add-on agents for BP-lowering in “resistant hypertension” (29). However, they should be used with careful monitoring in participants with CKD or any tendency to hyperkalemia. Alpha-blockers have been used effectively as add-on therapy in clinical trials, including AASK and ACCORD. However, alpha-blockers should be used only in combination with one or more other agents proven to reduce CVD events in hypertensive patients (30). Sympatholytics, direct vasodilators, and/or loop diuretics may also be added for BP control in combination with agents proven to reduce CVD events.

The SPRINT trial has shown that a treatment strategy that includes a variety of antihypertensive agents can produce a 14.8 mmHg difference in systolic BP reduction between the two randomized groups (15). The average number of antihypertensive drugs used to produce this difference was 2.8 and 1.8 in the intensive and standard treatment groups, respectively (15).

Algorithm of blood pressure lowering therapy in people with diabetes recommended by the American Diabetes Association can be used as treatment reference (Figure 1).

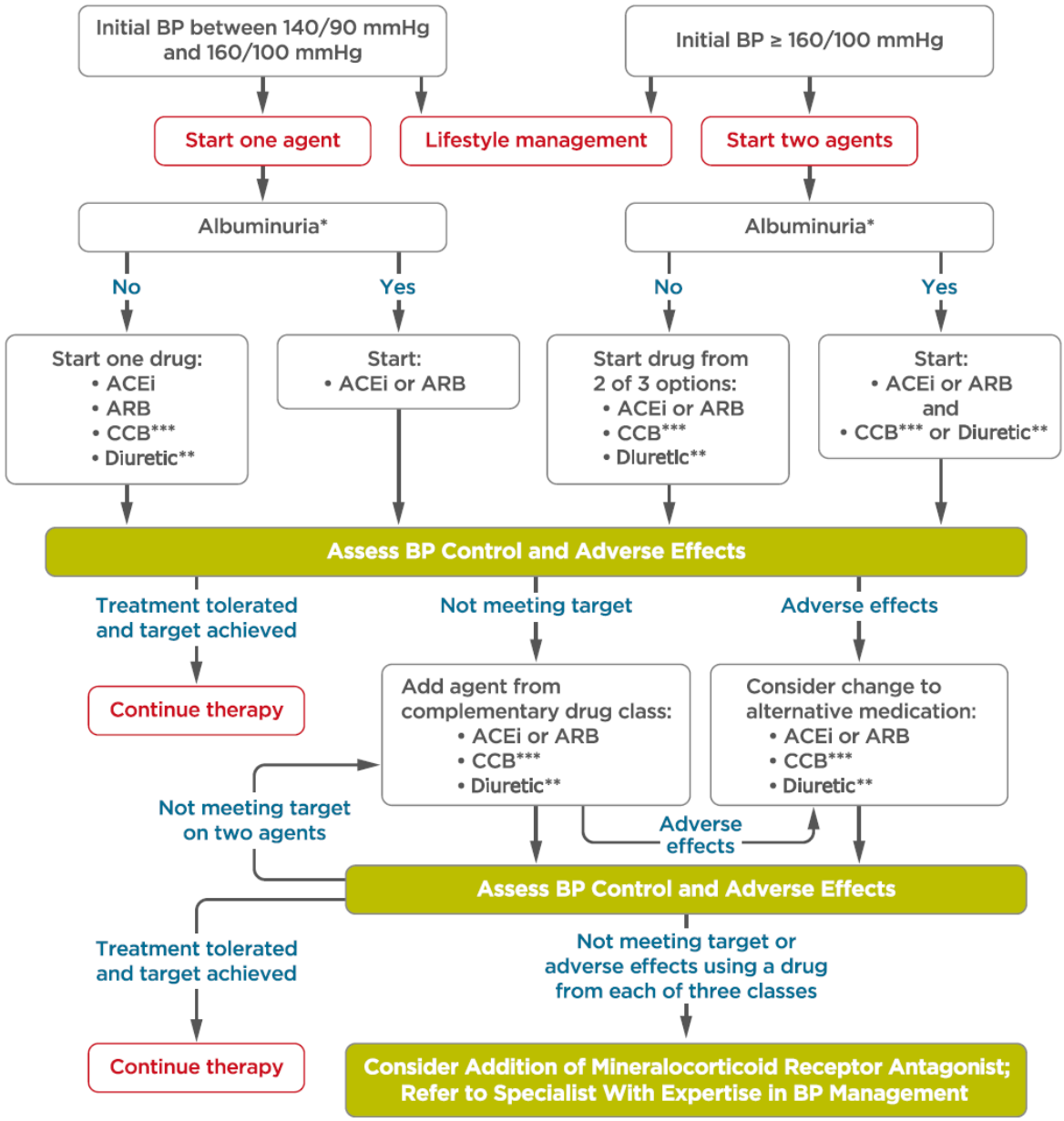


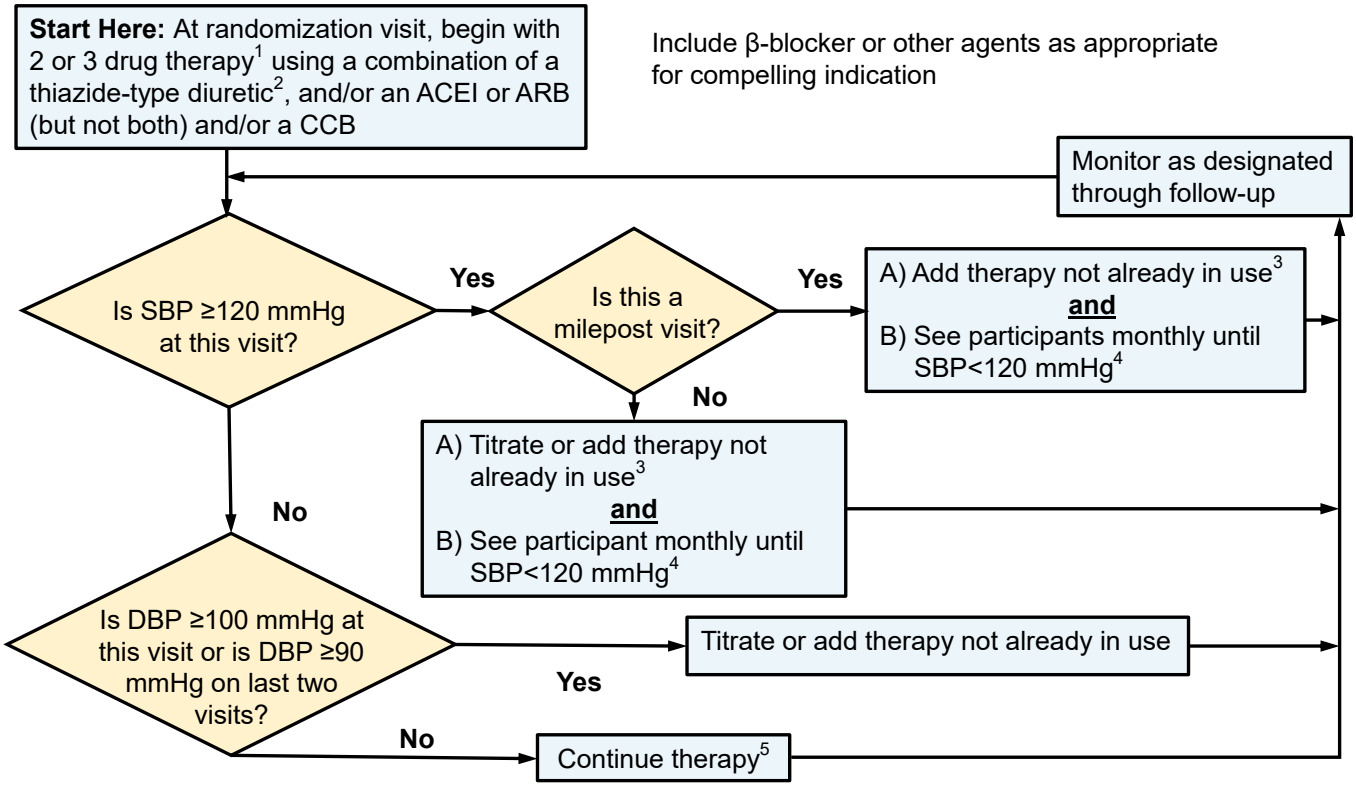
Figure 1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with UACR 30–299 mg/g creatinine and strongly recommended for patients with UACR ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine. BP, blood pressure.

4.4 Protocol visits

For both randomized groups, protocol visit frequency will be monthly for the first three months after randomization, then every three months for the duration of the trial. Monthly visits will continue in the intensive treatment group until systolic BP <120 mmHg (or no more titration planned) and in the standard treatment group until systolic BP <140 mmHg (or no more titration planned). Additional visits will be scheduled as needed for management of adverse effects or for monitoring significant medication changes or other clinical issues.

Intensive treatment group (Figure 2)

Figure 2. Treatment Algorithm for Intensive Treatment Group (Goal Systolic BP <120 mmHg)



[1] May begin with a single agent for patients ≥75 yrs with SBP<140 on 0-1 meds. A second medication should be added at the one month visit if patient is asymptomatic and SBP ≥130 mmHg. [2] May use loop diuretic for patients with advanced CKD. [3] Consider consulting a hypertension specialist before adding a fifth antihypertensive medication. [4] Or until clinical decision made that therapy should not be increased further. [5] Unless side effects warrant change in therapy.

The systolic BP goal for the intensive treatment group, <120 mm Hg, should be achievable in the majority of participants within 8-12 months of follow-up based on the ACCORD and SPRINT experience (14,15). For most participants in the intensive treatment group, a two- or three-drug regimen of a diuretic and either an ACEI or ARB and/or a CCB should be initiated at randomization. If a diuretic is contraindicated or not tolerated, an ACEI or ARB plus a CCB should be initiated. An ACEI or ARB is preferred in diabetes with albuminuria. A beta-blocker should be included in the initial regimen, if there is a compelling indication for a beta-blocker. Drug doses should be increased and/or additional antihypertensive medications should be added at each visit in the intensive treatment group, usually at monthly intervals, until the participant's goal of <120 mmHg has been reached or the study physician decides no further antihypertensive medications may be added.

For participants aged ≥75 years in the intensive treatment group who are on 0-1 antihypertensive medications and have baseline systolic BP <140 mmHg, antihypertensive therapy may be initiated with a single agent at the discretion of the study physician with a return visit scheduled in one month. If the participant is asymptomatic at the first post-randomization visit and systolic BP ≥130 mmHg, a second agent will be added and titration

continued as indicated above.

Milepost Visits: It has been observed in both clinical practice and clinical trials that clinicians fail to intensify therapy despite patients not being at BP goal. Therefore, milepost visits were used in the intensive treatment group in the ACCORD and SPRINT trials to assist in reaching goal systolic BP (14,15). In the proposed trial, milepost visits will be every 6 months throughout follow-up in the intensive treatment group, beginning at the 6-month visit. If the systolic BP is not <120 mm Hg at a milepost visit, then an antihypertensive drug from a class different from what is being taken should be added, unless there are compelling reasons to wait. A "Milepost Exemption Form" will be completed whenever a new drug is not added at a milepost visit in which the participant's systolic BP is not <120 mm Hg to document the reason for not adding a drug and to outline a plan for making progress toward goal in that participant. Milepost visit procedures do not apply to the standard treatment group. Once the intensive treatment group participant has been prescribed 5 drugs at maximally tolerated doses, if the BP remains above goal at subsequent milepost visits, it will be permitted to substitute a different class into the regimen instead of adding another drug or increasing the dose of a drug. However, additional (more than 5) drugs may be needed to achieve goal systolic BP in some participants. Medication adherence will be assessed routinely in the proposed trial and should be evaluated especially carefully for participants not at goal on 4 or more medications. Strategies to enhance adherence should be applied.

Standard treatment group (Figure 3)

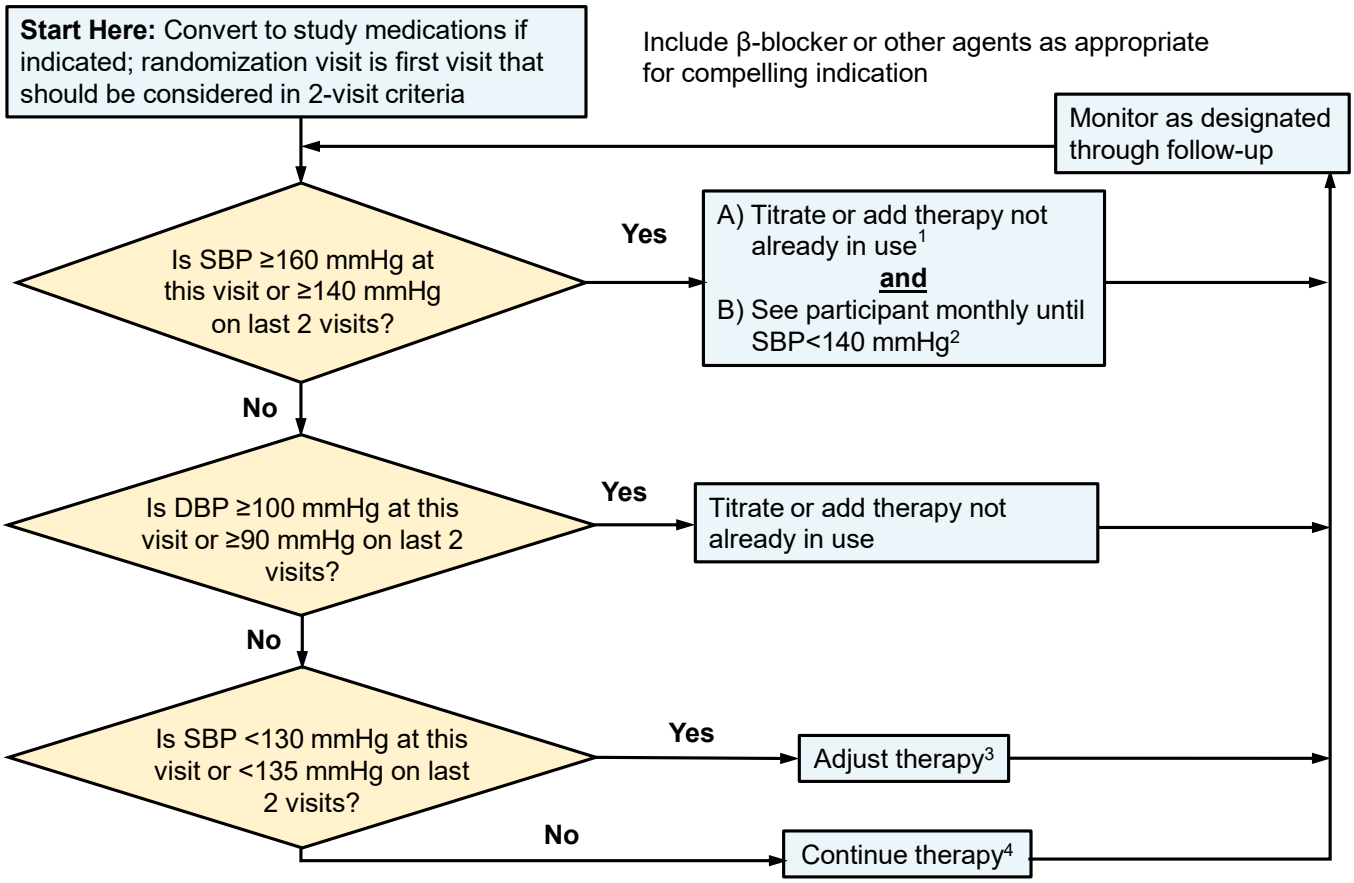
The systolic BP goal for the standard treatment group, <140 mmHg, should be achievable in the majority of participants within 3-6 months, based on experience from the ACCORD and SPRINT trials (14,15). The standard treatment protocol is designed to achieve a systolic BP of 135-139 mmHg in as many participants as possible. Participants in this group may or may not be on treatment with one or more antihypertensive medications. If antihypertensive medication(s) is indicated per protocol, consideration should be given to first-line drug classes such as the ACEIs/AREs, CCBs, and the thiazide-type diuretics as initial therapy, unless there is a compelling indication for another drug class. An ACEI or ARB is preferred in diabetes with albuminuria.

At the randomization visit, standard treatment group participants on previous antihypertensive drug therapy can be converted to the trial medications or no medications, depending on what the study physician believes is most likely to achieve a systolic BP level between 135-139 mmHg. Because we expect a decrease in average systolic BP within the standard treatment group following randomization due to improved adherence, lifestyle counseling, and "regression to the mean", treatment should not be intensified at the randomization visit for standard treatment group participants unless systolic BP ≥160 mmHg or there is a compelling reason to add medication. Following the randomization visit,

medication dose titration or addition of another drug is indicated if systolic BP is ≥160 mmHg at a single visit or is ≥140 mmHg at two successive visits.

Because it is not known if lowering systolic BP to the more intensive goal of <120 mmHg, compared with the standard goal of <140 mmHg, is beneficial, neutral, or harmful in patients with diabetes, careful adjustment of therapy (perhaps a reduction of the dose or number of antihypertensive drugs at the discretion of the BPROAD physician, after consultation with the participant) is allowed for participants in the standard treatment group. Down-titration was not permitted in the HOT Trial if diastolic BP was well below the goal for a participant – this likely contributed to the small differences in achieved BP between the three randomized groups and limited the study's ability to detect differences in outcomes (31). Therefore, down-titration was included in the ACCORD and SPRINT standard BP protocols and was successful in generating the planned differences in BP between treatment arms. Down titration can be carried out in BPROAD standard treatment group if the systolic BP is <130 mmHg at a single visit or <135 mmHg at two consecutive visits.

Figure 3. Treatment Algorithm for Standard Group (Goal Systolic BP <140 mmHg)



[1] Consider consulting a hypertension specialist before adding a fifth antihypertensive medication. [2] Or until clinical decision made that therapy should not be increased further. [3] This is allowed at the discretion of the BPROAD physician, after consultation with the participant. [4] Unless side effects warrant change in therapy.

4.5 Diastolic blood pressure treatment

Once the systolic BP goal has been achieved in any participant, the antihypertensive regimen should be intensified if diastolic BP remains ≥100 mmHg at a single visit or ≥90 mmHg at two successive visits to achieve diastolic BP <90 mm Hg. The visit intervals and decisions for titration (other than the BP levels) will be similar to those used for the systolic BP goal. Since beta-blockers reduce diastolic BP more than systolic BP relative to other antihypertensive medications, a beta-blocker could be considered for such participants.

4.6 Use of Home BP Devices

Home BP devices (Omron HEM-9200L) with BP readings transmittable through Bluetooth will be provided to all participants by the trial. Participants will be instructed on how to use the BP monitoring device at the baseline visit and any following visits should it be necessary. Participants are required to monitor their BP levels at home using the device according to a standard procedure. The study committee recognizes that home BP readings are subject to more bias and error and virtually all BP outcome trials have used office BP determinations, therefore titration of medications to goal will be based on office readings rather than home BP determinations. However, home BP readings will provide additional information on daily BP control and can be used as additional evidence to help study physicians in the management of BP levels.

4.7 Assessment of orthostatic hypotension, measurement of standing blood pressure

Standing BP will be measured at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter using the same BP device that is used to measure seated BP. After seated determinations, participants will be asked to stand. Beginning when their feet touch the floor, BP will be taken one minute later in the same arm used for the seated measurements, using the same BP device. Participants will be asked after the standing determination if they had any symptoms of orthostatic hypotension during the standing BP measurement. BP change using the standing measurements minus the mean of the seated measurements will be calculated. If the systolic BP decreases ≥20 mmHg or the diastolic BP decreases ≥10 mmHg when compared with BP from the sitting position, with or without symptoms, will be diagnosed as orthostatic hypotension.

Participants with orthostatic hypotension will not be eligible for randomization. However, the detection of asymptomatic orthostatic hypotension, i.e., orthostatic hypotension unaccompanied by orthostatic symptoms of dizziness, presyncope, or syncope, will not influence the antihypertensive drug treatment algorithm. Symptomatic orthostatic hypotension will be managed according to a standard protocol.

4.8 Standard care for diabetes and lifestyle recommendations

The purpose of including standard background therapy and lifestyle recommendations in the proposed trial is twofold. First, it fosters high quality general medical care in all study participants in accordance with current practice guidelines. Second, it is intended that background therapies will be utilized equally across both study arms in order to minimize the differences in the effects of non-study strategies on the systolic BP or CVD outcomes between arms. The background therapy recommendations will be provided to the participants and their physicians based on the clinical guidelines of the Chinese Diabetes Society and American Diabetes Association (32,33). Background therapy is considered part of usual recommended care for patients with diabetes. The delivery of these background therapies will be left up to the participants' own clinicians.

Chapter 5 – Clinical Outcome Measures

Clinical events occurring during follow-up will be ascertained equally in both treatment arms through surveillance of self-reported events and medical record data collected by the study staff. All clinical outcomes will be adjudicated by members of an Outcome Assessment Committee who will be masked to treatment assignment. At least two committee members will review the medical records independently.

5.1 Primary outcome

The primary outcome measure for BPROAD will be major cardiovascular events, defined as the composite endpoint of the first occurrence of non-fatal stroke, non-fatal myocardial infarction, hospitalized or treated heart failure, and cardiovascular deaths.

Stroke

We will use standard case definitions for both fatal and nonfatal stroke. Stroke will be defined based on all available data, including symptoms and signs, imaging of the brain and large vessels, and cardiac testing, e.g., echocardiography. Adjudicators will use their clinical judgment based on the available evidence to classify each case, and will be guided by pre-specified definitions and operational rules. Stroke is generally defined as neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours (World Health Organization, 1978 Cerebrovascular Disorders. Geneva: World Health Organization. ISBN 9241700432). Exclusionary conditions for stroke include major brain trauma, intracranial neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous system infections. Stroke will be classified as ischemic stroke, subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, other type, or unknown type. In the proposed trial, ischemic stroke is defined as a new lesion detected by computed tomography or magnetic resonance imaging or, in the absence of a new lesion on available imaging, clinical findings consistent with the occurrence of stroke that lasted for more than 24 hours (34). Ischemic stroke will be further sub-typed using the Causative Classification of Stroke system as evident, probable, or possible cases of large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes (35).

Myocardial infarction (MI)

MI will be defined as the death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombus, or rupture of a plaque. We will use standard case definitions for both fatal and nonfatal MI based on the combination of symptoms, elevation in biomarkers, and/or ECG findings. The algorithm for classifying

MI includes elements of the clinical presentation (signs and symptoms), results of cardiac biomarker determinations, and ECG readings, and is based on the SPRINT criteria (15). The definition includes MI that occurred during surgery/procedure and MI aborted by thrombolytic therapy or procedure. The study adjudicators will be guided by specific, pre-specified definitions and operational rules. Adjudicators will use their clinical interpretation of the ECGs and other available evidence for the event to classify MI cases as definite, probable, or possible, with all included in the primary outcome (36). MI will be ascertained both from adjudication of hospital records for clinical events and also from the finding of new significant Q waves from the standardized interpretation of the study visit-obtained ECG (silent or unrecognized MI). MIs that present clinically will include Q wave, ST elevation and non-ST elevation infarctions (segment elevation myocardial infarction (STEMI), and non-ST Segment elevation myocardial infarction (NSTEMI), as well as aborted MI and post-intervention MI.

Heart failure (HF)

HF will be defined as hospitalization, or emergency department visit requiring treatment with infusion therapy, for a clinical syndrome that presents with multiple signs and symptoms consistent with cardiac decompensation/inadequate cardiac pump function. Adjudication will use the ARIC study adjudication system (37). HF outcome will include definite or possible acute decompensation, including HF with preserved left ventricular ejection fraction as well as HF with reduced ejection fraction. HF will include a variety of clinical presentations, including acute or subacute HF as the primary reason for hospital admission or for emergency department visit where HF was diagnosed and intravenous treatment was given. The identification and classification of HF cases will rely on multiple pieces of key clinical data as well as adjudicators' clinical judgment, guided by specific, pre-specified definitions and operational rules. No identification of HF should rely on a single piece of data such as the presence of dyspnea or of edema, a low ejection fraction, or an increased brain naturetic peptide (BNP) value. Adjudicators will use both the available data and clinical judgment to distinguish between "definite" and "possible" decompensated HF. "Definite" decompensated HF will be assigned when decompensation is clearly present based on available data (satisfies criteria for decompensation). "Possible" decompensation will be assigned when decompensation is possibly but not definitively present, typically where the presence of co-morbidity could account for the acute symptoms (COPD exacerbation, for example).

Cardiovascular death

We will use standard case definitions for classification of CVD death. Definite CVD events will be defined based on temporal relationship to a documented event (e.g., hospitalization for MI or for stroke), or postmortem findings of an acute CVD event. Stroke deaths will be categorized based on the temporal relationship between the stroke event and

death, in cases where the underlying cause of death is attributed to stroke. Proximal stroke death is a death attributed to stroke and occurring within 30 days of stroke; remote stroke death is underlying cause attributed to stroke and more than 30 days from stroke to death. Probable coronary heart disease death will be defined based on autopsy findings consistent with chronic CHD, prior history of CHD or documented symptoms consistent with CHD prior to death, and the absence of another likely cause of death (38). Possible fatal CHD will be adjudicated based on death certificate information consistent with an underlying CHD cause and no evidence of a non-coronary cause. Other forms of CVD death will also be adjudicated and include ruptured abdominal aortic aneurysm and documented arrhythmia.

5.2 Secondary outcomes

In addition to the primary outcome, the following secondary clinical outcomes will be assessed in order to more fully evaluate the effects of intensive BP intervention compared to standard BP intervention.

- An expanded outcome including the composite primary outcome and all-cause mortality
- Macrovascular outcome including the composite primary outcome, hospitalized unstable angina, and all cardiovascular revascularization procedures (defined in 'other outcomes')
- Major coronary artery diseases including non-fatal MI, hospitalized unstable angina, revascularization of coronary arteries, and deaths due to coronary artery diseases
- Total stroke including fatal and non-fatal stroke
- Hospitalized or treated heart failure, or heart failure death
- Cardiovascular death
- Total mortality
- Cognitive function
- Health related quality of life

5.3 Kidney outcomes

- Progression of CKD defined as the composite of a 50% decrease in eGFR or development of end-stage renal disease requiring chronic dialysis or kidney transplantation in patients with CKD at baseline. The decrease in eGFR requires a confirmatory value in the next available official study laboratory check.
- Incident CKD defined as a >30% decrease in eGFR and eGFR <60 ml/min/1.73 m^2 among patients without CKD at baseline. This decrease in eGFR requires a confirmatory value in the next available official study laboratory check.
- Incident albuminuria defined as a doubling of urinary albumin-to-creatinine (ACR) ratio from a value <10 mg/g to a value of >10 mg/g in all patients with or without CKD. This increase in ACR requires a confirmatory value in the next available official study laboratory check.

5.4 Other outcomes

- All cardiovascular revascularization procedures including percutaneous transluminal coronary angioplasty (PTCA) with balloon or stent, CABG, carotid angioplasty with stent, carotid endarterectomy, peripheral angioplasty with or without stent, peripheral vascular surgery (including aortic aneurysm repair) and limb amputation including partial or digit amputation due to vascular disease
- Hospitalized unstable angina: unstable angina is new onset exertional angina, accelerated or rest angina, or both.
- Transient ischemic attack (TIA): TIA is defined as one or more transient episodes of the sudden onset of a focal neurological deficit, no lesion on brain imaging consistent with the deficit, and no signs or symptoms consistent with seizures, migraine, or other non-vascular causes.
- Left ventricular hypertrophy (LVH) diagnosed by ECG: ECG-diagnosed LVH will be defined primarily using the sex-specific Cornell voltage criteria. Other ECG-LVH criteria mentioned in the American Heart Association (AHA)/American College of Cardiology (ACC) statement on ECG changes associated with cardiac chamber hypertrophy (Hancock and others, 2009) will be also considered.
- Atrial fibrillation or flutter: atrial fibrillation/flutter will be primarily detected from the scheduled study ECGs using Minnesota ECG classification (Minnesota code 8.3). Other sources of detection include hospital discharge ICD code (ICD-10 code 148 or ICD-9 code 427.3) and self-report.
- All cancers
- Cost-effectiveness

Chapter 6 – Participant Follow-up

6.1 Schedule of follow-up visits

Post-randomization follow-up visit schedules for data collection do not differ by treatment group assignment. However, the visit schedule for treatment, that is achieving the BP goals, may differ by group while BP goals are being met because of PRN visits not shown in **Table 1**. Additional information on treatment schedules is contained in 4.4 protocol visits in Chapter 4. For data collection in both randomized groups, all participants will have post-randomization visits at months 1, 2, 3, 6, and every 3 months thereafter. For the purpose of event ascertainment, all participants in both treatment groups will be queried regarding the occurrence of a possible event on the same schedule, specifically every 3 months.

6.2. Procedures by visit

Scheduled examination components are shown by visit in **Table 1**. Assessments performed at the various visits include blood and urine collection, physical measures, and questionnaires. Assessments will be performed on the same schedule for both randomization groups. Baseline characteristics to define the patient population include socio-demographics, anthropometrics, fasting plasma glucose, HbA1c, BP, pulse, current and past medical history, concomitant medications, laboratory chemistry, cognitive function, and quality of life measurements. A clinical routine physical examination is included for safety but is not standardized, and left to the discretion of the study physician.

6.3 Blood and urine collection and laboratory assays

Specific laboratory assessments (e.g. fasting serum glucose, HbA1c, serum creatinine, etc.) are important for determining eligibility status. During follow-up, laboratory results will be used to monitor and adjust therapy in an effort to maintain BP goals, monitor co-treatments (i.e., HbA1c, cholesterol, etc.), assess safety (e.g. serum potassium concentrations), and assess for study-related outcomes (e.g. decline in estimated glomerular filtration rate or increased proteinuria).

Serum, plasma, and urine samples will be stored for future measurements of novel risk factors. White blood cells will be collected at baseline for DNA extraction for future genomic studies.

Table 1. Measurement and follow-up schedule

	Bs/ Rz	1 Mo	2 Mo	3 Mo	6 Mo	9 Mo	1 Yr	3 Mo	6 Mo	9 Mo	2 Yr	3 Mo	6 Mo	9 Mo	3 Yr	3 Mo	6 Mo	9 Mo	4 Yr	3 Mo	6 Mo	9 Mo	5 Yr/ Close
Questionnaires																							
Medical history	X																						
SES variables	X																						
Lifestyle factors	X						X				X				X				X				X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence and adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MMAS-8	X						X				X				X				X				X
Study outcomes				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examinations																							
Seated BP, pulse and medication adjustment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP	X	X			X		X				X				X				X				X
Weight	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																						
Waist and hip circumference	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X						X				X				X				X				X
Fasting blood collection																							
Liver and kidney function, electrolytes, glucose, lipids*	X	X		X	X		X		X		X				X				X				X

Serum creatinine, lipid profile, and HbA1c**	X						X				X				X				X				X
Serum storage	X						X				X				X				X				X
Plasma storage	X																						
DNA storage	X																						
Urine collection																							
Urinary albumin and creatinine**	X						X				X				X				X				X
Urine storage	X						X				X				X				X				X
Feces collection	X																						
Cognitive function																							
MMSE	X						X				X				X				X				X
MoCA	X						X				X				X				X				X
Health related quality of life																							
SF-12	X						X				X				X				X				X
PHQ-9	X						X				X				X				X				X
FES-I	X						X				X				X				X				X

Sc/Rz=screening and randomization visits; SES=socioeconomic; MMAS=The Morisky Medication Adherence Scale; BP=blood pressure; ECG=electrocardiography; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; SF-12=Short Form 12 Health Survey Questionnaire; PHQ-9=Patient Health Questionnaire-9; FES-I= Falls Efficacy Scale International.

* These variables will be monitored at local sites.

** These variables will be measured in core lab at the Coordinating Center.

6.4 Physical examination measures

Seated blood pressure and pulse

Three BP measurements will be obtained at each clinic visit and the mean of the 3 measurements will be used. BP will be measured according to a standard protocol recommended by the American Heart Association (39). BP is measured with the participant in a seated position after 5 minutes of quiet rest. In addition, participants are advised to avoid alcohol, cigarettes, coffee/tea and exercise for at least 30 minutes before their BP measurement. An auto-BP cuff will be used and 1 of 3 cuff sizes (pediatric, regular adult, or large) will be chosen on the basis of each participant's arm circumference. The automated device will be used as it offers reduced potential for observer biases and decreased demand on staff in terms of training and effort in data collection.

Standing (orthostatic) blood pressure

Standing BP will be measured at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter using the same BP device that is used to measure seated BP. After seated determinations, participants will be asked to stand. Beginning when their feet touch the floor, BP will be taken one minute later in the same arm used for the seated measurements, using the same BP device. Participants will be asked after the standing determination if they had any symptoms of orthostatic hypotension during the standing BP measurement. The Coordinating Center will calculate BP change using the standing measurements minus the mean of the seated measurements.

Anthropometric measurements (weight and height)

Body weight and height will be measured using standard methods for the calculation of body mass index.

Electrocardiography (ECG)

A 12-lead ECG will be obtained at baseline, annual follow-up visits and the close-out visit to ascertain the occurrence of silent (unrecognized) myocardial infarction, primarily, as well as atrial fibrillation and left ventricular hypertrophy. The baseline ECG is used to identify previous (including silent) myocardial infarction, and to identify evidence of left ventricular hypertrophy.

6.5 Questionnaires

Medical history

A detailed history of diabetes, hypertension, cardiovascular disease, and other medical conditions will be collected at baseline examination. History of cardiovascular disease serves as an eligibility factor.

Sociodemographics

Information will be collected during baseline examination regarding age, gender, level of education, marital status, persons living with participants, and employment. These data will be used to identify socioeconomic status and to characterize the final study population.

Lifestyle factors

Consumption of alcohol and tobacco have important implications on cardiovascular risk and adherence to medication regimens. Participants will be assessed at baseline for lifetime tobacco exposure, and alcohol intake. Physical activity, and dietary habits will also be recorded. At annual assessments, lifestyle factors will be re-assessed.

Concomitant medications

Information regarding the participants' concomitant non-BP medication therapy will be collected and documented at baseline and then reviewed at each follow-up visits. Participants will be required to bring all medication information to each visit and study physician will update concomitant medications if they are changed. Although data are collected on all current therapies, emphasis is placed on concurrent background risk reduction therapy such as aspirin, glucose-lowering and lipid-lowering drugs.

Monitoring adherence

An adherence scale will be administered to all participants at the baseline and annual follow-up visits in order to identify low adherence. In addition, at every medication management visit, participants will be administered a single item to screen for low adherence. If the participant's response to this item indicates a possible problem with adherence, or if the participant is not at the appropriate BP target, study personnel will address the specific issues and barriers for each study participant that may be preventing optimal adherence. In such instances, administration of the adherence scale (to identify reasons for nonadherence) is recommended.

Adverse events

Adverse events will be ascertained at protocol visits and severe adverse events will be reported to local IRB and the Coordinating Center as appropriate.

Study-related outcomes

Both randomized groups will be assessed for study related outcomes in the same way and on the same schedule. After randomization, participants will be assessed every 3 months for CVD and other clinical outcomes. Medical records will be collected for adjudication of study outcomes. Clinical center staff will use available resources and contact information to assess vital status annually on participants not attending study visits.

Health-related quality of life

All participants will be assessed for the effect of interventions on health-related quality of life (HRQoL). HRQoL data will be collected at baseline, annual follow-up visits and the close-out visit.

Cognitive function

All participants will undergo assessment of cognitive function at baseline, annual follow-up visits and the close-out visit. The tests will include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).

Chapter 7 – Safety Monitoring

The BPROAD trial is testing whether lowering SBP to a goal of <120 mm Hg results in better outcomes than a goal of <140 mm Hg in diabetes patients at risk for CVD events. BPROAD is not a study of specific antihypertensive agents. All antihypertensive agents provided by the trial or recommended by BPROAD have been approved by the Chinese Food and Drug Administration (CFDA) and are routinely prescribed for lowering blood pressure in daily clinical practice.

Patient safety will be carefully monitored. Each participating investigator has primary responsibility for the safety of the individual participants under his/her care. In addition, an independent Data and Safety Monitoring Board (DSMB) will have primary responsibility for monitoring the accumulating study data for signs of adverse trends in morbidity/mortality and treatment-related serious adverse events.

7.1 Participant population

Participants enrolled in BPROAD have elevated risk for CVD outcomes. Inclusion and exclusion criteria were set in order to maximize safety while facilitating inclusion of a trial population at risk for the major trial outcomes.

Inclusion criteria of the BPROAD did not have an upper limit for age. The SPRINT study found significant reductions in fatal and nonfatal major cardiovascular events and death from any cause in adults ≥75 years of age treating to a systolic BP <120 mmHg compared with a systolic BP <140 mmHg, without significant increase in adverse events. Therefore, we encourage participating sites to recruit patients ≥75 years of age, although no specific goal proportion is required. For those patients, anti-hypertensive treatment will start slow and will up-titrate to reach BP treatment targets in well-tolerant individuals. All participants including those age ≥75 years will be asked to identify at least 1 contact person at the time of enrollment that can provide information about the participant as it relates to the study in case of significant cognitive decline in those patients during the course of the trial.

7.2 Safety monitoring

Several types of safety issues and serious adverse events may occur in BPROAD and participants will be monitored for these regularly throughout the study.

7.2.1 Expected events

The potential adverse effects of the BP lowering drugs used in BPROAD have been well documented. For example, electrolyte abnormalities (hyponatremia or hypokalemia are known to be associated with diuretics; hyperkalemia and short-term decline in GFR with ACEIs or ARBs, hyperkalemia with potassium-sparing drugs; as well as bradycardia with

beta blockers and calcium channel blockers). Participants will be monitored routinely with interviews, vital signs, targeted physical examination and laboratory tests to ensure safety. In addition, site clinicians may also obtain lab results and ECGs if safety is a concern at non-scheduled intervals. Expected events are not considered serious adverse events (SAEs) unless they meet criteria for an SAE.

7.2.2 Serious adverse events

Because the burden of collecting and reporting data on every possible adverse event (AE) in BPROAD is excessive and side effects from the anti-hypertensive drugs to be used in BPROAD have been well defined, study sites will report all SAEs and selected AEs to the Coordinating Center.

By definition, SAEs are adverse events that meet any of the following criteria:

- fatal or life-threatening,
- result in significant or persistent disability,
- require or prolong hospitalization,
- result in a congenital anomaly/birth defect, or
- are important medical events that investigators judge to represent significant hazards or harm to research participants and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g. hospitalization, death, persistent disability).

Any adverse event that meets any of these criteria will be documented and reported as a serious adverse event. In addition, a select list of other important events which lead to emergency room visits, will also be considered in BPROAD, including:

- symptomatic hypotension
- arrhythmia
- acute kidney failure
- electrolyte abnormalities
- injurious falls
- syncope
- unexpected events for which the investigator believes that the BPROAD intervention caused the event or contributed to the immediate cause of the event

Participants will be queried for SAEs and selected AEs at quarterly clinic visits. Participants are also encouraged to report SAEs and selected AEs between visits. The study physician may consider modification of treatment if they judge that reported SAEs or AEs of interest are related to treatment choices. In response to safety concerns, the study physician may add, increase or reduce the dose, stop, or change antihypertensive drugs. Depending on the situation, the change may be temporary or permanent. Situations that may require temporary

reduction or elimination of a study medication include: side effects, worsening heart failure, acute kidney injury, symptomatic hypotensive episodes, and other illnesses. Orthostatic hypotension is usually related to specific drug classes and not BP level per se and thus should NOT usually alter target BP goals.

7.3 Safety Reporting

At each quarterly visit, BPROAD staff will specifically query participants for serious adverse events. In addition, information on serious adverse events may also be reported to study staff spontaneously by participants through telephone calls or emails between study visits. In addition to local reporting requirements, all serious adverse events will be reported to the Coordinating Center within 24 hours of knowledge of the event through the electronic data capture system. Information on SAEs will be collected and SAE forms will be filled out within 72 hours. SAEs will be followed until resolution, stabilization, or until it is determined that study participation is not the cause. The Coordinating Center will be responsible for timely reporting to the study sponsor, i.e. the National Clinical Research Center for Metabolic Diseases, and the DSMB. The Coordinating Center will provide reports of serious adverse events for review by the DSMB at their meetings.

7.4 Data and Safety Monitoring Board

A DSMB is established, with responsibility to monitor all aspects of the study. This independent DSMB will be established to monitor data and oversee participant safety. Members will be appointed by the National Clinical Research Center for Metabolic Diseases to provide oversight of the trial. The BPROAD DSMB includes experts in antihypertensive clinical trials, diabetes, cardiology, nephrology, neurology, and biostatistics. The DSMB normally meets once or twice a year to monitor safety, to advise the National Clinical Research Center for Metabolic Diseases about study progress and performance, and to make recommendations regarding study continuation and protocol changes. Before each DSMB meeting, the Coordinating Center will prepare and provide data on SAEs and selected AEs and any other safety information requested by the DSMB for discussion during open and closed sessions of DSMB meetings. The DSMB members vote during the closed sessions on recommendations to continue or terminate the study based on safety or efficacy data.

Chapter 8 – Statistical Considerations

8.1 Statistical power

The proposed trial has a single primary outcome (composite major CVD)) and several key secondary outcomes. The power calculation is based on the primary outcome and use of the following assumptions:

- Event rate of composite major CVD of 2.0% per year among patients with diabetes and elevated BP (based on the 4C Study 3.8-year follow-up data)
- 20% effect size for the intervention (hazard ratio of 0.80)
- Two-year uniform recruitment period and total study length of five years (defined by the time between randomization of the 1st participant and study closeout)
- 2% per year loss to follow-up rate
- Two-sided significance test at the 5% level, and a statistical power of 90%

Based on these assumptions, we will need to recruit a total of 12,702 patients (6,351 in each group) for the proposed trial. In addition, we analyzed statistical power for various assumptions (**Table 2**). If annual event rate of composite major CVD rate is only 1.8%, we will still have 87% statistical power to detect a 20% risk reduction. If the trial is extended to six years of follow-up, we will have 95% power.

Table 2. Power for the primary outcome (composite major cardiovascular disease)

Sample size/ Hazard ratio	Annual event rate								
	1.8%			*2.0%*			*2.2%*		
	0.75	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*
12000	96.8	84.9	60.0	98.0	88.3	64.3	98.7	91.0	68.3
12250	97.0	85.7	60.8	98.2	88.9	65.2	98.9	91.5	69.2
12500	97.3	86.3	61.6	98.3	89.5	66.0	99.0	92.0	70.0
12750	**97.5**	**87.0**	**62.5**	**98.5**	**90.1**	**66.9**	**99.1**	**92.5**	**70.9**
13000	97.7	87.6	63.3	98.7	90.7	67.7	99.2	93.0	71.7
13250	97.9	88.2	64.1	98.8	91.2	68.6	99.3	93.4	72.5
13500	98.1	88.8	65.0	98.9	91.7	69.4	99.4	93.8	73.3

Assumptions: 2-year recruitment with a uniform accrual rate and total study length of five years; annual proportion lost to follow-up = 2%; and 2-sided significance level = 0.05.

8.2 Data management

All study data will be entered through a web-based data management system first at the local hospitals and the data entry system will be maintained at the Coordinating Center. The Coordinating Center will check for missing data and unrealistic values and perform crosschecks for inconsistencies. Data queries generated from quality control will be sent to participating hospitals and a timely reply (within 3 days) will be required. This data management system has been used in previous trials.

8.3 Data analyses

Sex as a biological variable will be factored into the study design and analyses. Specifically, we anticipate that at least 40-50% of participants will be women. Sex differences will be an important subgroup hypothesis and will be tested using a sex-by-intervention interaction in Cox regression (see **subgroup analysis**).

8.3.1 Primary outcome

The primary analysis will be based on participants' randomization assignments regardless of their achieved BP levels (*intention-to-treat analysis*). For the primary outcome, time-to-event analysis will be used to compare the primary CVD composite endpoint between the intensive treatment and standard treatment groups. Cumulative event rates will be calculated using the Kaplan-Meier method and differences will be tested using the log-rank test. Cox proportional hazards regression will be used to compare the time from randomization to the first CVD event between the randomization groups. The model will include an indicator for intervention as its sole predictor variable. Clinical site at randomization will be a stratifying factor. Follow-up time will be censored at the last date of event ascertainment. The p-value from the primary analysis will be based on the χ^2 statistic from a likelihood ratio test obtained from proportional hazards models with and without the intervention term. This likelihood ratio test will constitute the primary test of statistical significance (two-sided *P*-value <0.05) for the primary analysis. Cox proportional hazards regression assumptions will be examined using standard methods.

8.3.2 Secondary outcomes

A number of secondary outcomes will be analyzed to clarify the interpretation of the results of the primary analysis. Each of these will be analyzed using a proportional hazards model as described for the primary analysis. These will be reported with 95% confidence intervals and nominal p values without an adjustment for multiple comparisons, since the intent is to articulate a pattern of effects closely related to the primary outcome, rather than to provide additional tests of efficacy.

8.3.3 Renal outcomes

Renal outcomes are of particular importance in BPROAD, both to assess the progression of kidney disease among those with CKD at baseline and to assess the incidence of new kidney disease among participants free of CKD at baseline. This will be analyzed using a Cox proportional hazards model as described for the primary CVD analysis.

8.3.4 Cognitive and HRQoL outcomes

The effect of the interventions on MMSE, MoCA, and SF-12 scores will be compared using mixed-effects analysis of covariance models. Mixed-effects models allow for departure from linearity in the relationship between the outcome and time. Estimates of the difference in mean levels of the outcome between the intensive and standard treatment groups will be obtained using maximum likelihood techniques.

8.3.5 Subgroup analysis

For each subgroup analysis, a proportional hazards model will be used that is similar to the one described for the primary analysis above, but with additional terms identifying subgroup membership and the intervention-by-subgroup interaction. Interactions between treatment effect and pre-specified subgroups will be assessed with a likelihood-ratio test. Effect estimates and related nominal 95% CIs within subgroups will be reported.

8.3.6 Missing data

For participants lost to follow-up, we plan to use all available information until the time of death or loss to follow-up. We will assume missing-at-random (MAR) for the primary analysis. In a sensitivity analysis, we will investigate whether loss to follow-up is related to the outcome being analyzed. The magnitude of this problem will be investigated by using measurements taken at previous visits to predict loss to follow-up. Variables determined to predict loss to follow-up will be included in our predictive models. In addition, we will examine several “worst-case” scenarios, including opposite and pooled imputation approaches. These types of scenarios are members of a broad class that can be parameterized as pattern mixture models and allow for examination of sensitivity of conclusions to missing-not-at-random (MNAR) mechanisms. Finally, the multiple imputation techniques will be used in the sensitivity analyses of the primary and secondary outcomes.

8.3.7 Interim analysis and trial stopping rules

Interim analysis will focus on patient recruitment, baseline comparability of treatment arms, achievement of treatment BP goals in both arms, sample size assumptions with regard to event rates, loss to follow-up, adverse effects data, and effect of treatment on the primary and secondary study outcomes. Interim outcome analyses will be performed for each meeting of the DSMB, with group-sequential stopping boundaries defined with the use of the Lan-DeMets method with an O’Brien-Fleming-type spending function. Trial investigators will be blinded to the interim outcome results.

Chapter 9 – Quality Control

Data integrity and quality are among the highest priorities in BPROAD. There are two primary purposes for quality control: to document the level of quality and to provide feedback to the clinical, reading and laboratory centers in order to maintain and improve the quality of the study data over the course of the trial.

Two phases will be used in BPROAD. The first, quality assurance, is the collection of manuals and procedures that will be in place to assure the integrity of the data. A subset of these procedures is referred to as quality control, which describes the monitoring and analytic activities that assess performance during data collection and its processing.

9.1 Manual of Procedures

The MOP will include detailed descriptions of all trial procedures and will be used for training purposes and as a reference for all study investigators and staff. The MOP is an important aspect of efforts to standardize study procedures across clinical sites in the BPROAD trial.

Key study procedures will be standardized; these include the use of a central lab and ECG reading center, and standard forms, equipment, and procedures in the clinics for BP measurement and other data collection procedures. Furthermore, standard event definitions and event validation procedures will be used.

9.2 Study forms

Quality assurance concepts were employed during the development of forms. Question-by-question instructions on how to fill out the forms will be listed and necessary explanations will also be available for easy reference. Web-based data entry screens will be developed from the forms, and enable the incorporation of range and logical checks at the time of data entry. A pilot examination using some of the forms such as the baseline information collection form to simulate study scenario will be conducted to identify space for improvement. These features will contribute to quality assurance.

9.3 Training

Training of staff and pilot testing of procedures are crucial to standardize procedures and assure data quality. BPROAD uses two different training models: face-to-face training and online-video training. In face-to-face training, we will organize up to 10 training sessions at different regions across mainland China. All relevant staff members from all clinical sites in the relevant region will be convened in a single, centrally administered face-to-face training session. This approach contributes to uniformity of the training experience and thereby to uniformity of data quality across sites. In addition, we will conduct a second face-to-face training at each site initiation to help individual study site to begin data collection. In online-video training, we will upload a training video to the trial website with details on standard

procedures and emphasis on data quality for study staff to watch at any time when they feel necessary. The online video will also help persons who were unable to attend the face-to-face training session and to newly hired staff as turnover occurs. In addition, the Coordinating Center will organize yearly refresher training sessions to study personnel of all study sites.

9.4 Data queries

The Coordinating Center will be responsible for data editing, which will include checks for missing data, unrealistic values, and crosschecks for inconsistencies. Data will be checked on form submission and any data queries presented to the data entry staff for immediate resolution, if possible. The Coordinating Center will also produce data query reports on the website that summarize the number and types of queries by study site. Study site staff will be responsible for reviewing and resolving the data queries in a timely manner. In case of unresponsiveness, telephone calls will be made from the Coordinating Center to study site investigators, and will be followed with site visits if unresponsiveness continues. Reports, including reports on timeliness of data entry and query resolution, will be shared within the network of all study sites.

9.5 Quality control reports

Using the electronic data capture system, a real-time monitoring at the Coordinating Center will be conducted on progress of participant recruitment, achieved systolic BP levels in both groups, recording of study outcome information, collection of blood and urine samples for centralized measurement and storage, etc. Routine (e.g., weekly) quality control reports will be generated by the Coordinating Center and will be distributed to all study sites on measures of process, impact, and outcomes.

Examples of process measures that will be tracked for quality control purposes include:

1. Days between data collection and data entry
2. Percent of forms with late data entry
3. Number of participants with missed or late visits by contact, number of missed or late visits clinic-wide, and number of participants missing two or more consecutive visits
4. Number, name and dose of prescribed antihypertensive medications for individual participants

Examples of impact measures that will be tracked for quality control purposes include:

Number (and percent) of participants at goal according to the BP target assignment as assessed by in-clinic BP measurements.

Examples of outcome measures that will be tracked for quality control purposes include:

1. Submission of medical record documentation for reported study events by the clinical site (e.g., timeliness, completeness)
2. Proportion of participants with ECG submitted to central ECG Reading Center overall and by quality grade
3. Proportion of participants with urine samples submitted for albuminuria assessment

4. Proportion of participants with blood samples submitted to central lab

5. Percent agreement of individual study adjudicators with the final outcome assignments for cases adjudicated

9.6 Monitoring the study sites

The Trial Monitoring Committee of BPROAD will be responsible for study site monitoring. Enough number of trial monitors (also called clinical research associates) will be hired to monitor performance at each of the study sites. The monitoring team will monitor clinical sites in all aspects of trial operations and performance and to assist in problem solving related to all aspects of the trial. Site monitoring can and will be performed using regular communications including WeChat, telephone calls, site visits and other means.

Trial monitors will visit individual study sites at site initiation to help with completion of appropriate regulatory approvals, site staff training, and the development of a recruitment plan. Additional visits may be conducted to ensure that the study enrollment process follows proper study procedures. During the course of the trial, the monitoring team will visit clinical sites at specified intervals, and as needed. The scope of these visits is broad and can include but is not limited to regulatory requirements, study communications, site initiation, site staffing, and general site performance. However, areas of emphasis and/or additional monitoring may vary according to the circumstances of a specific site and site visit. Site visits may be conducted to evaluate performance deficits in one or more critical areas, such as consistent departures from the protocol or MOP. Site visits are also an opportunity for refresher training and/or training of new staff, as needed. A summary of the site visit will be presented to the clinical site investigator and staff at the conclusion of the site visit and a written site visit report will be completed within a reasonable time-frame post visit. Copies of the site visit report will be sent to the clinical site investigator and the Coordinating Center. Proper follow-up of problems identified during site visits will be conducted and follow-up reports will also be completed and sent out to the clinical site investigator and the Coordinating Center.

9.7 Laboratory quality control

The Central Laboratory of BPROAD trial locates at the Shanghai Institute of Endocrine and Metabolic Diseases and has been participating in regular CAP auditing and accreditation. The Coordinating Center will work with the Central Laboratory to develop quality control procedures for the trial to ensure high quality measurement data. The results of quality control procedures performed at the Central Laboratory will be reported on a regular basis to the Coordinating Center.

Clinical site performance in acquisition, handling, storage and shipping of specimens will be tracked by the Central Laboratory. The first step in quality assurance at the site level consists of the training and certification process for staff within the clinical sites. Other steps include observation of technicians performing all steps of sample collection and processing

during site visits; reviewing study forms; reviewing and tracking the condition of samples received at the Central Laboratory for problems in shipment; and periodic analysis of the study data for participant compliance with fasting, where required, and for signs of problems in drawing or processing, such as hemolysis. Reports on clinical center performance will be submitted regularly by the Central Laboratory to the Coordinating Center. Quality Control procedures in the laboratory for assays include the use of the internal Laboratory Manual, training and certification of laboratory staff, laboratory participation in external standardization and certification quality control programs, and implementation of the BPROAD internal quality control program. As part of the internal quality control program, the Central Laboratory will regularly provide summaries of the internal quality control results to the Coordinating Center.

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Blood Pressure Control Target in Diabetes (BPROAD) Trial

Protocol Version 5.0

October 2022

Table of Contents

Changes of BPROAD study protocol versions 1.0 - 5.0

PROTOCOL VERSION 1.0 (June 2018)

PROTOCOL VERSION 2.0 (November 2018)

Changes in the BPROAD protocol version 2.0 include:

1. BPROAD Cognitive Study: This was added in a separate chapter (Chapter 9) with the objectives to determine whether a treatment strategy achieving systolic BP <120 mmHg is more effective than a treatment strategy achieving systolic BP <140 mmHg in reducing the risk of all-cause dementia and other cognitive outcomes among patients with diabetes over a follow-up period of up to 5 years.
2. Inclusion criteria: Requirement on replication of microalbuminuria was added, if it is the only criterion for increased risk of cardiovascular disease.
3. Exclusion criteria: 'cancer diagnosed and treated within the past two years' and 'any organ transplant' were dropped; 'orthostatic hypotension' was replaced with 'one minute standing systolic BP <110 mmHg'; 'procedures for renal artery disease" was added as an exclusion to secondary hypertension; EF < 35% was restricted to 'within 6 months' for heart failure exclusion. 'Arm circumference too large to allow accurate blood pressure measurement with available devices' and 'currently living with another BPROAD participant' were added.
4. BP measurement: The section 'BP measurement (seated blood pressure and pulse)' was updated in Chapter 6 on BP measurement device and presence/absence of observer. The section 'Use of Home BP Devices' was updated in Chapter 4.
5. Outcomes: 'laser treatment, VEGF inhibition, or surgical intervention for retinopathy' was added as one of the microvascular outcomes in 'Other outcomes' in Chapter 5. eGFR <15 ml/min/1.73 m^2 was added as component of composite outcome for CKD progression and the change in urinary ACR levels as a continuous variable was added as sensitivity analysis for albuminuria in 'Kidney outcomes' in Chapter 2 and Chapter 5. Clarifications were made to emergency treatment (infusion therapy) for heart failure and criteria for heart failure hospitalization in Chapter 5.
6. Subgroup analysis: subgroups of patients < vs. ≥80 years, patients with < vs. ≥ the median of high BP duration were added.
7. Interim analysis: The interim analysis table was added to the section 'Interim analysis and trial stopping rules' in Chapter 8.

8. Study extension: The section '10.8 Extension of study' was added to Chapter 10.
9. Table 2: Lifestyle factors will be reassessed at 24- and 48-month visits instead of annually. Waist/hip circumference will be recorded at baseline and annual visits instead of every 3 months. 24-h urine electrolytes, creatinine, and protein were added at baseline and annual visits. Feces collection was added. The Falls Efficacy Scale International (FES-I) was removed and the 5-level EQ-5D version (EQ-5D-5L) was added to evaluate the health related quality of life. These changes were made to Table 2 (Table 1 in v1.0) and in the corresponding text.
10. Other updates: Study personnel and their required state of blinding were listed in Table 1 in Chapter 3. Information on providing clinically relevant lab results to providers of participants was added in Chapter 6. AE monitoring forms are required at drug titration visits and will be documented as AEs reported at non-protocol visits in Chapter 7. Statistical powers for CKD outcomes were listed in Chapter 10.

PROTOCOL VERSION 3.0 (February 2020):

Changes in the BPROAD protocol version 3.0 include:

1. Outcomes: 'Total MI including fatal and non-fatal MI', 'ischemic stroke', and 'hemorrhagic stroke' were added as pre-specified 'Secondary outcomes' in Chapter 2 and Chapter 5.
2. Subgroup analysis: It was specified that data from the screening visit will be used to define subgroups, which was added to Chapter 2.
3. Interim analysis: Early interim analysis was dropped and the interim analysis will be conducted when the accumulating primary case number is at 50% and 75% of the total anticipated number. These changes were made to Chapter 8.
4. Cognitive study: A composite of all-cause dementia and mild cognitive function (MCI) was used instead of dementia alone as the primary outcome of the BPROAD Cognitive Study. Dementia alone and MCI alone were two secondary outcomes, among others. Two occurrences of an adjudicated classification of MCI will be required for the MCI diagnosis. The statistical power for BPROAD Cognitive Study was re-calculated using the new primary outcome and updated findings from the SPRINT MIND Study. These changes were made to Chapter 9.

When the COVID-19 pandemic broke out in December 2019 in China, some clinical sites limited the number of in-person visits, and many participants became reluctant to go to clinics. We quickly issued an urgent response plan to each participating site and encouraged home blood pressure monitoring by providing each participants an automated blood pressure measurement device and a blood pressure diary chart with access to a training video made by the trial coordinating center for a standard home blood pressure measurement and recording. Study physician used telephone interviews to collect home blood pressure levels, which were used for adjustment of antihypertensive medications. The same targets for home and clinic blood pressure were recommended. Information on study outcomes was also asked during

telephone interview and supporting clinical materials were obtained afterwards whenever possible. BPROAD Data and Safety Monitoring Board (DSMB) agreed that home blood pressure monitoring should be used when the study participant is not able to visit the clinic on schedule. Therefore, home blood pressure monitoring was added to the BPROAD protocol version 3.0. This protocol change was approved immediately by the institutional review board at Ruijin Hospital. Changes were made to the section '4.6 Use of home BP devices'. The response plan was attached at the end of the protocol.

PROTOCOL VERSION 4.0 (June 2020):

In this updated version, we indicated how the trial intends to end the cognitive component in the section '9.5 Study Power', consistent with BPROAD Statistical Analysis Plan v3.0.

PROTOCOL VERSION 5.0 (October 2022):

In this updated version, we replaced study sites with seven geographical regions in which a study site locates to use as a stratifying factor in '8.3.1 Primary outcome', recommended by BPROAD DSMB and consistent with BPROAD Statistical Analysis Plan v4.0.

Executive Summary

Cardiovascular disease and stroke are the leading causes of death in the world and in China (1-3). Over the past decades, type 2 diabetes mellitus and hypertension have reached epidemic proportions in China (4-8). Diabetes and hypertension are major preventable risk factors for cardiovascular disease (9-11). Previous clinical trials have demonstrated that blood pressure reduction lowers the risk of cardiovascular disease and all-cause mortality among patients with diabetes (12,13). However, the most appropriate target for blood pressure reduction in patients with diabetes is uncertain. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, no significant overall difference in cardiovascular events (hazard ratio 0.88, 95% confidence interval [CI] 0.73 to 1.06, P=0.20) or all-cause mortality (hazard ratio 1.07, 95% CI 0.85 to 1.35, P=0.55) between patients with diabetes assigned to a systolic blood pressure target of <120 mmHg and those assigned to a target of <140 mmHg was observed (14). In the recently published Systolic Blood Pressure Intervention Trial (SPRINT), the risks of cardiovascular events (hazard ratio 0.75, 95% CI 0.64 to 0.89, P<0.001) and all-cause mortality (hazard ratio 0.73, 95% CI 0.60 to 0.90, P=0.003) were significantly reduced in the intensive treatment group (a systolic blood pressure target of <120 mmHg) compared to the standard treatment group (a systolic blood pressure target of <140 mmHg) (15). In the SPRINT trial, however, patients with a history of diabetes were excluded.

This multicenter randomized controlled trial will test the primary hypothesis of whether an intensive treatment strategy (a systolic blood pressure target of <120 mmHg) is more effective than a standard treatment strategy (a systolic blood pressure target of <140 mmHg) in reducing the risk of major cardiovascular disease (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) over a follow-up period of up to 5 years among patients with a history of diabetes and elevated systolic blood pressure. The secondary hypotheses are to compare the intensive blood pressure treatment strategy with the standard treatment strategy on total stroke (fatal and non-fatal stroke), total myocardial infarction (fatal and non-fatal myocardial infarction), heart failure (treated or hospitalized heart failure and heart failure death), cardiovascular disease mortality, all-cause mortality, cognitive function, kidney outcomes, quality of life, *etc.*

The trial will recruit 12,702 patients from approximately 150 hospitals within the China Diabetes Clinical Research Network. Eligible criteria include men and women aged ≥50 years; type 2 diabetes mellitus; elevated systolic blood pressure; and a history of clinical cardiovascular disease or increased risk for cardiovascular disease. Main exclusion criteria

include known secondary cause of hypertension, symptomatic heart failure, end-stage renal disease, and other serious illness. The current trial has 90% statistical power to detect a 20% reduction (hazard ratio of 0.80) in major cardiovascular disease between intensive and standard treatment groups at a 2-sided significance level of 0.05. We further assume an event rate of major cardiovascular disease of 2.0% per year in the control arm based on 3.8-year follow-up data from the China Cardiometabolic Disease and Cancer Cohort (4C) study, 2-year uniform recruitment period, total study length of 5 years, and 2% per year rate of loss to follow-up.

To achieve the study objectives, we plan to perform the following specific aims:

1. Recruit 12,702 study participants who meet the eligibility criteria and randomly assign 6,351 to the intensive blood pressure treatment and 6,351 to the standard blood pressure treatment groups;

2. Achieve and maintain two-level targets of systolic blood pressure (<120 mmHg vs. <140 mmHg);

3. Employ a study-wide strategy to encourage standard of care for all participants for the treatment of type 2 diabetes and dyslipidemia other than blood pressure;

4. Obtain clinical data on study outcomes for up to 60 months of follow-up among all trial participants;

5. Perform strict quality control procedures for intervention and data collection;

6. Conduct data analysis according to the intention-to-treat principle; and

7. Disseminate the study findings to influence clinical practice and clinical guidelines.

Impact: The optimal blood pressure levels for reducing cardiovascular disease and all-cause mortality in patients with type 2 diabetes have not been well defined. The findings from this trial will provide evidence as to whether intensive blood pressure management to achieve a systolic blood pressure target of <120 mmHg has additional benefits over standard management of systolic blood pressure <140 mmHg. These findings will help in the development of clinical guidelines for blood pressure management among patients with type 2 diabetes and will have important clinical impact.

Chapter 1 – Introduction and Rationale

1.1 Epidemic of Type 2 Diabetes Mellitus

The global age-standardized prevalence of type 2 diabetes increased from 4.3% (95% CI 2.4 to 7.0%) in 1980 to 9.0% (7.2 to 11.1%) in 2014 in men, and from 5.0% (2.9 to 7.9%) to 7.9% (6.4 to 9.7%) in women (16). The number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014 (16). In the same period, the prevalence of diabetes in China has increased even more strikingly and has now reached epidemic proportions (5). For example, the prevalence of diabetes was less than 1% in the Chinese population in 1980 (17). In subsequent national surveys conducted in 1994, 2000-2001, and 2007, the prevalence of diabetes was 2.5%, 5.5%, and 9.7%, respectively (4,18,19). The recent national survey in 2010 reported that the overall prevalence of diabetes was estimated to be 11.6% (95% CI, 11.3 to 11.8%) in the Chinese adult population, representing an estimated 113.9 million adults in China with diabetes (5). Although different sampling methods, screening procedures, and diagnostic criteria were used, these data document a rapid increase in diabetes in the Chinese population.

1.2 Type 2 Diabetes, Hypertension and Risk of Cardiovascular Disease

Individuals with type 2 diabetes are at elevated risk for a number of serious health problems, including cardiovascular disease (CVD), kidney failure, dementia, and premature death (20-22). It was estimated that, worldwide, 1,490,000 deaths from coronary heart disease (CHD) and 709,000 from stroke were attributable to high blood glucose, in addition to 959,000 deaths directly assigned to diabetes (21).

Hypertension is common in patients with type 2 diabetes and confers an elevated risk of CVD (23). For example, the prevalence of hypertension was 66.3% in patients with a history of diabetes, compared to 21.9% in those with normal glucose regulation in Chinese adults (24). More troublesome, the hypertension control rate was only 4.7% in patients with a history of diabetes, compared to 19.6% in those with normal glucose regulation. Hypertension is an important and modifiable risk factor for CVD in patients with type 2 diabetes and the results of prospective cohort studies suggest that 35% to 75% of the cardiovascular risk in patients with diabetes can be attributed to hypertension (25,26).

1.3 Blood Pressure Lowering Clinical Trials

Randomized clinical trials have demonstrated the benefit (reduction in the risk of CVD and all-cause mortality) of lowering blood pressure (BP) to <140 mmHg systolic and <90 mmHg diastolic in patients with diabetes (12,13). For example, in a meta-analysis of 40 clinical trials (100,354 participants), each 10–mmHg lower systolic BP was associated with a significantly lower risk of mortality (relative risk [RR] 0.87, 95% CI 0.78-0.96) and

cardiovascular events (RR 0.89, 95% CI 0.83-0.95). The mean achieved systolic BP in the active treatment group at the end of intervention was 139 mmHg among the included trials (12). There are limited data from clinical trials on the benefit of more intensive BP control in patients with type 2 diabetes.

ACCORD (Action to Control Cardiovascular Risk in Diabetes): The ACCORD trial examined whether a lower systolic BP of <120 mmHg in patients with type 2 diabetes at high risk for CVD provided greater cardiovascular protection than a systolic BP of 130-140 mmHg (14). The ACCORD trial reported no significant difference in cardiovascular events (hazard ratio 0.88, 95% CI 0.73 to 1.06, P=0.20) or all-cause mortality (hazard ratio 1.07, 95% CI 0.85 to 1.35, P=0.55) comparing intensive BP treatment (goal <120 mmHg, average BP achieved = 119/64 mmHg) with standard treatment (average BP achieved = 143/70 mmHg). However, the incidence rate of the primary outcome in the control group was only half of the incidence rate used for sample size calculation (2.09% vs. 4% per year), leading to reduced statistical power to detect a true difference between intensive and standard blood pressure lowering groups. In addition, interaction may exist between glucose control and blood pressure control because subgroup analysis revealed a statistically significant reduction in cardiovascular risks for intensive blood pressure lowering in people assigned to standard glycemic control group whereas no significant difference in people assigned to intensive glycemic control group (p for interaction = 0.08).

ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation): The ADVANCE trial assessed the effects of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination compared to placebo on composites of major macrovascular and microvascular events (death from CVD, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease). Compared with the placebo group (141.6/75.2 mmHg), the patients treated with a single-pill, fixed-dose combination of perindopril and indapamide experienced an average reduction of 5.6 mmHg in systolic and 2.2 mmHg in diastolic BP with a final BP of 136/73 mmHg in the treated group (27). The primary outcome (major macrovascular or microvascular event) was significantly reduced by 9% (hazard ratio 0.91, 95% CI 0.83 to 1.00, p=0.04) but not CVD (hazard ratio 0.92, 95% CI 0.81 to 1.04, p=0.16). All-cause death was reduced by 14% (hazard ratio 0.86, 95% CI 0.75 to 0.98, p=0.03). ADVANCE trial tested intensive vs. standard blood pressure lowering strategies rather than different blood pressure lowering targets. In addition, there were no blood pressure criteria for inclusion.

SPRINT (Systolic Blood Pressure Intervention Trial): SPRINT was a multicenter, randomized controlled trial comparing a systolic BP target of <120 mmHg (intensive treatment) with a target of <140 mmHg (standard treatment) on a composite outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from

cardiovascular causes (15). The SPRINT trial showed that compared to standard treatment, intensive treatment significantly lowered cardiovascular events (hazard ratio 0.75, 95% CI 0.64 to 0.89, p<0.001) and all-cause mortality (hazard ratio 0.73, 95% CI 0.60 to 0.90, P=0.003) among 9,361 patients with a systolic BP of ≥130 mmHg and an increased CVD risk, but without diabetes (15). The risk of incident stroke was not significantly different (hazard ratio 0.89, 95% CI 0.63 to 1.25, p=0.50) between the intensive treatment and standard treatment groups. Patients with diabetes were excluded from participating in this trial, so the results have no direct implications for BP management in this population.

In summary, uncertainty remains about the optimal systolic BP levels for the prevention of CVD and all-cause mortality among patients with diabetes.

1.4 Clinical and Public Health Significance

CVD and stroke are the leading causes of death in the world and in China and have a huge public health impact on society as a whole (1-3). Over the past several decades, type 2 diabetes has reached epidemic proportions in China (4,5). Hypertension is the most common modifiable risk factor for CVD and stroke in patients with diabetes and contributes to 35% to 75% of the cardiovascular risk (25,26). Previous clinical trials have demonstrated that BP reduction lowers the risk of CVD and all-cause mortality among patients with diabetes (12,13). However, the most appropriate target for BP reduction in patients with diabetes is uncertain. In the ACCORD trial, no significant overall difference in cardiovascular events or all-cause mortality between patients with diabetes assigned to a systolic BP target of <120 mmHg and those assigned to a target of <140 mmHg was observed (14). In the recently published SPRINT trial, the risks of cardiovascular events and all-cause mortality were significantly reduced in patients randomized to the systolic BP target of <120 mmHg compared to the systolic BP target of <140 mm Hg) (15). In the SPRINT trial, however, patients with a history of diabetes were excluded.

This trial will test the hypotheses of whether intensive BP management to achieve a systolic BP target of <120 mmHg has additional benefits over standard management of systolic BP <140 mmHg in patients with diabetes. The findings from this trial will help in the development of clinical guidelines for BP management among patients with diabetes.

Chapter 2 – Objectives

The primary objective of this randomized controlled trial is to determine whether randomization to an antihypertensive treatment strategy achieving systolic BP <120 mmHg is more effective than a treatment strategy achieving systolic BP <140 mmHg in reducing the risk of major CVD events (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) among patients with diabetes over a follow-up period of up to 5 years. Other important study objectives are to assess the impact of different systolic BP treatment goals on the risk of total stroke, total myocardial infarction, treated or hospitalized heart failure, CVD mortality, all-cause mortality, kidney outcomes, cognitive function, quality of life, *etc.* Target systolic BP goals will be <120 vs. <140 mmHg in the intensive vs. standard treatment group.

2.1 Primary Hypothesis

In patients with diabetes, aged ≥50 years, and with a systolic BP ≥140 mmHg (or systolic BP ≥130 mmHg if on ≥1 medication), does a treatment strategy that targets a systolic BP of <120 mmHg reduce the risk of major CVD events (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) compared to a strategy that targets a systolic BP of <140 mmHg over a follow-up period of up to 5 years?

2.2 Subgroup Hypotheses

Is the effect of an intervention achieving systolic BP <120 mmHg vs. systolic BP <140 mmHg on the primary study outcome (major CVD) consistent in the following subgroups?

- Age at baseline (<65 vs. ≥65 years; <80 vs. ≥80 years)
- Men vs. women
- Previous CVD
- Previous chronic kidney disease (CKD, eGFR<60 ml/min/1.73 m^2)
- Systolic BP levels at baseline (tertiles)
- HbA1c at baseline (tertiles)
- Diabetes duration at baseline (< vs. ≥ the median)
- High BP duration at baseline (< vs. ≥ the median)

Subgroups will be defined using data collected at the screening visit except for those not collected, in which case data collected at the baseline visit will be used.

2.3 Secondary Hypotheses

2.3.1 Secondary outcomes

Does a treatment strategy that targets a systolic BP of <120 mm Hg reduce the risk of the following secondary CVD outcomes compared to a strategy that targets a systolic BP of <140 mm Hg?

- An expanded outcome including the composite primary outcome and all-cause mortality
- Macrovascular outcome including the composite primary outcome, hospitalized unstable angina, and all cardiovascular revascularization procedures (defined in 'other outcomes')
- Major coronary artery diseases including non-fatal MI, hospitalized unstable angina, revascularization of coronary arteries, and deaths due to coronary artery diseases
- Total MI including fatal and non-fatal MI
- Total stroke including fatal and non-fatal stroke
- Ischemic stroke
- Hemorrhagic stroke
- Hospitalized or treated heart failure, or heart failure death
- Cardiovascular death
- Total mortality
- Cognitive function
- Health related quality of life

2.3.2 Kidney outcomes

- Progression of CKD: In patients with CKD, we will determine whether a treatment strategy that targets a systolic BP of <120 mmHg slows CKD progression (a composite outcome of end-stage renal disease, eGFR<15 ml/min/1.73 m^2, or 50% decline in eGFR from baseline) compared to a strategy that targets a systolic BP of <140 mmHg.

- Development of CKD: In patients without CKD, we will determine whether a treatment strategy that targets a systolic BP of <120 mmHg reduces the risk of CKD (eGFR <60 ml/min/1.73 m^2 and 30% decrease from baseline eGFR) compared to a strategy that targets a systolic BP of <140 mmHg.

- Incident albuminuria: In all patients with or without CKD, we will determine whether a treatment strategy that targets a systolic BP of <120 mmHg reduces the risk of albuminuria (a doubling of urinary albumin-to-creatinine ratio [ACR] from a value <10 mg/g to a value of >10 mg/g) compared to a strategy that targets a systolic BP of <140 mmHg. In addition, changes in urinary ACR levels will be compared as sensitivity analysis.

2.3.3 Other outcomes

- All cardiovascular revascularization procedures including percutaneous transluminal coronary angioplasty (PTCA) with balloon or stent, coronary artery bypass grafting (CABG), carotid angioplasty with stent, carotid endarterectomy, peripheral angioplasty

with or without stent, peripheral vascular surgery (including aortic aneurysm repair) and limb amputation including partial or digit amputation due to vascular disease

- Hospitalized unstable angina
- Retinopathy
- Transient ischemic attack (TIA)
- Left ventricular hypertrophy (LVH) diagnosed by ECG
- Atrial fibrillation or flutter
- All cancers
- Cost-effectiveness

2.3.4 Adverse effects

- Symptomatic hypotension
- Arrhythmia
- Acute renal failure
- Electrolyte abnormalities
- Injurious falls
- Syncope

Chapter 3 – Participant Selection and Recruitment

3.1 Eligibility Criteria

The current trial will compare the intensive and standard BP treatment strategies on the risk of CVD. Thus, the trial will be conducted among diabetes patients aged ≥50 years with elevated systolic BP and increased risk of CVD.

a) Inclusion Criteria

1. Men and women aged ≥50 years
2. Diabetes defined as (28):

- A self-reported previous diagnosis by health care professionals and taking anti-diabetic medications;
- Fasting plasma glucose level of ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours;
- 2-hour plasma glucose level of ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; or
- HbA1c concentration of ≥6.5% (48 mmol/mol)

- The diagnosis of diabetes must be confirmed on a subsequent day by repeat measurement, repeating the same test for confirmation. However, if two different tests are available and are concordant for the diagnosis of diabetes, additional testing is not needed. If two different tests are discordant, the test that is diagnostic of diabetes should be repeated to confirm the diagnosis.

3. Systolic blood pressure

- ≥140 mmHg on 0 medication;
- 130-180 mmHg on 1 medication;
- 130-170 mmHg on up to 2 medications;
- 130-160 mmHg on up to 3 medications; or
- 130-150 mmHg on up to 4 medications

- There are no diastolic BP inclusion criteria. If a screenee is otherwise eligible for the current trial but presents with a treated BP and/or number of medications that fall outside the inclusion criteria, BP-lowering medications may be adjusted prior to the randomization visit to determine whether, with such adjustments, the screenee will meet

eligibility criteria. A screenee who presents on no BP medications should have documentation of systolic BP ≥140 mmHg on 2 visits within 3 months prior to the randomization visit in order to be eligible for the trial.

4. Increased risk of cardiovascular disease (one or more of the following):

- Previous history of clinical CVD (≥ 3 months)
  - Stroke
  - Myocardial infarction
  - Percutaneous coronary intervention (PCI) or CABG
  - Carotid endarterectomy or carotid stenting
  - Peripheral artery disease (PAD) with revascularization
  - Acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test, or positive cardiac imaging study
- Subclinical CVD within 3 years
  - Microalbuminuria
  - ≥50% stenosis of a coronary, carotid, or lower extremity artery
  - Coronary artery calcium score ≥400 Agatston units
  - Ankle brachial index (ABI) ≤0.90
  - Left ventricular hypertrophy

If microalbuminuria is the only criterion satisfied for increased risk of cardiovascular disease, replication to confirm is required.

- 2 or more CVD risk factors
  - Current cigarette smoking
  - Body-mass index (BMI) ≥28 kg/m^2 or waist circumference ≥90 cm (in men) or ≥85 cm (in women)
  - Current lipid-lowering medications or LDL-cholesterol ≥130 mg/dl (3.38 mmol/l)
  - Current lipid-lowering medications or HDL-cholesterol <40 mg/dl (1.04 mmol/l)
  - Current lipid-lowering medications or triglycerides ≥150 mg/dl (1.69 mmol/l)
- Estimated glomerular filtration rate (eGFR) 30-59 ml/min/1.73 m^2

b) Exclusion Criteria

1. History consistent with type 1 diabetes

2. Known secondary cause of hypertension (including procedures for renal artery disease)
3. One minute standing systolic BP <110 mmHg
4. Arm circumference too large to allow accurate blood pressure measurement with available devices
5. Cardiovascular event or procedure (as defined above as clinical CVD for study entry) or hospitalization for unstable angina within the past 3 months
6. Symptomatic heart failure or left ventricular ejection fraction (by any method) <35% within the past 6 months
7. ALT or AST levels more than twice the upper limit of the normal range or active liver diseases
8. Dialysis or eGFR <30 ml/min/1.73 m^2 or serum creatinine >2.0 mg/dl
9. Proteinuria
    - 24-hour urinary protein excretion ≥1 g/d, or
    - 24-hour urinary albumin excretion ≥600 mg/d, or
    - Spot urine protein/creatinine ratio ≥1 g/g, or
    - Albumin/creatinine ratio ≥600 mg/g
10. Previous diagnosis of polycystic kidney disease or glomerulonephritis
11. A medical condition likely to limit survival to less than 5 years
12. Any factors judged by the clinic team to be likely to limit adherence to interventions:
    - Active alcohol or substance abuse within the last 12 months
    - Significant history of poor compliance with medications or attendance at clinic visits
    - Residence too far from the study clinic site, or plans to move outside the clinic catchment area in the next 5 years
    - Clinical diagnosis of dementia, treatment with medications for dementia, or in the judgment of the clinician cognitively unable to follow the protocol
    - Other medical, psychiatric, or behavioral factors that in the judgment of the research staff may interfere with study participation or the ability to follow the intervention protocol
13. Failure to obtain informed consent from participant
14. Currently participating in another intervention study
15. Currently living with another BPROAD participant

16. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not using birth control

3.2 Participant recruitment

Participants will be recruited from hospital visits at outpatient and inpatient department of Endocrine and Metabolic Diseases at each study sites. Retrospective review of medical records for potential participants can also be conducted at study sites where electronical medical record system is accessible. A brief screening form with simple questions such as age, history of diabetes and hypertension, and the willingness to participate will be completed at outpatient and inpatient departments. Potential participants will be contacted by study staff and a screening visit will be arranged, during which the written informed consent will be obtained, and a detailed inquisition of medical history, physical examination, and biochemical evaluation if necessary, will be conducted to assess eligibility according to study inclusion and exclusion criteria.

3.3 Randomization and blindness

Information of eligible patients such as medical records and measurement results will be entered into the electronic data capture system and reviewed by staff at the Coordinating Center, who will review item-by-item inclusion and exclusion criteria and queries will be sent to study staff at study sites if confirmations are needed regarding participant eligibility. After eligibility is confirmed at the Coordinating Center, the electronic data capture system will generate a randomization number and the participant will be assigned to either treatment groups. The randomization will be conducted on stratification of study sites. At each study site, block randomization will be used with randomly selected block sizes of 2, 4, and 6. Study investigators at each study sites will be informed of the assignment of specific participants via the electronic data capture system.

Because BPROAD is a trial comparing 2 different levels of systolic BP control in patients with diabetes, blindness is not possible for study participants and study physician. However, study staff collecting information on study outcomes will be blinded to treatment assignment. In addition, adjudicators of study outcomes as well as statisticians will also be blinded to treatment assignment (Table 1).

Table 1. Study personnel and their required state of blinding

Study personnel	**Blinding**
Study physician	Not blinded
Study staff collecting information on study outcomes	Blinded
Members of the executive committee	Blinded
Adjudicators of study outcomes	Blinded
Statisticians	Blinded
Members of the Coordinating Center who present data to the DSMB at the closed session	Not blinded
Safety officer at the Coordinating Center	Not blinded

Chapter 4 – Interventions

4.1 Blood pressure goals

Participants eligible for the trial will be randomized to one of two goals:

- Systolic BP <120 mmHg for the intensive treatment group
- Systolic BP <140 mmHg for the standard treatment group

Although there are no diastolic BP inclusion criteria, participants in both groups with diastolic BP ≥90 mmHg will be treated to a diastolic BP goal of <90 mmHg if needed after meeting the systolic BP goal based on clinical guidelines.

4.2 Antihypertensive agents

Use of once-daily preparations of antihypertensive agents will be encouraged unless alternative dosing frequency (e.g., BID) is indicated/necessary. One or more medications from the following classes of agents will be intended for use in managing participants in both randomization groups to achieve study goals:

- Angiotension converting enzyme-inhibitors (ACEIs)
- Angiotension receptor blockers (ARBs)
- Calcium channel blockers (CCBs)
- Thiazide-type diuretics
- Loop diuretics
- Potassium-sparing diuretics
- Beta-blockers
- Alpha1-receptor blockers
- Sympatholytics
- Direct vasodilators

Combination products of different classes will also be used.

4.3 Selection of antihypertensive medications

The current trial will test a treatment strategy question regarding different systolic BP goals and not test specific medications. Therefore, the BP treatment protocol is flexible in terms of the choice and doses of antihypertensive medications, but there should be preferences among the drug classes, based on CVD outcome trial results and current clinical guidelines. The new 2018 Chinese Guidelines for the Prevention and Management of

Hypertension will be recommended to guide drug choices. In addition, updates of hypertension recommendations in Chinese adults, along with any new scientific developments, will be considered during and following BPROAD protocol development and throughout the trial.

The study physician may select among the available antihypertensive medications for initiation of therapy. Other drugs may also be used as the study physician determines appropriate. However, all antihypertensive regimens should include one or more drug classes with strong CVD outcome data from large randomized controlled hypertension trials, i.e., a thiazide-type diuretic, CCB, ACEI, or ARB. All major antihypertensive drug classes (i.e., ACE inhibitors, ARBs, CCBs, and diuretics) are useful in the treatment of hypertension in diabetes. ACEIs and ARBs have the best efficacy among the drug classes on urinary albumin excretion. Therefore, an ACEI or ARB may be considered as part of the combination. A meta-analysis of RCTs of primary prevention of albuminuria in patients with diabetes demonstrated a significant reduction in progression of moderately to severely increased albuminuria with the use of ACEIs or ARBs. However, the combination of an ACEI and an ARB should be avoided. The preference for the order in which these agents are selected is left to the study physician as long as the systolic BP goals are achieved.

Since more than three drugs will be necessary in many participants to reach the intensive systolic BP goal, other classes of antihypertensive agents will also be used in the current study. These include the potassium-sparing diuretics, spironolactone and/or amiloride, which are very effective as add-on agents for BP-lowering in “resistant hypertension” (29). However, they should be used with careful monitoring in participants with CKD or any tendency to hyperkalemia. Alpha-blockers have been used effectively as add-on therapy in clinical trials, including AASK and ACCORD. However, alpha-blockers should be used only in combination with one or more other agents proven to reduce CVD events in hypertensive patients (30). Sympatholytics, direct vasodilators, and/or loop diuretics may also be added for BP control in combination with agents proven to reduce CVD events.

The SPRINT trial has shown that a treatment strategy that includes a variety of antihypertensive agents can produce a 14.8 mmHg difference in systolic BP reduction between the two randomized groups (15). The average number of antihypertensive drugs used to produce this difference was 2.8 and 1.8 in the intensive and standard treatment groups, respectively (15).

Algorithm of blood pressure lowering therapy in people with diabetes recommended by the American Diabetes Association can be used as treatment reference (Figure 1).

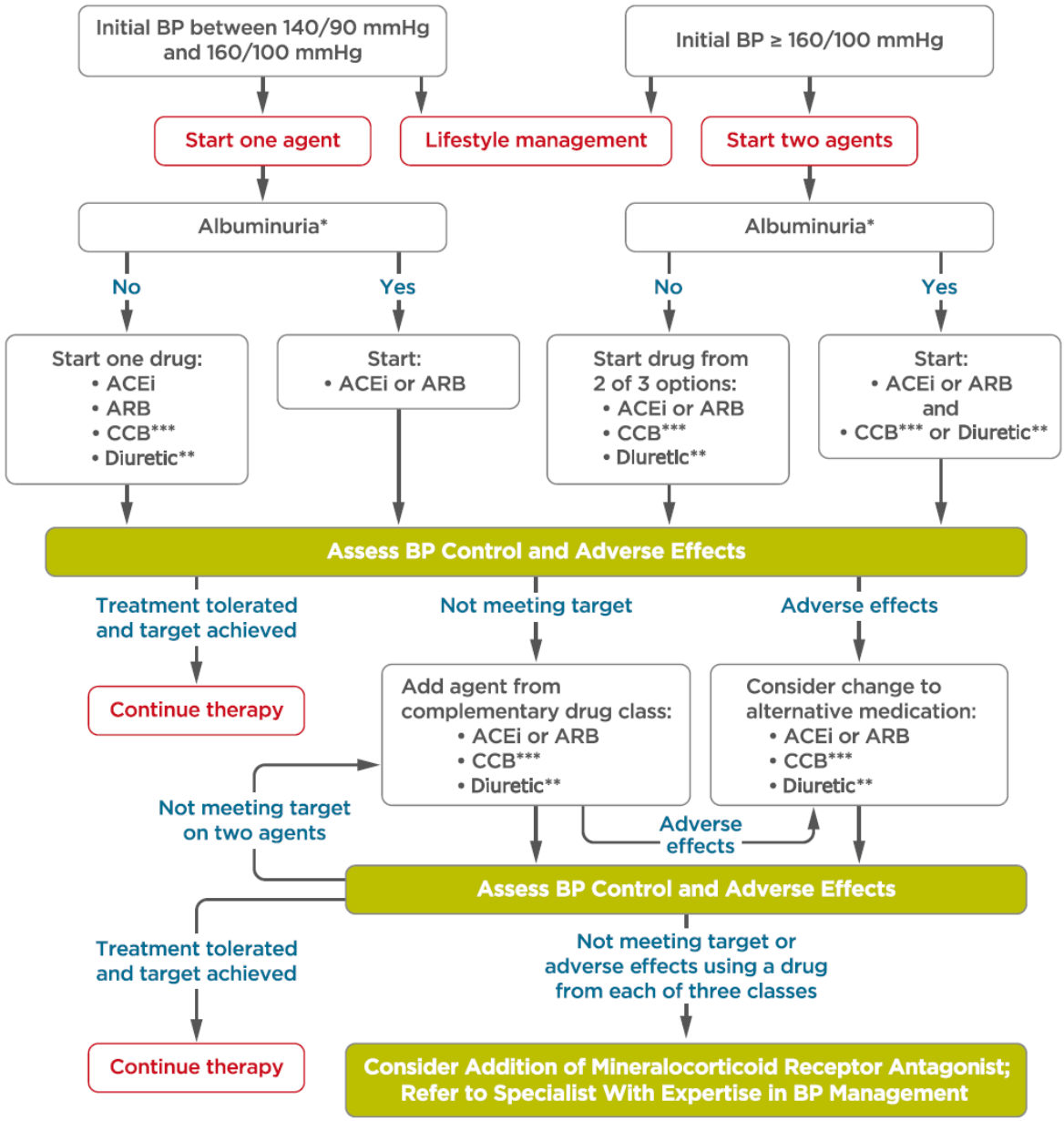


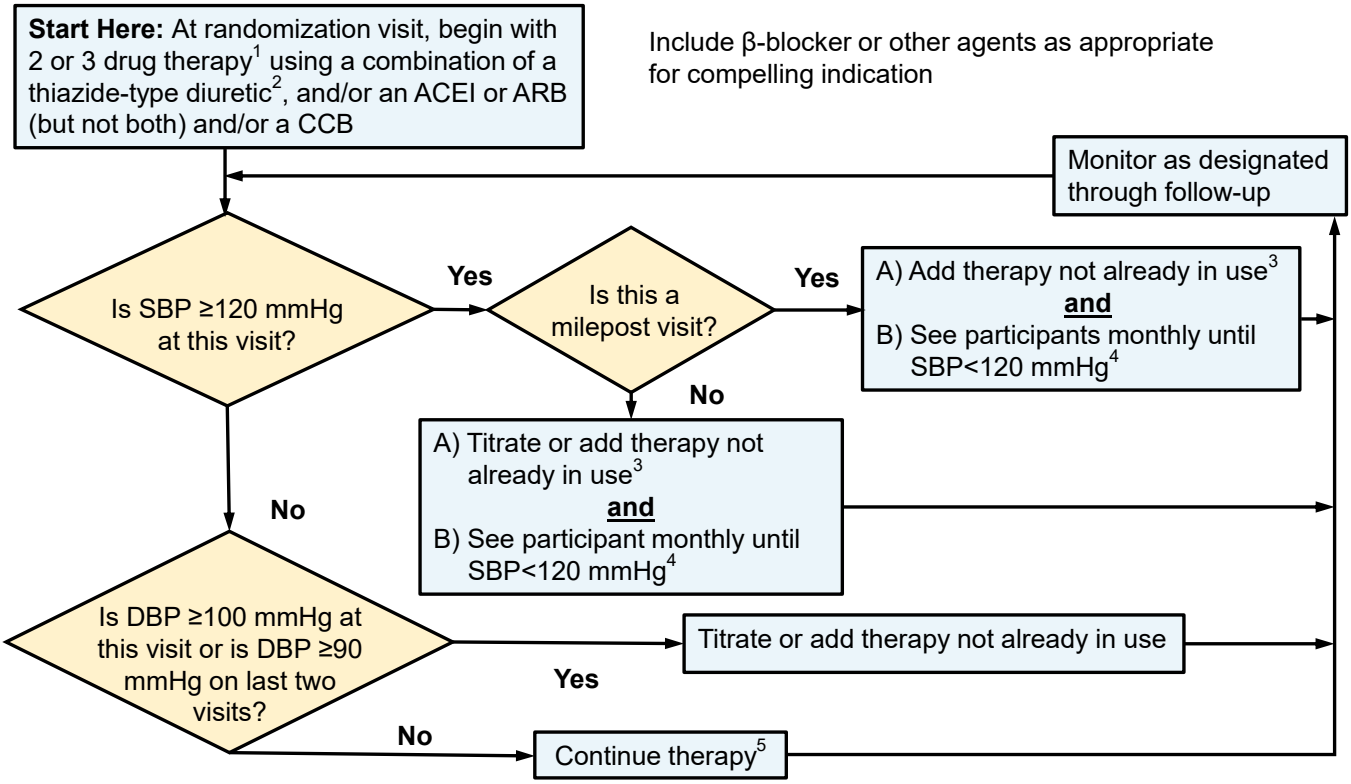
Figure 1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with UACR 30–299 mg/g creatinine and strongly recommended for patients with UACR ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine. BP, blood pressure.

4.4 Protocol visits

For both randomized groups, protocol visit frequency will be monthly for the first three months after randomization, then every three months for the duration of the trial. Monthly visits will continue in the intensive treatment group until systolic BP <120 mmHg (or no more titration planned) and in the standard treatment group until systolic BP <140 mmHg (or no more titration planned). Additional visits will be scheduled as needed for management of adverse effects or for monitoring significant medication changes or other clinical issues.

Intensive treatment group (Figure 2)

Figure 2. Treatment Algorithm for Intensive Treatment Group (Goal Systolic BP <120 mmHg)



[1] May begin with a single agent for patients ≥75 yrs with SBP<140 on 0-1 meds. A second medication should be added at the one month visit if patient is asymptomatic and SBP ≥130 mmHg. [2] May use loop diuretic for patients with advanced CKD. [3] Consider consulting a hypertension specialist before adding a fifth antihypertensive medication. [4] Or until clinical decision made that therapy should not be increased further. [5] Unless side effects warrant change in therapy.

The systolic BP goal for the intensive treatment group, <120 mm Hg, should be achievable in the majority of participants within 8-12 months of follow-up based on the ACCORD and SPRINT experience (14,15). For most participants in the intensive treatment group, a two- or three-drug regimen of a diuretic and either an ACEI or ARB and/or a CCB should be initiated at randomization. If a diuretic is contraindicated or not tolerated, an ACEI or ARB plus a CCB should be initiated. An ACEI or ARB is preferred in diabetes with albuminuria. A beta-blocker should be included in the initial regimen, if there is a compelling indication for a beta-blocker. Drug doses should be increased and/or additional antihypertensive medications should be added at each visit in the intensive treatment group, usually at monthly intervals, until the participant's goal of <120 mmHg has been reached or the study physician decides no further antihypertensive medications may be added.

For participants aged ≥75 years in the intensive treatment group who are on 0-1 antihypertensive medications and have baseline systolic BP <140 mmHg, antihypertensive therapy may be initiated with a single agent at the discretion of the study physician with a return visit scheduled in one month. If the participant is asymptomatic at the first post-randomization visit and systolic BP ≥130 mmHg, a second agent will be added and titration

continued as indicated above.

Milepost Visits: It has been observed in both clinical practice and clinical trials that clinicians fail to intensify therapy despite patients not being at BP goal. Therefore, milepost visits were used in the intensive treatment group in the ACCORD and SPRINT trials to assist in reaching goal systolic BP (14,15). In the BPROAD trial, milepost visits will be every 6 months throughout follow-up in the intensive treatment group, beginning at the 6-month visit. If the systolic BP is not <120 mm Hg at a milepost visit, then an antihypertensive drug from a class different from what is being taken should be added, unless there are compelling reasons to wait. A "Milepost Exemption Form" will be completed whenever a new drug is not added at a milepost visit in which the participant's systolic BP is not <120 mm Hg to document the reason for not adding a drug and to outline a plan for making progress toward goal in that participant. Milepost visit procedures do not apply to the standard treatment group. Once the intensive treatment group participant has been prescribed 5 drugs at maximally tolerated doses, if the BP remains above goal at subsequent milepost visits, it will be permitted to substitute a different class into the regimen instead of adding another drug or increasing the dose of a drug. However, additional (more than 5) drugs may be needed to achieve goal systolic BP in some participants. Medication adherence will be assessed routinely in the current trial and should be evaluated especially carefully for participants not at goal on 4 or more medications. Strategies to enhance adherence should be applied.

Standard treatment group (Figure 3)

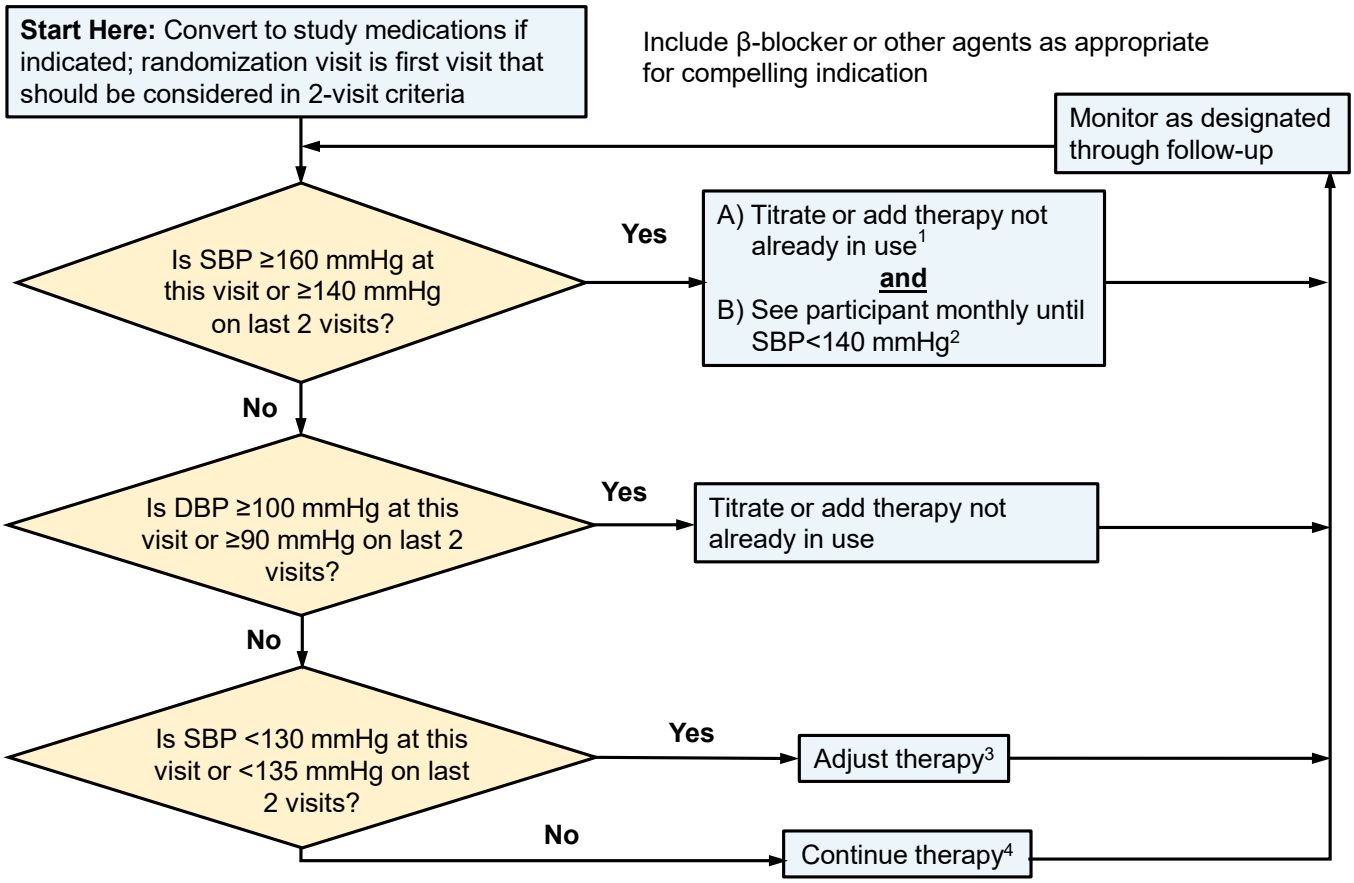
The systolic BP goal for the standard treatment group, <140 mmHg, should be achievable in the majority of participants within 3-6 months, based on experience from the ACCORD and SPRINT trials (14,15). The standard treatment protocol is designed to achieve a systolic BP of 135-139 mmHg in as many participants as possible. Participants in this group may or may not be on treatment with one or more antihypertensive medications. If antihypertensive medication(s) is indicated per protocol, consideration should be given to first-line drug classes such as the ACEIs/AREs, CCBs, and the thiazide-type diuretics as initial therapy, unless there is a compelling indication for another drug class. An ACEI or ARB is preferred in diabetes with albuminuria.

At the randomization visit, standard treatment group participants on previous antihypertensive drug therapy can be converted to the trial medications or no medications, depending on what the study physician believes is most likely to achieve a systolic BP level between 135-139 mmHg. Because we expect a decrease in average systolic BP within the standard treatment group following randomization due to improved adherence, lifestyle counseling, and "regression to the mean", treatment should not be intensified at the randomization visit for standard treatment group participants unless systolic BP ≥160 mmHg or there is a compelling reason to add medication. Following the randomization visit,

medication dose titration or addition of another drug is indicated if systolic BP is ≥160 mmHg at a single visit or is ≥140 mmHg at two successive visits.

Because it is not known if lowering systolic BP to the more intensive goal of <120 mmHg, compared with the standard goal of <140 mmHg, is beneficial, neutral, or harmful in patients with diabetes, careful adjustment of therapy (perhaps a reduction of the dose or number of antihypertensive drugs at the discretion of the BPROAD physician, after consultation with the participant) is allowed for participants in the standard treatment group. Down-titration was not permitted in the HOT Trial if diastolic BP was well below the goal for a participant – this likely contributed to the small differences in achieved BP between the three randomized groups and limited the study's ability to detect differences in outcomes (31). Therefore, down-titration was included in the ACCORD and SPRINT standard BP protocols and was successful in generating the planned differences in BP between treatment arms. Down titration can be carried out in BPROAD standard treatment group if the systolic BP is <130 mmHg at a single visit or <135 mmHg at two consecutive visits.

Figure 3. Treatment Algorithm for Standard Group (Goal Systolic BP <140 mmHg)



[1] Consider consulting a hypertension specialist before adding a fifth antihypertensive medication. [2] Or until clinical decision made that therapy should not be increased further. [3] This is allowed at the discretion of the BPROAD physician, after consultation with the participant. [4] Unless side effects warrant change in therapy.

4.5 Diastolic blood pressure treatment

Once the systolic BP goal has been achieved in any participant, the antihypertensive regimen should be intensified if diastolic BP remains ≥100 mmHg at a single visit or ≥90 mmHg at two successive visits to achieve diastolic BP <90 mm Hg. The visit intervals and decisions for titration (other than the BP levels) will be similar to those used for the systolic BP goal. Since beta-blockers reduce diastolic BP more than systolic BP relative to other antihypertensive medications, a beta-blocker could be considered for such participants.

4.6 Use of home BP devices

The study committee recognizes that home BP readings are subject to more bias and error and virtually all BP outcome trials have used office BP determinations, therefore titration of medications to goal will be based on office readings rather than home BP determinations. However, since the first outbreak of the coronavirus disease 2019 (COVID-19) in early 2020 in mainland China, there are lockdowns in cities, counties, or hospitals, during which the in-person follow-up of BPROAD participants with their doctors/investigators is difficult. During these times, home BP monitoring using an electronic BP measurement device (OMRON HEM-7121) according to a standard monitoring procedure (as detailed in the 'BPROAD Response Plan to the Outbreak of Coronavirus Disease 2019 (COVID-19) in Mainland China') will be used for BP levels and control.

4.7 Assessment of orthostatic hypotension, measurement of standing blood pressure

Standing BP will be measured at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter using the same BP device that is used to measure seated BP. After seated determinations, participants will be asked to stand. Beginning when their feet touch the floor, BP will be taken one minute later in the same arm used for the seated measurements, using the same BP device. Participants will be asked after the standing determination if they had any symptoms of orthostatic hypotension during the standing BP measurement. BP change using the standing measurements minus the mean of the seated measurements will be calculated. If the systolic BP decreases ≥20 mmHg or the diastolic BP decreases ≥10 mmHg when compared with BP from the sitting position, with or without symptoms, will be diagnosed as orthostatic hypotension.

Participants with 1-min standing systolic BP <110 mmHg will not be eligible for randomization. However, the detection of asymptomatic orthostatic hypotension, i.e., orthostatic hypotension unaccompanied by orthostatic symptoms of dizziness, presyncope, or syncope, will not influence the antihypertensive drug treatment algorithm. Symptomatic orthostatic hypotension will be managed according to a standard protocol.

4.8 Standard care for diabetes and lifestyle recommendations

The purpose of including standard background therapy and lifestyle recommendations in the current trial is twofold. First, it fosters high quality general medical care in all study participants in accordance with current practice guidelines. Second, it is intended that background therapies will be utilized equally across both study arms in order to minimize the differences in the effects of non-study strategies on the systolic BP or CVD outcomes between arms. The background therapy recommendations will be provided to the participants and their physicians based on the clinical guidelines of the Chinese Diabetes Society and the American Diabetes Association (32,33). Background therapy is considered part of usual recommended care for patients with diabetes. The delivery of these background therapies will be left up to the participants' own clinicians.

Chapter 5 – Clinical Outcome Measures

Clinical events occurring during follow-up will be ascertained equally in both treatment arms through surveillance of self-reported events and medical record data collected by the study staff. All clinical outcomes will be adjudicated by members of an Outcome Assessment Committee who will be masked to treatment assignment. At least two committee members will review the medical records independently.

5.1 Primary outcome

The primary outcome measure for BPROAD will be major cardiovascular events, defined as the composite endpoint of the first occurrence of non-fatal stroke, non-fatal myocardial infarction, hospitalized or treated heart failure, and cardiovascular deaths.

Stroke

We will use standard case definitions for both fatal and nonfatal stroke. Stroke will be defined based on all available data, including symptoms and signs, imaging of the brain and large vessels, and cardiac testing, e.g., echocardiography. Adjudicators will use their clinical judgment based on the available evidence to classify each case, and will be guided by pre-specified definitions and operational rules. Stroke is generally defined as neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours (World Health Organization, 1978 Cerebrovascular Disorders. Geneva: World Health Organization. ISBN 9241700432). Exclusionary conditions for stroke include major brain trauma, intracranial neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous system infections. Stroke will be classified as ischemic stroke, subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, other type, or unknown type. In the BPROAD trial, ischemic stroke is defined as a new lesion detected by computed tomography or magnetic resonance imaging or, in the absence of a new lesion on available imaging, clinical findings consistent with the occurrence of stroke that lasted for more than 24 hours (34). Ischemic stroke will be further sub-typed using the Causative Classification of Stroke system as evident, probable, or possible cases of large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes (35).

Myocardial infarction (MI)

MI will be defined as the death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombus, or rupture of a plaque. We will use standard case definitions for both fatal and nonfatal MI based on the combination of symptoms, elevation in biomarkers, and/or ECG findings. The algorithm for classifying

MI includes elements of the clinical presentation (signs and symptoms), results of cardiac biomarker determinations, and ECG readings, and is based on the SPRINT criteria (15). The definition includes MI that occurred during surgery/procedure and MI aborted by thrombolytic therapy or procedure. The study adjudicators will be guided by specific, pre-specified definitions and operational rules. Adjudicators will use their clinical interpretation of the ECGs and other available evidence for the event to classify MI cases as definite, probable, or possible, with all included in the primary outcome (36). MI will be ascertained both from adjudication of hospital records for clinical events and also from the finding of new significant Q waves from the standardized interpretation of the study visit-obtained ECG (silent or unrecognized MI). MIs that present clinically will include Q wave, ST elevation and non-ST elevation infarctions (segment elevation myocardial infarction (STEMI), and non-ST segment elevation myocardial infarction (NSTEMI)), as well as aborted MI and post-intervention MI.

Heart failure (HF)

HF will be defined as hospitalization, or emergency department visit requiring treatment with infusion therapy, for a clinical syndrome that presents with multiple signs and symptoms consistent with cardiac decompensation/inadequate cardiac pump function. Only a hospitalization for decompensated HF or an emergency department visit where decompensated HF was diagnosed and intravenous treatment was given will be a potential HF outcome. Thus, diagnosis and treatment of HF by a physician or other provider in the office or clinic setting without hospital admission or an emergency department visit without intravenous therapy for decompensation will not be considered a BPROAD HF outcome. Adjudication will use the ARIC study adjudication system (37). HF outcome will include definite or possible acute decompensation, including HF with preserved left ventricular ejection fraction as well as HF with reduced ejection fraction. HF will include a variety of clinical presentations, including acute or subacute HF as the primary reason for hospital admission or for emergency department visit where HF was diagnosed and intravenous treatment was given. For HF hospitalization, we will focus on the admitting diagnoses and will consider HF hospitalization if both HF is a reason for admission AND there is evidence of new onset or progression according to hospital records; the mere presence of HF is not sufficient. The identification and classification of HF cases will rely on multiple pieces of key clinical data as well as adjudicators' clinical judgment, guided by specific, pre-specified definitions and operational rules. No identification of HF should rely on a single piece of data such as the presence of dyspnea or of edema, a low ejection fraction, or an increased brain natriuretic peptide (BNP) value. Adjudicators will use both the available data and clinical judgment to distinguish between "definite" and "possible" decompensated HF. "Definite" decompensated HF will be assigned when decompensation is clearly present based on available data (satisfies criteria for decompensation). "Possible" decompensation will be

assigned when decompensation is possibly but not definitively present, typically where the presence of co-morbidity could account for the acute symptoms (COPD exacerbation, for example).

Cardiovascular death

We will use standard case definitions for classification of CVD death. Definite CVD events will be defined based on temporal relationship to a documented event (e.g., hospitalization for MI or for stroke), or postmortem findings of an acute CVD event. Stroke deaths will be categorized based on the temporal relationship between the stroke event and death, in cases where the underlying cause of death is attributed to stroke. Proximal stroke death is a death attributed to stroke and occurring within 30 days of stroke; remote stroke death is underlying cause attributed to stroke and more than 30 days from stroke to death. Probable coronary heart disease death will be defined based on autopsy findings consistent with chronic CHD, prior history of CHD or documented symptoms consistent with CHD prior to death, and the absence of another likely cause of death (38). Possible fatal CHD will be adjudicated based on death certificate information consistent with an underlying CHD cause and no evidence of a non-coronary cause. Other forms of CVD death will also be adjudicated and include ruptured abdominal aortic aneurysm and documented arrhythmia.

5.2 Secondary outcomes

In addition to the primary outcome, the following secondary clinical outcomes will be assessed in order to more fully evaluate the effects of intensive BP intervention compared to standard BP intervention.

- An expanded outcome including the composite primary outcome and all-cause mortality
- Macrovascular outcome including the composite primary outcome, hospitalized unstable angina, and all cardiovascular revascularization procedures (defined in ‘other outcomes’)
- Major coronary artery diseases including non-fatal MI, hospitalized unstable angina, revascularization of coronary arteries, and deaths due to coronary artery diseases
- Total MI including fatal and non-fatal MI
- Total stroke including fatal and non-fatal stroke
- Ischemic stroke
- Hemorrhagic stroke
- Hospitalized or treated heart failure, or heart failure death
- Cardiovascular death
- Total mortality
- Cognitive function
- Health related quality of life

5.3 Kidney outcomes

- Progression of CKD defined as the composite of a 50% decrease in eGFR, development of end-stage renal disease requiring chronic dialysis or kidney transplantation, or eGFR<15 ml/min/1.73 m^2 in patients with CKD at baseline. The decrease in eGFR requires a confirmatory value in the next available official study laboratory check.
- Incident CKD defined as a >30% decrease in eGFR and eGFR <60 ml/min/1.73 m^2 among patients without CKD at baseline. This decrease in eGFR requires a confirmatory value in the next available official study laboratory check.
- Incident albuminuria defined as a doubling of urinary ACR from a value of <10 mg/g to a value of >10 mg/g in all patients with or without CKD. This increase in ACR requires a confirmatory value in the next available official study laboratory check. In addition, changes in urinary ACR levels will be compared as sensitivity analysis.

5.4 Other outcomes

- All cardiovascular revascularization procedures including PTCA with balloon or stent, CABG, carotid angioplasty with stent, carotid endarterectomy, peripheral angioplasty with or without stent, peripheral vascular surgery (including aortic aneurysm repair) and limb amputation including partial or digit amputation due to vascular disease
- Hospitalized unstable angina: unstable angina is new onset exertional angina, accelerated or rest angina, or both.
- Retinopathy: laser treatment, vascular endothelial growth factor (VEGF) inhibition, or surgical intervention.
- TIA: TIA is defined as one or more transient episodes of the sudden onset of a focal neurological deficit, no lesion on brain imaging consistent with the deficit, and no signs or symptoms consistent with seizures, migraine, or other non-vascular causes.
- LVH diagnosed by ECG: ECG-diagnosed LVH will be defined primarily using the sex-specific Cornell voltage criteria. Other ECG-LVH criteria mentioned in the American Heart Association (AHA)/American College of Cardiology (ACC) statement on ECG changes associated with cardiac chamber hypertrophy (Hancock and others, 2009) will be also considered.
- Atrial fibrillation or flutter: atrial fibrillation/flutter will be primarily detected from the scheduled study ECGs using Minnesota ECG classification (Minnesota code 8.3). Other sources of detection include hospital discharge ICD code (ICD-10 code 148 or ICD-9 code 427.3) and self-report.
- All cancers
- Cost-effectiveness

Chapter 6 – Participant Follow-up

6.1 Schedule of follow-up visits

Post-randomization follow-up visit schedules for data collection do not differ by treatment group assignment. However, the visit schedule for treatment, that is achieving the BP goals, may differ by group while BP goals are being met because of PRN visits not shown in **Table 2**. Additional information on treatment schedules is contained in **4.4 Protocol visits** in **Chapter 4**. For data collection in both randomized groups, all participants will have post-randomization visits at months 1, 2, 3, 6, and every 3 months thereafter. For the purpose of event ascertainment, all participants in both treatment groups will be queried regarding the occurrence of a possible event on the same schedule, specifically every 3 months.

6.2. Procedures by visit

Scheduled examination components are shown by visit in **Table 2**. Assessments performed at the various visits include blood and urine collection, physical measures, and questionnaires. Assessments will be performed on the same schedule for both randomization groups. Baseline characteristics to define the patient population include socio-demographics, anthropometrics, fasting plasma glucose, HbA1c, BP, pulse, current and past medical history, concomitant medications, laboratory chemistry, cognitive function, and quality of life measurements. A clinical routine physical examination is included for safety but is not standardized, and left to the discretion of the study physician.

6.3 Blood and urine collection and laboratory assays

Specific laboratory assessments (e.g. fasting serum glucose, HbA1c, serum creatinine, etc.) are important for determining eligibility status. During follow-up, laboratory results will be used to monitor and adjust therapy in an effort to maintain BP goals, monitor co-treatments (i.e., HbA1c, cholesterol, etc.), assess safety (e.g. serum potassium concentrations), and assess for study-related outcomes (e.g. decline in estimated glomerular filtration rate or increased proteinuria). Results from laboratories at local sites will be returned to providers of participants immediately. Results from the central laboratory at the Coordinating Center will be returned to providers of participants within 2 weeks.

Serum, plasma, urine and feces samples will be stored for future measurements of novel risk factors. White blood cells will be collected at baseline for DNA extraction for future genomic studies.

Table 2. Measurement and follow-up schedule

	Bs/ Rz	1 Mo	2 Mo	3 Mo	6 Mo	9 Mo	1 Yr	3 Mo	6 Mo	9 Mo	2 Yr	3 Mo	6 Mo	9 Mo	3 Yr	3 Mo	6 Mo	9 Mo	4 Yr	3 Mo	6 Mo	9 Mo	5 Yr/ Close out
Questionnaires																							
Medical history	X																						
SES variables	X																						
Lifestyle factors	X										X								X				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence and adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MMAS-8	X						X				X				X				X				X
Study outcomes				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examinations																							
Seated BP, pulse and medication adjustment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standing BP	X	X			X		X				X				X				X				X
Weight	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																						
Waist and hip circumference	X						X				X				X				X				X
ECG	X						X				X				X				X				X
Lab Measurements																							
Liver and kidney function, electrolytes, glucose*	X	X		X	X		X		X		X				X				X				X

Blood routine, 24-h urinary electrolytes, protein, and creatinine excretion*	X						X				X				X				X				X
Fasting blood collection																							
Serum creatinine, lipid profile, and HbA1c**	X						X				X				X				X				X
Serum storage	X						X				X				X				X				X
Plasma storage	X																						
DNA storage	X																						
Urine collection																							
Urinary albumin and creatinine**	X						X				X				X				X				X
Urine storage	X						X				X				X				X				X
Feces collection	X																						X
Cognitive function	X						X				X				X				X				X
Health related quality of life																							
SF-12	X						X				X				X				X				X
PHQ-9	X						X				X				X				X				X
EQ-5D-5L	X						X				X				X				X				X

Bs/Rz=baseline and randomization visits; SES=socioeconomic status; MMAS=The Morisky Medication Adherence Scale; BP=blood pressure; ECG=electrocardiography; SF-12=Short Form 12 Health Survey Questionnaire; PHQ-9=Patient Health Questionnaire-9; EQ-5D-5L= EuroQol-5 Dimensions-5 Levels.

* These variables will be monitored at local sites.

** These variables will be measured in the central lab at the Coordinating Center.

6.4 Physical examination measures

BP measurement (seated blood pressure and pulse)

BP will be measured according to a standard protocol recommended by the American Heart Association (39). Participants are advised to avoid alcohol, cigarettes, coffee/tea and exercise for at least 30 minutes before their BP measurement. Participants should be seated comfortably with the back supported and the upper arm bared without constrictive clothing. The legs should not be crossed. The arm should be supported at heart level, and an auto-BP cuff will be used and 1 of 3 cuff sizes (pediatric, regular adult, or large) will be chosen on the basis of each participant's arm circumference. BP is measured three times after 5 minutes of seated rest with 1-minute intervals between measurements, at the presence of observer. Neither the participant nor the observer should talk during the rest period or during the measurement. The automated device (Omron HEM-907) will be used as it offers reduced potential for observer biases and decreased demand on staff in terms of training and effort in data collection. The mean of the 3 measurements will be used.

Standing (orthostatic) blood pressure

Standing BP will be measured at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter using the same BP device that is used to measure seated BP. After seated determinations, participants will be asked to stand. Beginning when their feet touch the floor, BP will be taken one minute later in the same arm used for the seated measurements, using the same BP device. Participants will be asked after the standing determination if they had any symptoms of orthostatic hypotension during the standing BP measurement. The Coordinating Center will calculate BP change using the standing measurements minus the mean of the seated measurements.

Anthropometric measurements

Body weight and height, waist and hip circumferences will be measured at baseline using standard methods. Weight will also be measured at 3-month intervals and waist and hip circumferences will be measured annually during follow-up.

Electrocardiography (ECG)

A 12-lead ECG will be obtained at baseline, annual follow-up visits and the close-out visit to ascertain the occurrence of silent (unrecognized) myocardial infarction, primarily, as well as atrial fibrillation and left ventricular hypertrophy. The baseline ECG is used to identify previous (including silent) myocardial infarction, and to identify evidence of left ventricular hypertrophy.

6.5 Questionnaires

Medical history

A detailed history of diabetes, hypertension, cardiovascular disease, and other medical conditions will be collected at baseline examination. History of cardiovascular disease serves as an eligibility factor.

Sociodemographics

Information will be collected during baseline examination regarding age, gender, level of education, marital status, persons living with participants, and employment. These data will be used to identify socioeconomic status and to characterize the final study population.

Lifestyle factors

Consumption of alcohol and tobacco have important implications on cardiovascular risk and adherence to medication regimens. Participants will be assessed at baseline for lifetime tobacco exposure, and alcohol intake. Physical activity and dietary habits will also be recorded. At 24- and 48-month visits, lifestyle factors will be re-assessed.

Concomitant medications

Information regarding the participants' concomitant non-BP medication therapy will be collected and documented at baseline and then reviewed at each follow-up visits. Participants will be required to bring all medication information to each visit and study physician will update concomitant medications if they are changed. Although data are collected on all current therapies, emphasis is placed on concurrent background risk reduction therapy such as aspirin, glucose-lowering and lipid-lowering drugs.

Monitoring adherence

An adherence scale will be administered to all participants at the baseline and annual follow-up visits in order to identify low adherence. In addition, at every medication management visit, participants will be administered a single item to screen for low adherence. If the participant's response to this item indicates a possible problem with adherence, or if the participant is not at the appropriate BP target, study personnel will address the specific issues and barriers for each study participant that may be preventing optimal adherence. In such instances, administration of the adherence scale (to identify reasons for nonadherence) is recommended.

Adverse events

Adverse events will be reported if they met criteria of serious adverse events (SAE) defined in this protocol at protocol visits as well as at non-protocol visits. In addition, SAEs will be reported to local IRB and the Coordinating Center as appropriate.

Study-related outcomes

Both randomized groups will be assessed for study related outcomes in the same way and

on the same schedule. After randomization, participants will be assessed every 3 months for CVD and other clinical outcomes. Medical records will be collected for adjudication of study outcomes. Clinical center staff will use available resources and contact information to assess vital status annually on participants not attending study visits.

Health-related quality of life

All participants will be assessed for the effect of interventions on health-related quality of life (HRQoL). HRQoL data will be collected at baseline, annual follow-up visits and the close-out visit.

Cognitive function

All participants will undergo assessment of cognitive function at the baseline visit, annual follow-up visits and the close-out visit. The tests will include the Montreal Cognitive Assessment (MoCA), the Auditory Verbal Learning Test (AVLT), the Digit Span Test (DST), *etc.* See '**Chapter 9 - Cognitive Study**' for details.

Chapter 7 – Safety Monitoring

The BPROAD trial is testing whether lowering SBP to a goal of <120 mm Hg results in better outcomes than a goal of <140 mm Hg in diabetes patients at risk for CVD events. BPROAD is not a study of specific antihypertensive agents. All antihypertensive agents provided by the trial or recommended by BPROAD have been approved by the Chinese Food and Drug Administration (CFDA) and are routinely prescribed for lowering blood pressure in daily clinical practice.

Patient safety will be carefully monitored. Each participating investigator has primary responsibility for the safety of the individual participants under his/her care. In addition, an independent Data and Safety Monitoring Board (DSMB) will have primary responsibility for monitoring the accumulating study data for signs of adverse trends in morbidity/mortality and treatment-related serious adverse events.

7.1 Participant population

Participants enrolled in BPROAD have elevated risk for CVD outcomes. Inclusion and exclusion criteria were set in order to maximize safety while facilitating inclusion of a trial population at risk for the major trial outcomes.

Inclusion criteria of the BPROAD did not have an upper limit for age. The SPRINT study found significant reductions in fatal and nonfatal major cardiovascular events and death from any cause in adults ≥75 years of age treating to a systolic BP <120 mmHg compared with a systolic BP <140 mmHg, without significant increase in adverse events. Therefore, we encourage participating sites to recruit patients ≥75 years of age, although no specific goal proportion is required. Recruiting more elderly patients is also helpful for the assessment of cognitive impacts of different BP reduction targets. For those patients, anti-hypertensive treatment will start slow and will up-titrate to reach BP treatment targets in well-tolerant individuals. All participants including those age ≥75 years will be asked to identify at least 1 contact person at the time of enrollment that can provide information about the participant as it relates to the study in case of significant cognitive decline in those patients during the course of the trial.

7.2 Safety monitoring

Several types of safety issues and serious adverse events may occur in BPROAD and participants will be monitored for these regularly throughout the study.

7.2.1 Expected events

The potential adverse effects of the BP lowering drugs used in BPROAD have been well documented. For example, electrolyte abnormalities (hyponatremia or hypokalemia are

known to be associated with diuretics; hyperkalemia and short-term decline in GFR with ACEIs or ARBs, hyperkalemia with potassium-sparing drugs; as well as bradycardia with beta blockers and calcium channel blockers). Participants will be monitored routinely with interviews, vital signs, targeted physical examination and laboratory tests to ensure safety. In addition, site clinicians may also obtain lab results and ECGs if safety is a concern at non-scheduled intervals. Expected events are not considered serious adverse events (SAEs) unless they meet criteria for an SAE.

7.2.2 Serious adverse events

Because the burden of collecting and reporting data on every possible adverse event (AE) in BPROAD is excessive and side effects from the anti-hypertensive drugs to be used in BPROAD have been well defined, study sites will report all SAEs and selected AEs to the Coordinating Center.

By definition, SAEs are adverse events that meet any of the following criteria:

- fatal or life-threatening,
- result in significant or persistent disability,
- require or prolong hospitalization,
- result in a congenital anomaly/birth defect, or
- are important medical events that investigators judge to represent significant hazards or harm to research participants and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g. hospitalization, death, persistent disability).

Any adverse event that meets any of these criteria will be documented and reported as a serious adverse event. In addition, a select list of other important events which lead to emergency room visits, will also be considered in BPROAD, including:

- symptomatic hypotension
- arrhythmia
- acute kidney failure
- electrolyte abnormalities
- injurious falls
- syncope
- unexpected events for which the investigator believes that the BPROAD intervention caused the event or contributed to the immediate cause of the event

Participants will be queried for SAEs and selected AEs at quarterly clinic visits. Participants are also encouraged to report SAEs and selected AEs between visits. The study physician may consider modification of treatment if they judge that reported SAEs or AEs of interest are related to treatment choices. In response to safety concerns, the study physician may add,

increase or reduce the dose, stop, or change antihypertensive drugs. Depending on the situation, the change may be temporary or permanent. Situations that may require temporary reduction or elimination of a study medication include: side effects, worsening congestive heart failure, acute kidney injury, symptomatic hypotensive episodes, and other illnesses. Orthostatic hypotension is usually related to specific drug classes and not BP level per se and thus should NOT usually alter target BP goals.

7.3 Safety Reporting

At each quarterly visit, BPROAD staff will specifically query participants for serious adverse events. In addition, information on serious adverse events may also be reported to study staff spontaneously by participants through telephone calls or emails between study visits. AEs at drug titration visits will be reported in the SAE form if they met criteria of SAE defined in this protocol and will be documented as SAEs reported at non-protocol visits. In addition to local reporting requirements, all serious adverse events will be reported to the Coordinating Center within 24 hours of knowledge of the event through the electronic data capture system. Information on SAEs will be collected and SAE forms will be filled out within 72 hours. SAEs will be followed until resolution, stabilization, or until it is determined that study participation is not the cause. The Coordinating Center will be responsible for timely reporting to the study sponsor, i.e. the National Clinical Research Center for Metabolic Diseases, and the DSMB. The Coordinating Center will provide reports of serious adverse events for review by the DSMB at their meetings.

7.4 Data and Safety Monitoring Board

A DSMB is established, with responsibility to monitor all aspects of the study. This independent DSMB will be established to monitor data and oversee participant safety. Members will be appointed by the National Clinical Research Center for Metabolic Diseases to provide oversight of the trial. The BPROAD DSMB includes experts in antihypertensive clinical trials, diabetes, cardiology, nephrology, neurology, and biostatistics. The DSMB normally meets once or twice a year to monitor safety, to advise the National Clinical Research Center for Metabolic Diseases about study progress and performance, and to make recommendations regarding study continuation and protocol changes. Before each DSMB meeting, the Coordinating Center will prepare and provide data on SAEs and selected AEs and any other safety information requested by the DSMB for discussion during open and closed sessions of DSMB meetings. The DSMB members vote during the closed sessions on recommendations to continue or terminate the study based on safety or efficacy data.

Chapter 8 – Statistical Considerations

8.1 Statistical power

The current trial has a single primary outcome (composite major CVD) and several key secondary outcomes. The power calculation is based on the primary outcome and use of the following assumptions:

- Event rate of composite major CVD of 2.0% per year among patients with diabetes and elevated BP (based on the 4C Study 3.8-year follow-up data)
- 20% effect size for the intervention (hazard ratio of 0.80)
- Two-year uniform recruitment period and total study length of five years (defined by the time between randomization of the 1st participant and study closeout)
- 2% per year loss to follow-up rate
- Two-sided significance test at the 5% level, and a statistical power of 90%

Based on these assumptions, we will need to recruit a total of 12,702 patients (6,351 in each group) for the BPROAD trial. In addition, we analyzed statistical power for various assumptions (**Table 3**). If annual event rate of composite major CVD is only 1.8%, we will still have 87% statistical power to detect a 20% risk reduction.

Table 3. Power for the primary outcome (composite major cardiovascular disease)

Sample size/ Hazard ratio	Annual event rate								
	1.8%			*2.0%*			*2.2%*		
	0.75	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*
12000	96.8	84.9	60.0	98.0	88.3	64.3	98.7	91.0	68.3
12250	97.0	85.7	60.8	98.2	88.9	65.2	98.9	91.5	69.2
12500	97.3	86.3	61.6	98.3	89.5	66.0	99.0	92.0	70.0
12750	**97.5**	**87.0**	**62.5**	**98.5**	**90.1**	**66.9**	**99.1**	**92.5**	**70.9**
13000	97.7	87.6	63.3	98.7	90.7	67.7	99.2	93.0	71.7
13250	97.9	88.2	64.1	98.8	91.2	68.6	99.3	93.4	72.5
13500	98.1	88.8	65.0	98.9	91.7	69.4	99.4	93.8	73.3

Assumptions: 2-year recruitment with a uniform accrual rate and total study length of five years; annual proportion lost to follow-up = 2%; and 2-sided significance level = 0.05.

8.2 Data management

All study data will be entered through a web-based data management system first at the local hospitals and the data entry system will be maintained at the Coordinating Center. The Coordinating Center will check for missing data and unrealistic values and perform crosschecks for inconsistencies. Data queries generated from quality control will be sent to participating hospitals and a timely reply (within 3 days) will be required. This data management system has been used in previous trials.

8.3 Data analyses

Sex as a biological variable will be factored into the study design and analyses. Specifically, we anticipate that at least 40-50% of participants will be women. Sex differences will be an important subgroup hypothesis and will be tested using a sex-by-intervention interaction in Cox regression (see **subgroup analysis**).

8.3.1 Primary outcome

The primary analysis will be based on participants' randomization assignments regardless of their achieved BP levels (*intention-to-treat analysis*). For the primary outcome, time-to-event analysis will be used to compare the primary CVD composite endpoint between the intensive treatment and standard treatment groups. Cumulative event rates will be calculated using the Kaplan-Meier method and differences will be tested using the log-rank test. Cox proportional hazards regression will be used to compare the time from randomization to the first CVD event between the randomization groups. The model will include an indicator for intervention as its sole predictor variable. Seven geographical regions in mainland China in which a study site locates will be used as a stratifying factor. Follow-up time will be censored at the last date of event ascertainment. The p-value from the primary analysis will be based on the χ^2 statistic from a likelihood ratio test obtained from proportional hazards models with and without the intervention term. This likelihood ratio test will constitute the primary test of statistical significance (two-sided p-value <0.05) for the primary analysis. Cox proportional hazards regression assumptions will be examined using standard methods.

8.3.2 Secondary outcomes

A number of secondary outcomes will be analyzed to clarify the interpretation of the results of the primary analysis. Each of these will be analyzed using a proportional hazards model as described for the primary analysis. These will be reported with 95% confidence intervals and nominal p values without an adjustment for multiple comparisons, since the intent is to articulate a pattern of effects closely related to the primary outcome, rather than to provide additional tests of efficacy.

8.3.3 Renal outcomes

Renal outcomes are of particular importance in BPROAD, both to assess the progression of kidney disease among those with CKD at baseline and to assess the incidence of new kidney disease among participants free of CKD at baseline. This will be analyzed using a Cox proportional hazards model as described for the primary CVD analysis.

8.3.4 Cognitive and HRQoL outcomes

The effect of the interventions on cognitive function and HRQoL scores will be compared using mixed-effects analysis of covariance models. Mixed-effects models allow for departure from linearity in the relationship between the outcome and time. Estimates of the difference in mean levels of the outcome between the intensive and standard treatment groups will be obtained using maximum likelihood techniques.

8.3.5 Subgroup analysis

For each subgroup analysis, a proportional hazards model will be used that is similar to the one described for the primary analysis above, but with additional terms identifying subgroup membership and the intervention-by-subgroup interaction. Interactions between treatment effect and pre-specified subgroups will be assessed with a likelihood-ratio test. Effect estimates and related nominal 95% CIs within subgroups will be reported.

8.3.6 Missing data

For participants lost to follow-up, we plan to use all available information until the time of death or loss to follow-up. We will assume missing-at-random (MAR) for the primary analysis. In a sensitivity analysis, we will investigate whether loss to follow-up is related to the outcome being analyzed. The magnitude of this problem will be investigated by using measurements taken at previous visits to predict loss to follow-up. Variables determined to predict loss to follow-up will be included in our predictive models. In addition, we will examine several “worst-case” scenarios, including opposite and pooled imputation approaches. These types of scenarios are members of a broad class that can be parameterized as pattern mixture models and allow for examination of sensitivity of conclusions to missing-not-at-random (MNAR) mechanisms. Finally, the multiple imputation techniques will be used in the sensitivity analyses of the primary and secondary outcomes.

8.3.7 Interim analysis and trial stopping rules

Interim analysis will focus on patient recruitment, baseline comparability of treatment arms, achievement of treatment BP goals in both arms, sample size assumptions with regard to event rates, loss to follow-up, adverse effects data, and effect of treatment on the primary and secondary study outcomes. Interim analyses of the intervention effectiveness will be performed at times coinciding with the meetings of the DSMB, and will be controlled to protect the overall Type I error of the trial. These results will be for the use of the DSMB and will not be revealed to the investigators. The purpose of these analyses will be for the DSMB

to assess the trial progress with respect to intervention efficacy and safety, for possible recommendations regarding early termination of the trial.

The interim analysis is based on the stopping boundaries calculated by the Lan-DeMets method with an O'Brien-Fleming type alpha spending function. Two interim and one final analyses are planned to be conducted, whereby the interim analysis would occur after approximately 50% and 75% of the total anticipated number of primary endpoint events had been observed and adjudicated. Let hr^ be the observed hazard ratio. The following table lists the stopping boundaries, which are defined by the log hazard ratios, for the interim analysis.

Table 4. Interim analysis for testing H_0: d=0 vs H_a: d≠0, where d is the log hazard ratio

Stage	Information fraction (Expected number of composite CVD events)	Efficacy boundary value (in log hazard ratio)	Rule	Total type I error achieved
1	0.50 (433)	0.284	If hr^>1.329 or hr^<0.752, reject H_0 and stop; otherwise continue to the next stage	0.003
2	0.75 (650)	0.185	If hr^>1.203 or hr^<0.831, reject H_0 and stop; otherwise continue to the next stage	0.019
3	1.0 (866)	0.137	If hr^>1.147 or hr^<0.872, reject H_0 and stop; otherwise stop and accept H_0	0.050

Chapter 9 – Cognitive Study

Studies have reported adverse changes in cognitive function, brain structure, and neurophysiology in type 2 diabetes [40-44]. Hyperglycemia is associated with increased blood viscosity, impairment of vascular endothelial function and abundance of inflammatory mediators, thereby leading to vascular stenosis, microcirculatory hemodynamic disorders and neurodegeneration. Type 2 diabetes is associated with a 2- to 4-fold increased risk of vascular dementia and a 1.5- to 2-fold increased risk of Alzheimer's disease. The risk of developing dementia is even higher for type 2 diabetes with comorbidities such as hypertension [45].

Hypertension is one of the strongest risk factors for dementia [46]. Long-term hypertension induces vascular atherosclerosis, arterial aneurysm, microembolism, inflammation and changes in cerebral hemodynamics, which leads to ischemia and hypoxia in the brain. This process ultimately results in neuron loss and development of vascular dementia.

Both hypertension and diabetes are risk factors of dementia. However, few studies have examined the impact of blood pressure and glycemic control on dementia. The Memory in Diabetes (MIND) sub-study embedded in the ACCORD trial found that there was no significant difference in delaying cognitive impairment between intensive glycemic treatment targeting HbA1c at <6.0% and standard glycemic treatment targeting HbA1c at 7.0%–7.9%. However, the total brain volume favored the intensive glycemic treatment group [47]. The Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) was designed to compare the effects of intensive BP lowering to target systolic BP <120 mmHg versus standard BP lowering to target systolic BP <140 mmHg on the incidence of all-cause dementia. No statistically significant difference was found for probable dementia between the 2 treatment groups. However, the study was terminated early due to significant benefits of lowering cardiovascular disease risk with intensive BP treatment. Therefore, fewer than expected cases of dementia were observed and the study was underpowered for this end point. In addition, risks of mild cognitive impairment were reduced in the intensive BP treatment group [48].

Therefore, the scientific question whether intensive BP lowering benefits brain health in diabetes, still remains to be answered.

9.1 Objectives

The primary objective of BPROAD Cognitive Study is to determine whether randomization to an antihypertensive treatment strategy achieving systolic BP <120 mmHg is more effective than a treatment strategy achieving systolic BP <140 mmHg in reducing the risk of a composite outcome of all-cause dementia and mild cognitive function (MCI) among

patients with diabetes over a follow-up period of up to 5 years. In addition, other objectives are to compare between intensive and standard BP treatment groups:

- occurrence of all-cause dementia;
- occurrence of MCI;
- changes in global and specific cognitive domains including learning and memory, complex attention, executive functioning, language, and visuospatial skills; and
- changes in total brain volume, incidence of cerebral small vessel disease, *etc.* assessed by brain magnetic resonance imaging (MRI).

9.2 Study Population

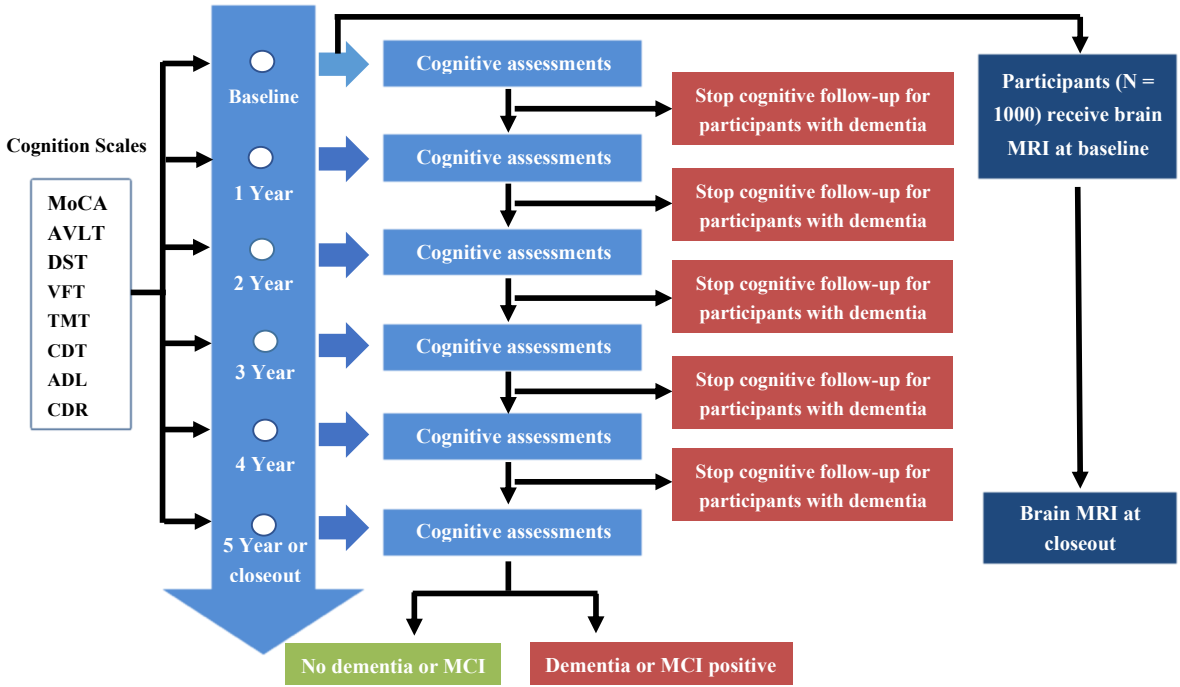
All BPROAD participants will receive cognitive assessments using cognition scales at the baseline visit and will be reassessed at annual follow-up visits and the close-out visit to examine changes in cognitive function. In addition, 10-20 study sites will be selected for MRI sub-study based on location, MRI scanner type, and willingness to participate. All participants recruited in these study sites will receive brain MRI at the baseline visit and at the close-out visit after excluding the following:

- subjects with cardiac pacemaker or automatic implantable cardioverter defibrillator;
- subjects without written informed consent for MRI examination; and
- subjects with following conditions judged by a radiologist not appropriate to conduct brain MRI assessment: implanted neurostimulator, cerebral aneurysm clip, cochlear, otologic or other ear implant, heart stent/valve, dentures, artificial eye, artificial limb, metals in body, or diagnosed as epilepsy or claustrophobia.

9.3 Follow-up Visits

9.3.1 Schedule of follow-up visits

Follow-up visit schedules for Cognitive Study data collection do not differ by treatment group assignment. Cognitive assessments using cognition scales will be administered to all participants at the baseline visit, at annual follow-up visits, and at the close-out visit. Participants in MRI sub-study will receive brain MRI at the baseline visit and at the close-out visit. The data collectors of cognitive assessments at each study site are unaware of participants' randomization assignments.



MoCA, Montreal cognitive assessment; AVLT, auditory verbal learning test; DST, digit span test; VFT, verbal fluency test; TMT, trail making test; CDT, clock drawing test; ADL, activities of daily living; CDR, clinical dementia rating; MRI, magnetic resonance imaging; MCI, mild cognitive impairment.

9.3.2 Cognitive assessment

9.3.2.1 Cognition scales

(1) Montreal cognitive assessment (MoCA)

In BPROAD Cognitive Study, we will use the MoCA to assess global cognitive function. It assesses different cognitive domains including attention and concentration, executive functions, naming, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. We will use the Mandarin version of MoCA (v7.1). According to a validation study, the sensitivity and specificity of the MoCA for detecting MCI were 90% and 87%, respectively.

(2) Auditory verbal learning test (AVLT)

In BPROAD Cognitive Study, we will use the AVLT-Huashan version to assess learning and memory. The AVLT-Huashan version was compiled based on the California Verbal Learning Test and the Chinese University of Hong Kong Verbal Learning Test in 1998. The AVLT assesses basic processes of brain encoding, storing and retrieving of memories. There are three immediate recall trials, followed by the short-term delayed free recall, long-term delayed free recall, long-term delayed cued recall, and Yes/No recognition trials.

(3) Verbal fluency test (VFT)

In BPROAD Cognitive Study, we will use the VFT to assess language ability. The VFT is originated from the Controlled Verbal Fluency Test (CVFT) [49]. The initial format of the CVFT involves asking the patient to name as many words as possible for each of the letters F, A, or S separately within a 1-minute time limit. In 2001, both the category fluency (sometimes called semantic fluency) and letter fluency (sometimes called phonemic fluency) were included in the Delis-Kaplan Executive Function System [50]. In VFT, participants are given 1 minute to produce as many unique words as possible. The participant's score in each task is converted based on the number of unique correct words.

(4) Trail making test (TMT)

In BPROAD Cognitive Study, we will use the modified TMT to assess executive functioning. The test consists of two parts: the TMT-A (Shape Trail Test) [51] and TMT-B (Color Trail Test) [52]. In TMT-A, participants are instructed to connect a set of 25 numbers as quickly as possible while still maintaining accuracy. In TMT-B, the numbers are colored with red or yellow. The test can provide information on visual search speed, scanning, speed of processing, mental flexibility as well as executive functioning. Studies have reported that the TMT-B is superior to TMT-A in discrimination of healthy people, patients at high risk of Alzheimer’s disease (AD) and patients with AD.

(5) Digit span test (DST)

In BPROAD Cognitive Study, we will use the DST, which is a subtest from the Wechsler Memory Scale to assess complex attention. After being read a series of numbers, participants are told to repeat the numbers in forward or backward order. The forward DST assesses both attention and short-term memory, while the backward DST also measures working memory.

(6) Clock drawing test (CDT)

In BPROAD Cognitive Study, we use the CDT to assess visuospatial skills. Participants are required to draw a clock with all the numbers and pointers making a particular time (10 after 11). The test also evaluates executive functions by integrating spatial, digital and temporal capacities. Because clock drawing is also included in the MoCA, we will use the clock a participant draws in the MoCA for the CDT. According to previous studies, both sensitivity and specificity of the CDT to identify AD were 85%, respectively.

(7) Activities of daily living (ADL)

The decline in activities of daily living is core symptoms of dementia. In BPROAD Cognitive Study, we will use the ADL-Zhang Mingyuan Revised Version to assess a participant's functional status. The ADL contains 20 items, including physical self-maintenance and instrumental activities of daily living. Performance for each item will be rated as follows: 1- independent; 2- has difficulty, but does by self; 3- require assistance; 4- dependent. Activities that could not be rated, either because the respondent does not know them or because the patient has never performed them will not be scored and will be assigned the number '9'. The ADL can be used in diagnosis of dementia with great reliability and validity.

(8) Clinical dementia rating (CDR)

In BPROAD Cognitive Study, we will use the Washington University CDR scale to quantify the severity of symptoms of dementia. It is a 5-point scale used to characterize six domains of cognitive and functional performance including memory, orientation, judgment and problem solving, community affairs, home activities and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview with the participant and a reliable informant or collateral source (e.g., family member). The sensitivity and specificity of the CDR for detecting dementia were 95% and 100%, respectively.

9.3.2.2 Brain MRI

Participants in the MRI sub-study will receive brain MRI at the baseline visit and at the close-out visit. An MRI technologist should be assigned to this study at each study site to facilitate MRI protocol compliance, technical issues, and communication. For each MRI sub-study participant, scanning pulse sequences should be performed in the following order:

Sequence 1 – 3-plane gradient echo localizer for positioning;

Sequence 2 - Sagittal 3D T1-weighted sequence for entire brain coverage;

Sequence 3 - Sagittal 3D FLAIR images from matching slice positions in Sequence 2;

Sequence 4 - Axial BOLD (Blood Oxygen Level Dependent) fMRI sequence (resting);

Sequence 5 - Axial ASL (Arterial Spin Labeling) perfusion sequence;

Sequence 6 - SWI (Susceptibility Weighted Imaging) sequence;

Sequence 7 - Time of flight magnetic resonance angiography.

9.4 Outcomes

Cognitive assessment data and brain MRI images will be transferred to the Coordinating Center via the electronic data capture system. A cognitive outcome adjudication committee of cognitive decline experts as well as a brain MRI image reading panel of experienced radiologists will be assembled prior to the start of the BPROAD Cognitive Study. The committee members will assess all cognitive data independently and give their diagnosis. MRI images will also be read by at least 2 radiologists independently. The assessors are blinded to treatment assignment.

9.4.1 Primary outcome

The primary outcome of the BPROAD Cognitive Study is a composite of occurrence of all-cause dementia or MCI, defined as the time to the first diagnosis of all-cause dementia or MCI.

Criteria used for identifying dementia will be those described in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) [53]. These are:

- Significant decline in memory and at least one additional cognitive domain; and
- Significant functional impairment due to cognitive problems; and
- Cognitive deficits are not due to obvious reversible causes such as acute illness, metabolic disturbances, infections, mood disorders or substance-induced conditions; and cognitive deficits do not occur exclusively during the course of delirium.

No attempt to classify dementia subtype will be made.

Criteria used for identifying MCI will be those described in the 2011 Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [54]. These are:

- Concern regarding a change in cognition; and
- Impairment in one or more cognitive domains; and
- Preservation of independence in functional abilities; and

- Not demented.

Two occurrences of an adjudicated classification of MCI will be required for the MCI diagnosis. The 2nd adjudication of MCI need not to be consecutive. Similarly, MCI then a later dementia adjudication is also acceptable for the MCI diagnosis.

9.4.2 Secondary outcomes

(1) All-cause dementia

(2) MCI

MCI represents a transitional state between no cognitive impairment and dementia. Specific subtypes of MCI are highly predictive of subsequent dementia. Two occurrences of an adjudicated classification of MCI will be required for the MCI diagnosis.

(3) Changes in cognitive performance

Apart from dementia and MCI incidence, changes in global cognitive function as well as cognitive performance of specific domains will also be evaluated, which include:

- The decline in global cognition;
- The decline in learning and memory;
- The decline in complex attention;
- The decline in language ability;
- The decline in executive functioning;
- The decline in visuospatial skills.

(4) Brain MRI

The following MRI parameters will be evaluated in brain MRI sub-study:

- Changes in total brain volume;
- Number of high signal lesions of white matter in brain;
- Occurrence of cerebral small vessel disease.

9.5 Study Power

All BPROAD participants will be included in the Cognitive Study for cognitive assessments. According to the SPRINT MIND findings, we assume a 2.4% per year event rate of the primary outcome in the standard treatment group, a 15% effect size for the intervention (hazard ratio of 0.85), a two-year uniform recruitment period, a total study length of 5 years, a 2.0% per year loss to follow-up, and a two-sided significance at the 5% level. With these assumptions and 12,702 participants, the statistical power for the BPROAD Cognitive Study is 74%.

It should be noted that because of the greater lag in the effects of BP reduction on cognitive effects than on CVD effects, the end of the trial for the cognitive decline and

publication of those results will likely occur after the end of the trial and publication of the CVD results. The annual event rate depends on the age of the final recruited population. Because we may have a study population younger than the SPRINT MIND population, we assume a range between 1.8% to 2.4% per year event rate of the primary outcome in the standard treatment group and calculated the anticipated total event number and statistical power at different annual event rate and total study length shown in **Table 5**. The BPROAD cognitive study will continue until 1374 cases of dementia or MCI (85% power) are observed.

Table 5. The anticipated total cognitive event number (statistical power)

Total Study Length	Event Rate (% per year)						
	1.8	1.9	2.0	2.1	2.2	2.3	2.4
5 years	785 (62%)	827 (65%)	869 (67%)	911 (69%)	952 (71%)	994 (73%)	1035 (74%)
6 years	964 (71%)	1015 (73%)	1066 (76%)	1117 (77%)	1168 (79%)	1218 (81%)	1268 (82%)
7 years	1137 (78%)	1197 (80%)	1256 (82%)	1315 (84%)	**1374 (85%)**	1433 (87%)	1491 (88%)

Assumptions: 15% effect size for the intervention (hazard ratio of 0.85); 2-year recruitment with a uniform accrual rate; annual proportion lost to follow-up = 2%; 2-sided significance level = 0.05; and an overall sample size = 12,702

Chapter 10 – Quality Control

Data integrity and quality are among the highest priorities in BPROAD. There are two primary purposes for quality control: to document the level of quality and to provide feedback to the clinical, reading and laboratory centers in order to maintain and improve the quality of the study data over the course of the trial.

Two phases will be used in BPROAD. The first, quality assurance, is the collection of manuals and procedures that will be in place to assure the integrity of the data. A subset of these procedures is referred to as quality control, which describes the monitoring and analytic activities that assess performance during data collection and its processing.

10.1 Manual of Procedures

The MOP will include detailed descriptions of all trial procedures and will be used for training purposes and as a reference for all study investigators and staff. The MOP is an important aspect of efforts to standardize study procedures across clinical sites in the BPROAD trial.

Key study procedures will be standardized; these include the use of a central lab and ECG reading center, and standard forms, equipment, and procedures in the clinics for BP measurement and other data collection procedures. Furthermore, standard event definitions and event validation procedures will be used.

10.2 Study forms

Quality assurance concepts were employed during the development of forms. Question-by-question instructions on how to fill out the forms will be listed and necessary explanations will also be available for easy reference. Web-based data entry screens will be developed from the forms, and enable the incorporation of range and logical checks at the time of data entry. A pilot examination using some of the forms such as the baseline information collection form to simulate study scenario will be conducted to identify space for improvement. These features will contribute to quality assurance.

10.3 Training

Training of staff and pilot testing of procedures are crucial to standardize procedures and assure data quality. BPROAD uses two different training models: face-to-face training and online-video training. In face-to-face training, we will organize up to 10 training sessions at different regions across mainland China. All relevant staff members from all clinical sites in the relevant region will be convened in a single, centrally administered face-to-face training session. This approach contributes to uniformity of the training experience and thereby to uniformity of data quality across sites. In addition, we will conduct a second face-to-face training at each site initiation to help individual study site to begin data collection. In online-video training, we will upload a training video to the trial website with details on standard

procedures and emphasis on data quality for study staff to watch at any time when they feel necessary. The online video will also help persons who were unable to attend the face-to-face training session and newly hired staff as turnover occurs. In addition, the Coordinating Center will organize yearly refresher training sessions to the study personnel of all study sites.

10.4 Data queries

The Coordinating Center will be responsible for data editing, which will include checks for missing data, unrealistic values, and crosschecks for inconsistencies. Data will be checked on form submission and any data queries presented to the data entry staff for immediate resolution, if possible. The Coordinating Center will also produce data query reports on the website that summarize the number and types of queries by study site. Study site staff will be responsible for reviewing and resolving the data queries in a timely manner. In case of unresponsiveness, telephone calls will be made from the Coordinating Center to study site investigators, and will be followed with site visits if unresponsiveness continues. Reports, including reports on timeliness of data entry and query resolution, will be shared within the network of all study sites.

10.5 Quality control reports

Using the electronic data capture system, a real-time monitoring at the Coordinating Center will be conducted on progress of participant recruitment, achieved systolic BP levels in both groups, recording of study outcome information, collection of blood and urine samples for centralized measurement and storage, *etc.* Routine (e.g., weekly) quality control reports will be generated by the Coordinating Center and will be distributed to all study sites on measures of process, impact, and outcomes.

Examples of process measures that will be tracked for quality control purposes include:

1. Days between data collection and data entry
2. Percent of forms with late data entry
3. Number of participants with missed or late visits by contact, number of missed or late visits clinic-wide, and number of participants missing two or more consecutive visits
4. Number, name and dose of prescribed antihypertensive medications for individual participants

Examples of impact measures that will be tracked for quality control purposes include:

Number (and percent) of participants at goal according to the BP target assignment as assessed by in-clinic BP measurements.

Examples of outcome measures that will be tracked for quality control purposes include:

1. Submission of medical record documentation for reported study events by the study site (e.g., timeliness, completeness)
2. Proportion of participants with ECG submitted to central ECG Reading Center overall and by quality grade
3. Proportion of participants with urine samples submitted for albuminuria assessment

4. Proportion of participants with blood samples submitted to central lab

5. Percent agreement of individual study adjudicators with the final outcome assignments for cases adjudicated

10.6 Monitoring the study sites

The Trial Monitoring Committee of BPROAD will be responsible for study site monitoring. Enough number of trial monitors (also called clinical research associates) will be hired to monitor performance at each of the study sites. The monitoring team will monitor clinical sites in all aspects of trial operations and performance and to assist in problem solving related to all aspects of the trial. Site monitoring can and will be performed using regular communications including WeChat, telephone calls, site visits and other means.

Trial monitors will visit individual study sites at site initiation to help with completion of appropriate regulatory approvals, site staff training, and the development of a recruitment plan. Additional visits may be conducted to ensure that the study enrollment process follows proper study procedures. During the course of the trial, the monitoring team will visit clinical sites at specified intervals, and as needed. The scope of these visits is broad and can include but is not limited to regulatory requirements, study communications, site initiation, site staffing, and general site performance. However, areas of emphasis and/or additional monitoring may vary according to the circumstances of a specific site and site visit. Site visits may be conducted to evaluate performance deficits in one or more critical areas, such as consistent departures from the protocol or MOP. Site visits are also an opportunity for refresher training and/or training of new staff, as needed. A summary of the site visit will be presented to the clinical site investigator and staff at the conclusion of the site visit and a written site visit report will be completed within a reasonable time-frame post visit. Copies of the site visit report will be sent to the clinical site investigator and the Coordinating Center. Proper follow-up of problems identified during site visits will be conducted and follow-up reports will also be completed and sent out to the clinical site investigator and the Coordinating Center.

10.7 Laboratory quality control

The Central Laboratory of BPROAD trial locates at the Shanghai Institute of Endocrine and Metabolic Diseases and has been participating in regular CAP auditing and accreditation. The Coordinating Center will work with the Central Laboratory to develop quality control procedures for the trial to ensure high quality measurement data. The results of quality control procedures performed at the Central Laboratory will be reported on a regular basis to the Coordinating Center.

Clinical site performance in acquisition, handling, storage and shipping of specimens will be tracked by the Central Laboratory. The first step in quality assurance at the site level consists of the training and certification process for staff within the clinical sites. Other steps include observation of technicians performing all steps of sample collection and processing

during site visits; reviewing study forms; reviewing and tracking the condition of samples received at the Central Laboratory for problems in shipment; and periodic analysis of the study data for participant compliance with fasting, where required, and for signs of problems in drawing or processing, such as hemolysis. Reports on clinical center performance will be submitted regularly by the Central Laboratory to the Coordinating Center. Quality Control procedures in the laboratory for assays include the use of the internal Laboratory Manual, training and certification of laboratory staff, laboratory participation in external standardization and certification quality control programs, and implementation of the BPROAD internal quality control program. As part of the internal quality control program, the Central Laboratory will regularly provide summaries of the internal quality control results to the Coordinating Center.

10.8 Extension of study

It is possible that we might have to extend the trial, depending on emerging results. For example, if the event rate of major CVDs in the standard group is substantially less than 2.0%, or the event rate of a composite of dementia and MCI in BPROAD Cognitive Study in the standard group is substantially less than 2.4%, depending on early outcomes, we may ask that the DSMB consider recommending extension of the trial or extension for outcome ascertainment without intervention. Statistical powers after extension are listed in Table 6.

For kidney outcomes, observational data from the 4C study revealed 1) an approximately 10% CKD patients (eGFR<60 ml/min/1.73 m^2), 2) an annual event rate of CKD progression of approximately 1.5%, and 3) an annual event rate of CKD development of approximately 1.2% among patients aged ≥50 years with treated diabetes and hypertension at baseline. Statistical powers for CKD outcomes stratified on CKD status at baseline as well as for the composite CKD development and CKD progression outcomes are listed in Tables 7 and 8. Recruitment of participants with or without CKD and early CKD outcomes will be closely monitored and updates of statistical powers will be done when necessary.

Table 6. Statistical power (%) under different hazard ratio, study duration, and annual event rate

Hazard ratio	**Total duration (years)**	**Annual event rate**				
		0.8%	***1.0%***	***1.2%***	***1.5%***	***1.8%***
0.85	*5 (total study length)*	33.3	40.0	46.2	54.8	62.3
	7 (2 year extension)	45.5	54.0	61.5	70.8	78.2

	9 (4 year extension)	55.8	65.1	72.7	81.3	87.4
0.80	*5 (total study length)*	54.3	63.7	71.4	80.5	86.9
	7 (2 year extension)	70.6	79.7	86.2	92.5	96.0
	9 (4 year extension)	81.4	88.9	93.5	97.2	98.8

Assumptions: 2-year recruitment with a uniform accrual rate; annual proportion lost to follow-up = 2%; 2-sided significance level = 0.05; and an overall sample size = 12,702.

Table 7. Statistical power (%) for CKD outcomes stratified on participants with or without CKD at baseline

Population		**Total duration (years)**	**Hazard ratio**	
			0.85	*0.80*
10% CKD in BPROAD participants	Without CKD at baseline (N=11,432)	*5 (total study length)*	42.5	66.9
		7 (2 year extension)	57.0	82.5
		9 (4 year extension)	68.1	90.9
	With CKD at baseline (N=1,270)	*5 (total study length)*	10.0	14.3
		7 (2 year extension)	12.4	18.7
		9 (4 year extension)	14.6	22.9
20% CKD in BPROAD participants	Without CKD at baseline (N=10,162)	*5 (total study length)*	38.5	61.7
		7 (2 year extension)	52.2	77.9
		9 (4 year extension)	63.0	87.4
	With CKD at baseline (N=2,540)	*5 (total study length)*	15.3	24.1
		7 (2 year extension)	20.1	32.8
		9 (4 year extension)	24.6	40.6

Assumptions: 2-year recruitment with a uniform accrual rate; annual proportion lost to follow-up = 2%; 2-sided significance level = 0.05; annual incidence of CKD development = 1.2%, annual incidence of CKD progression = 1.5%; and an overall sample size = 12,702.

Table 8. Power for composite CKD development and CKD progression outcomes

Population	**Annual incidence of composite CKD development and CKD progression**	**Total duration (years)**	**Hazard ratio**	
			0.85	*0.80*
10% CKD in BPROAD participants	0.012*0.9+0.015*0.1 =0.0123	*5 (total study length)*	47.2	72.5
		7 (2 year extension)	62.5	87.0
		9 (4 year extension)	73.7	94.0
20% CKD in BPROAD participants	0.012*0.8+0.015*0.2 =0.0126	*5 (total study length)*	48.0	73.5
		7 (2 year extension)	63.5	87.8
		9 (4 year extension)	74.6	94.5

Assumptions: 2-year recruitment with a uniform accrual rate; annual proportion lost to follow-up = 2%; 2-sided significance level = 0.05; annual incidence of CKD development = 1.2%, annual incidence of CKD progression = 1.5%; and an overall sample size = 12,702.

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BPROAD Response Plan to the Outbreak of Coronavirus Disease 2019 (COVID-19) in Mainland China

BPROAD Trial Executive Committee

Since early 2020, there is an outbreak of the coronavirus disease 2019 (COVID-19) in mainland China. Due to the possibility of virus transmission during clinic visits, the in-person follow-up of BPROAD participants with their doctors/investigators is difficult. To protect the rights and interests of participants, we developed this Response Plan according to the *Consensus on Clinical Trial Management under First-level Response to Major Public Health Emergencies (Infectious Diseases)* which was formulated by the China Forums of Clinical Research Capacity Building and Human Research Participants Protection (CCHRPP). This response plan is to be implemented on the date of notification until March 15th, 2020 or notified otherwise.

The following decisions have been made regarding BPROAD participant visits as a response to the COVID-19 outbreak:

1. Cancel or suspend all screening, baseline/randomization, and the first yearly visits;
2. Collect trial data by telephone interviews at the scheduled date;
3. Complete data collection in window (target date ± 2 weeks).

Because some study sites may have a shortage of BPROAD study personnel at this critical time, separate procedures have been recommended regarding BPROAD data collection through telephone interview.

1. Study sites with full BPROAD personnel

The following forms have to be completed for each telephone interview:

1.1 *Blood Pressure Management Form* (completed by investigators on BP management)

Blood pressure (BP) levels will be obtained using home BP monitoring (HBPM). Training and instructions on HBPM (Appendix 1) will be provided to each participant for them to measure and record BP levels at home accurately and report to their doctors/investigators.

For participants who do not have an HBPM device, we suggest they go to the community healthcare center or other places adjacent to their home such as a pharmaceutical store with BP measurement devices to obtain and record BP levels. For participants without any means of BP monitoring, notification should be made in the BPROAD electronic data capture (EDC) system.

1.2 *Blood Pressure Medication Log* (completed by investigators on BP management)

Medications will be adjusted at the discretion of the study physician taking into account the target systolic BP and the validity of BP numbers provided by the participant. We

recommend the same targets for home BP and clinic BP because according to the *2017 ACC/AHA Guideline for BP Management*,[1] similar levels were found for home BP and clinic BP when systolic BP is <140 mmHg (page 31, Table 11).

In addition, given the limitations of a telephone interview and potential inaccuracies in HBPM practice by some participants, safety will be the first priority when giving antihypertensive recommendations and changes in drug dosages will be the major recommendation instead of changes in drug classes or drug types.

A drug prescription for 90 days on each fill is encouraged by the government for chronic diseases during this time, including antihypertensive drugs. Although BPROAD in-person visits are not required due to the COVID-19, patients can still go to clinics for prescriptions if drug refill is needed. Therefore, drug delivery to participants is not arranged at the current time.

1.3 *Concomitant Medications Form* (completed by investigators on BP management)

Investigators on BP management should ask participants their daily medications besides antihypertensive drugs since the last visit. If participants are not able to report drug names, pictures of pill boxes should be taken and sent to the investigators via WeChat or email.

1.4 *Events Ascertainment Form* (completed by investigators on events)

Investigators on events who are blinded to treatment assignment will ask participants for information on events such as hospitalization, emergency department visits, syncope, injurious falls, *etc*. Information on adverse events will also be collected if they met criteria of serious adverse events (SAE) defined in the BPROAD protocol. SAEs will be reported to the local IRB and the Coordinating Center as appropriate.

1.5 *Participant Status Log Form* (completed by investigators on BP management)

After the telephone interview, the *Participant Status Log Form* should be completed based on the information collected.

2. **Study sites without full BPROAD personnel**

A few study sites will be short of BPROAD research personnel because investigators are called upon to the Wuhan city or to the emergency department. When this happens, the study site is required to contact the Coordinating Center to discuss about a solution.

In the case of a shortage of investigators on BP management, the Coordinating Center, after a written authorization notification by the study site, will arrange telephone interviews with participants who have been notified about the change of follow-up plans. Information on home BP levels and concomitant medications will be collected and antihypertensive regimens will be recommended to the participant by investigators in the Coordinating Center.

In the case of a shortage of investigators on events, information on events will be collected as early as possible after the COVID-19 is contained and it is safe to continue in-person visits for BPROAD participants.

Reference:

1. Paul K Whelton, Robert M Carey, Wilbert S Aronow, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138: e426-e483.

Appendix 1: Recommendations for Home Blood Pressure Monitoring

The correct measurement of blood pressure (BP) is essential for the management of BP levels. For BPROAD participants who cannot complete in-person visits, BP levels from home BP monitoring (HBPM) should be provided to investigators during telephone interview.

We developed this recommendation for HBPM for BPROAD participants according to the 2019 American Heart Association (AHA) Scientific Statement on the Measurement of Blood Pressure in Humans, the 2011 Chinese Blood Pressure Measurement Guideline, and the 2019 Chinese Home Blood Pressure Monitoring Guideline.

General information:

1. BP measurements at home are assisted by patients' family members or completed by patients themselves.

2. Use a fully-automated oscillometric device with an upper-arm cuff that has been validated before use. Mercury phygmomanometer can be used if the automated device is unavailable.

3. Use a cuff that is appropriately sized for the patient’s arm circumference.

Home BP measurement:

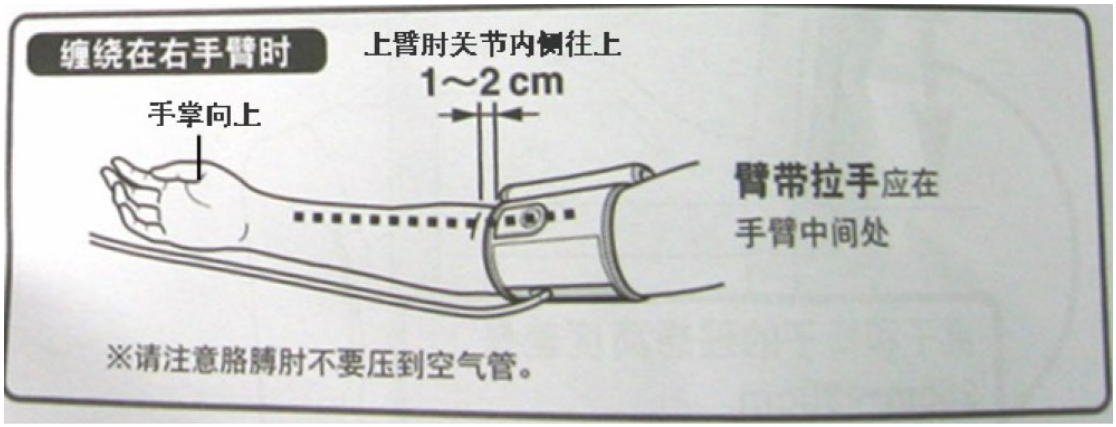
1. Before measurement:

- Avoid caffeine, exercise, and smoking for at least 30 mins before measurement
- Have an empty bladder
- Rest quietly in seated position without conversation for at least 5 minutes

2. During measurement:

- Sit with back supported
- Keep both feet flat on the floor
- Legs should not be crossed
- BP cuff should be placed on the bare arm (or over single layer clothes), preferably on the right arm
- BP cuff should be placed directly above the antecubital fossa (bend of the arm)
- Center of the bladder of the cuff (commonly marked on the cuff by the manufacturer) should be placed over the arterial pulsation of the patient’s bare upper arm
- Cuff should be pulled taut, with comparable tightness at the top and bottom edges of the cuff, around the bare upper arm

- The arm with the cuff should be supported on a flat surface such as a table to keep the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum)
- Do not talk or move



Home BP monitoring

1. Number of readings per day:

Take 2 readings at least 1 min apart in the morning before breakfast and taking antihypertensive medications and 2 readings at least 1 min apart in the evening before going to bed.

2. Duration of monitoring:

Minimum period of 3 days (ie, 12 readings) before scheduled visit (monitoring conducted over consecutive days is ideal)

Record the daily average of 4 readings (2 in the morning and 2 in the evening) measured at the latest 3 days on the BPROAD *Blood Pressure Management Form*.

Blood Pressure Control Target in Diabetes (BPROAD) Trial

Statistical Analysis Plan

Version 1.0

June 30, 2019

CONTENTS

1. Summary of study design

The Blood Pressure Control Target in Diabetes (BPROAD) Trial is a multi-center, open-label, parallel-group, randomized controlled trial. It will test the primary hypothesis of whether an intensive treatment strategy (a systolic blood pressure target of <120 mmHg) is more effective than a standard treatment strategy (a systolic blood pressure target of <140 mmHg) in reducing the risk of major cardiovascular disease (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) over a follow-up period of up to 5 years among patients with a history of diabetes and elevated systolic blood pressure. The secondary hypotheses are to compare the intensive blood pressure treatment strategy with the standard treatment strategy on total stroke (ischemic and hemorrhagic stroke), major coronary heart disease events (fatal coronary heart disease, nonfatal myocardial infarction, and hospitalized unstable angina), treated or hospitalized heart failure, cardiovascular disease mortality, all-cause mortality, cognitive function, kidney outcomes, quality of life, and falls with serious injury, etc.

The trial will recruit 12,702 patients from approximately 200 hospitals within the China Diabetes Clinical Research Network. Eligible criteria include men and women aged ≥50 years; type 2 diabetes mellitus; elevated systolic blood pressure; and a history of clinical cardiovascular disease or increased risk for cardiovascular disease. Main exclusion criteria include known secondary cause of hypertension, symptomatic heart failure, end-stage renal disease, and other serious illness. The proposed trial has 90% statistical power to detect a 20% reduction (hazard ratio of 0.80) in major cardiovascular disease between intensive and standard treatment groups at a 2-sided significance level of 0.05. We further assume an event rate of major cardiovascular disease of 2.0% per year in the control arm based on 3.8-year follow-up data from the China Cardiometabolic Disease and Cancer Cohort (4C) study, 2-year uniform recruitment period, total study length of 5 years, and 2% per year rate of loss to follow-up. The findings from this trial will provide evidence as to whether intensive blood pressure management to achieve a systolic blood pressure target of <120 mmHg has additional benefits over standard management of systolic blood pressure <140 mmHg.

The primary objective of the BPROAD Cognitive Study is to determine whether randomization to an antihypertensive treatment strategy achieving systolic BP <120 mmHg is more effective than a treatment strategy achieving systolic BP <140 mmHg in reducing the risk of all-cause dementia among patients with diabetes over a follow-up period of up to 5 years. In addition, other objectives are to compare between intensive and standard BP treatment groups: 1) incidence of mild cognitive impairment (MCI); 2) incidence of a composite of dementia and MCI; 3) changes in global and specific cognitive domains including learning and memory, complex attention, executive functioning, language, and visuospatial skills; and 4) changes in total brain volume, incidence of cerebral small vessel disease, etc. assessed by brain magnetic resonance imaging (MRI). All BPROAD participants will receive cognitive assessments using cognition scales at the baseline visit and will be reassessed at annual follow-up visits to examine changes in global and domain-specific cognition. In addition, 10-20 study sites will be selected for MRI sub-study and participants

recruited in these study sites will receive brain MRI at the baseline visit and at the close-out visit. The BPROAD Cognitive Study will provide evidence as to whether intensive BP lowering benefits brain health in diabetes.

This Statistical Analysis Plan (SAP) is based on the planned analysis specification as written in BPROAD Study Protocol Chapter 8 "Statistical Considerations". Therefore, SAP readers may consult the protocol for more detailed background information of the trial, e.g., trial objectives, trial design and participants, treatments, endpoints, etc.

2. Endpoints

2.1 Primary endpoint

The primary endpoint is time to first occurrence of a composite of non-fatal myocardial infarction (MI), non-fatal stroke, treated or hospitalized heart failure, and death of cardiovascular causes.

2.2 Secondary endpoints

A few secondary endpoints will also be analyzed in BPROAD. These include time to first occurrence of the following:

- An expanded outcome including the composite primary outcome and all-cause mortality
- Macrovascular outcome including the composite primary outcome, hospitalized unstable angina, and all cardiovascular revascularization procedures
- Major coronary artery diseases including non-fatal MI, hospitalized unstable angina, revascularization of coronary arteries, and death due to coronary artery diseases
- Total stroke including fatal and non-fatal stroke
- Hospitalized or treated heart failure, or death due to heart failure
- Cardiovascular mortality
- All-cause mortality

In addition, health-related quality of life (HRQoL) is another secondary outcome, which will be assessed by the SF-12, PHQ-9, and EQ-5D at baseline and annual follow-up visits. The HRQoL endpoints are changes in scores of these 3 scales from baseline.

2.3 Kidney endpoints

The kidney related endpoints are time to first occurrence of the following:

- CKD progression: a composite of end-stage renal disease, eGFR<15 ml/min/1.73 m^2, or 50% decline in eGFR from baseline in patients with CKD at baseline
- CKD development: eGFR <60 ml/min/1.73 m^2 and ≥30% decrease from baseline eGFR in patients without CKD
- Incident albuminuria: a doubling of urinary albumin-to-creatinine ratio (ACR) from

a value <10 mg/g to a value of >10 mg/g in all patients with or without CKD

2.4 Cognitive endpoints

The primary endpoint in the BPROAD Cognitive Study is time to first identification of all-cause dementia. Secondary endpoints include time to first identification of mild cognitive impairment (MCI), a composite of dementia and MCI, changes in global and specific cognitive domains including learning and memory, complex attention, executive functioning, language, and visuospatial skills, and changes in total brain volume, incidence of cerebral small vessel disease, etc. assessed by brain MRI.

2.5 Other efficacy endpoints

- All cardiovascular revascularization procedures including percutaneous transluminal coronary angioplasty (PTCA) with balloon or stent, coronary artery bypass grafting (CABG), carotid angioplasty with stent, carotid endarterectomy, peripheral angioplasty with or without stent, peripheral vascular surgery (including aortic aneurysm repair) and limb amputation including partial or digit amputation due to vascular disease
- Hospitalized unstable angina
- Retinopathy
- Transient ischemic attack (TIA)
- Left ventricular hypertrophy (LVH) diagnosed by ECG
- Atrial fibrillation or flutter
- All cancers
- Cost-effectiveness

2.6 Safety endpoints

Adverse events will be reported if they met criteria of serious adverse events (SAE) defined as an event that is:

- fatal or life-threatening
- result in clinically significant or persistent disability
- require or prolong hospitalization
- important medical events that investigators judge to represent significant hazards or harm to research participants and may require medical or surgical intervention to prevent one of the other outcomes listed above

In addition, a selected list of other important events which lead to emergency room visits will also be reported in BPROAD:

- symptomatic hypotension
- arrhythmia
- acute kidney failure
- electrolyte abnormalities
- injurious falls
- syncope

3. General analysis definitions

3.1 Treatments

Participants eligible for the trial will be randomized to one of two treatment groups:

- Systolic BP <120 mmHg for the intensive treatment group
- Systolic BP <140 mmHg for the standard treatment group

3.2 Analysis sets

1) **Screened Set (SS):** This will include all patients who signed the informed consent.

2) **Randomized Set (RS):** All screened patients who were randomized, including those who violated inclusion criteria.

3) **Full Analysis Set (FAS):** According to the Intention to Treatment (ITT) principle, all inclusion eligible randomized subjects will be included into the full analysis set and will be grouped according to their intervention assignment at randomization, whether BP goals achieved or not. The FAS is the main data set for outcomes and safety analysis.

4) **Per Protocol Set (PPS):** All eligible patients who enrolled in the study, completed ≥80% of the protocol visits, reached BP goals in ≥80% of the protocol visits (except visits during the BP level titration period) and without other important protocol violation constitute the PPS for this study. The PPS will be used for sensitivity analysis.

Table 1 specifies the patient set for each planned analysis.

Table 1. Specifying patient sets for analysis

	SS	RS	FAS	PPS
Disposition	X	X		
Demographic and baseline characteristics			X	
Outcome and safety endpoints			X	X*

*Sensitivity analysis.

3.3 Missing data

3.3.1 Missing on baseline characteristics and BP levels

Every effort will be made to collect data as complete as possible. Missing data on baseline information will not be replaced in the patients baseline characteristics displayed. Patients with baseline missing information for a subgroup definition will not be included in the respective subgroup analysis.

BP levels will be assessed at every visit during the study. The mean and median of the BP levels at each visit will be calculated and compared between the two treatment groups. Missing data on BP levels during the study will not be imputed. Patients with missing BP measurements will not be included in the calculation.

3.3.2 Missing on endpoints

The principles given below are the planned methods for imputation depending upon the type of the endpoints.

For each time to event analysis, patients who are lost to follow-up and who do not have a particular endpoint will be censored. In the case that only the year is documented, the day and month will be imputed as 01 January unless the subsequently derived date is before randomization; in this case the date of randomization will be used as the censoring date. If year and month is present, the day will be imputed as first of the month unless the subsequently derived date is before randomization; in this case the date of randomization will be used.

For continuous endpoints such as eGFR, UACR, HRQoL scores, cognitive function scores, and total brain volume, all available data will be considered. Missing data will not be replaced. All subjects with a non-missing baseline value and at least one non-missing post-baseline value will be included in these analyses. Subjects with a missing baseline value or without a non-missing post-baseline value will not contribute to the analyses.

For participants lost to follow-up, all available information until the time of death or loss to follow-up will be used. We will assume missing-at-random (MAR) for the primary analysis. In a sensitivity analysis, we will investigate whether loss to follow-up is related to the outcome being analyzed. The magnitude of this problem will be investigated by using measurements taken at previous visits to predict loss to follow-up. Variables determined to predict loss to follow-up will be included in our predictive models. In addition, we will examine several “worst-case” scenarios, including opposite and pooled imputation approaches. These types of scenarios are members of a broad class that can be parameterized as pattern mixture models and allow for examination of sensitivity of conclusions to missing-not-at-random (MNAR) mechanisms. Finally, the multiple imputation techniques will be used in the sensitivity analyses of the primary and secondary outcomes.

3.4 Time to event

The time to occurrence of primary and secondary endpoints, as well as safety events has to be calculated for analysis. This section describes the calculation of the time to event and the time that patients without an event in the trial (under risk).

The respective time intervals determine the start and end for the derivation of occurrence of a specific event.

For patients with an event, the time to event is calculated as:

<date of event> - < start date> + 1

For patients without an event, the time at risk is calculated as:

<date of censoring> - < start date > + 1

1) Start date

In general, the time to event will be derived from the date of randomization for outcomes and safety events.

2) Date of event

For composite outcomes, e.g. the primary composite endpoint, the earliest onset date of the corresponding components will be used. For fatal MI, fatal stroke, and fatal heart failure, the onset date of the event is used. While for other cardiovascular (CV) deaths, the date of death is used. A patient with at least one event in any of the components of the composite will be considered to have an event and the date of the first event will be used for the composite endpoint.

The dates determined by the outcome adjudication committee will be used; these can be different from the investigator reported dates. For the endpoints of time to CV death and time to all-cause mortality and other endpoints only based on a fatal component, the respective death date will be used.

For events with multiple episodes, such as adverse events (AE), the onset date of the first episode will be used.

The time to first occurrence of endpoints based on laboratory data or performance test, e.g. ‘time to incident albuminuria’ is determined by the date of the first laboratory measurement, in this example urinary albumin measurement, that fulfils this condition.

3) Censoring

Primary and other endpoints (except for the stand-alone endpoints of CV death, all-cause mortality):

The underlying principle is that the censoring date should be the date at which the patient

was last known to be free of the endpoint event (e.g. free of each component of the primary composite outcome).

Patients without occurrence of a specific endpoint (composite endpoint or individual components) will be considered censored at the individual day of trial completion, which is defined as the date of last visit or the date of last contact if lost to follow-up.

For patients who died during the study, the date of death will be used for censoring.

Endpoints of CV or all-cause mortality:

For CV mortality, a patient who did not die or died from causes other than cardiovascular diseases will be censored at the individual day of trial completion (if alive) or date of death (if died from another event).

For all-cause mortality, a patient will be censored at the individual day of trial completion.

Endpoints based on laboratory data

Patients who already fulfil the respective condition at baseline are generally not considered in the number of patients at risk for this endpoint.

If a baseline laboratory measurement is not available for the parameter of interest, it is assumed that the patient did not experience the condition corresponding to the endpoint at baseline and the patient is included in the patients at risk for this endpoint.

Patients without an event and available post-baseline laboratory measurements will be considered censored at the date of last laboratory sampling of the corresponding parameter.

3.5 Loss to follow-up

If a patient could not be followed up at study termination for primary endpoint or other endpoints, this patient will be considered as loss to follow-up (LTFU) for primary endpoint or respectively as LTFU for other endpoints. Study termination is defined by the start of the close-out period. The number of patients and frequency will be provided.

Patients with an adjudicated event for the primary endpoint are not regarded as LTFU for primary endpoint. Patients who died are not regarded as LTFU for all endpoints.

4. Sample size and statistical power

4.1 Estimation of sample size

The proposed trial has a single primary outcome (a composite of major cardiovascular diseases) and several key secondary outcomes. The sample size calculation is based on the primary outcome and use of the following assumptions:

- Event rate of composite major CVD of 2.0% per year among patients with diabetes and elevated BP (based on the 4C Study 3.8-year follow-up data)
- 20% effect size for the intervention (hazard ratio of 0.80)
- 2-year uniform recruitment period and total study length of 5 years
- 2% per year loss to follow-up
- Two-sided significance test at the 5% level, and a statistical power of 90%

The calculated size of samples is 12,702 and the expected total number of events is 866. In addition, we analyzed statistical powers for various assumptions (**Table 2**). If annual event rate of composite major CVD is only 1.8%, we will still have 87% statistical power to detect a 20% risk reduction.

Table 2. Power for the primary outcome (composite major cardiovascular disease)

Sample size/ Hazard ratio	Annual event rate								
	1.8%			*2.0%*			*2.2%*		
	0.75	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*
12000	96.8	84.9	60.0	98.0	88.3	64.3	98.7	91.0	68.3
12250	97.0	85.7	60.8	98.2	88.9	65.2	98.9	91.5	69.2
12500	97.3	86.3	61.6	98.3	89.5	66.0	99.0	92.0	70.0
12750	**97.5**	**87.0**	**62.5**	**98.5**	**90.1**	**66.9**	**99.1**	**92.5**	**70.9**
13000	97.7	87.6	63.3	98.7	90.7	67.7	99.2	93.0	71.7
13250	97.9	88.2	64.1	98.8	91.2	68.6	99.3	93.4	72.5
13500	98.1	88.8	65.0	98.9	91.7	69.4	99.4	93.8	73.3

4.2 Statistical power for cognitive outcome

All BPROAD participants will be included in the BPROAD Cognitive Study. We have assumed a 1.5% per year event rate for the cognitive study primary outcome (the first identification of adjudicated dementia) in the standard treatment group, a 20% effect size for the intervention (hazard ratio of 0.8), a two-year uniform recruitment period, a total study length of 5 years, a 2.0% per year loss to follow-up, and a two-sided test at the 5% level. With these assumptions and the sample size of 12,702 participants, the statistical power for the cognitive study primary outcome is 80%.

4.3 Statistical power for kidney outcome

For kidney outcome, observational data from the 4C study revealed: 1) an approximately 10% CKD patients (eGFR<60 ml/min/1.73 m^2), 2) an annual event rate of CKD progression of approximately 1.5%, and 3) an annual event rate of CKD development of approximately 1.2% among patients aged ≥50 years with treated diabetes and hypertension

at baseline. Statistical powers for kidney outcome are presented in **Table 3** for a range of event rates.

Table 3. Power for the kidney outcome

Hazard	Event Rate (% per year)						
Ratio	1.0	1.1	1.2	1.3	1.4	1.5	1.6
0.80	0.6366	0.6774	0.7144	0.7478	0.7778	0.8047	0.8286
0.81	0.5898	0.6301	0.6673	0.7013	0.7324	0.7608	0.7864
0.82	0.542	0.5811	0.6177	0.6517	0.6832	0.7123	0.7392
0.83	0.4939	0.5312	0.5664	0.5996	0.6308	0.6601	0.6874
0.84	0.4463	0.4811	0.5144	0.5461	0.5763	0.605	0.6321
0.85	0.3997	0.4316	0.4624	0.4922	0.5207	0.5481	0.5743

Assumptions: 2-year recruitment with a uniform accrual rate; annual proportion lost to follow-up = 2%; 2-sided significance level = 0.05; and an overall sample size = 12,702

5. Interim analysis

The interim analyses are based on the stopping boundaries for the primary outcome calculated by the Lan-DeMets method with an O'Brien-Fleming type alpha spending function with the sample size of 12,702. Four interim and one final analysis are planned to be conducted, whereby the interim analysis would occur after approximately 1/5, 2/5, 3/5 and 4/5 of the total anticipated number of primary endpoint events had been observed and adjudicated. The statistical methods for the interim analysis will be the same as the final analysis (see section 6.3.1 'primary endpoint').

Let hr^ be the observed hazard ratio. **Table 4** lists the stopping efficacy boundaries, which is defined by the log hazard ratio, for the interim analysis. Efficacy boundaries are the threshold for early stop the trial due to significantly effective treatment.

Results of the interim analysis will be for the use of the Data Safety and Monitoring Board (DSMB) and will not be revealed to the investigators.

Table 4. Interim analysis for testing H_0: d=0 vs H_a: d≠0, where d is the log hazard ratio

Stage	Information fraction (Expected number of composite CVD events)	Efficacy boundary value (in log hazard ratio)	Rule	Total type I error achieved
1	0.2 (173)	0.742	If hr^>2.100 or hr^<0.476, reject H_0 and stop; otherwise continue to the next stage	0.000001
2	0.4 (346)	0.361	If hr^>1.435 or hr^<0.697, reject H_0 and stop; otherwise continue to the next stage	0.001
3	0.6 (520)	0.235	If hr^>1.265 or hr^<0.791, reject H_0 and stop; otherwise continue to the next stage	0.008
4	0.8 (693)	0.174	If hr^>1.190 or hr^<0.840, reject H_0 and stop; otherwise continue to the next stage	0.024
5	1.0 (866)	0.138	If hr^>1.148 or hr^<0.871, reject H_0 and stop; otherwise stop and accept H_0	0.050

6. Planned analysis

6.1 Subject disposition

A general overview on patient disposition will include the number of patients screened, randomized, screened but not randomized, randomized and inclusion eligible, randomized but not inclusion eligible. For subjects not randomized and randomized but not inclusion eligible, the number and percentage of subjects by primary reasons will be summarized.

In addition, the number and percentage of randomized subjects who completed planned study visits, and who discontinued the study prematurely by reason for premature discontinuation will be summarized.

6.2 Baseline characteristics

Descriptive analysis of the following characteristics and variables measured at baseline will be presented by treatment groups and in total for the FAS.

1) Demographics and behavior characteristics

- Gender (categorized as men and women), age (continuous and categorized as 50-<60, 60-<70, 70-<75 and ≥75 years), education (categorical), household income (categorical), current working status (categorical)
- height (continuous), weight (continuous), BMI (continuous and categorized as <25, 25-<28 and ≥28 kg/m^2), waist circumference (continuous), hip circumference (continuous), waist-to-hip ratio (continuous)
- Smoking history: current smoking (yes/no), cigarettes smoked per day (continuous), smoking years (continuous), pack-years (continuous), second-hand smoke exposure (yes/no)
- Drinking history: current drinking (yes/no), alcohol consumption per week (continuous)

- Physical activity (continuous and categorized as <600 and ≥600 MET-Mins/week)
- Salt intake (continuous), Dietary Approaches to Stop Hypertension (DASH) score

2) History of cardiovascular disease

- Clinical CVD (yes/no, including stroke, MI, PCI or CABG, carotid endarterectomy or carotid stenting, peripheral artery disease with revascularization, and acute coronary syndrome)
- Subclinical CVD (yes/no, including microalbuminuria; ≥50% stenosis of a coronary artery, a carotid artery, or a lower extremity artery; coronary artery calcium score ≥400 Agatston units; ankle brachial index (ABI) ≤0.90; and left ventricular hypertrophy)

3) Renal function

- Serum creatinine (continuous)
- eGFR (continuous and categorized as <60 or ≥60 mL/min/1.73m², calculated using the CKD-EPI equation)
- UACR (continuous and categorized as <30, 30-<300 and ≥300mg/g)

4) Blood pressure

- Sitting systolic and diastolic BP (continuous and categorized into tertiles)
- Standing systolic and diastolic BP (continuous)

5) Glucose

- Fasting plasma glucose (continuous)
- HbA1c (continuous and categorized as <7.0% and ≥7.0%)

6) Lipid profile

- Fasting total cholesterol (continuous)
- Fasting LDL cholesterol (continuous)
- Fasting HDL cholesterol (continuous)
- Fasting triglycerides (continuous)

7) Other baseline characteristics

- diabetes duration (continuous and categorized as < and ≥ the median)
- hypertension duration (continuous and categorized as < and ≥ the median)
- family history of early onset of CVD (yes/no)
- number of antihypertensive agents (continuous)
- antihypertensive drugs such as ACEI, ARB, CCB, etc. (yes/no)
- antidiabetic drugs such as insulin, metformin, GLP-1 receptor agonist, SGLT-2 inhibitors, etc. (yes/no)
- statin (yes/no)
- aspirin (yes/no)
- sitting and standing heart rate (continuous)

The following principles will be used to describe the baseline characteristics.

1) Descriptive statistics for continuous variables:
   - The continuous variables will be tested for normal distribution, and statistics will be selected based on the distribution.
   - Describe central tendency: Normal distribution data will be described by means, and skewed distribution data will be described by medians.
   - Describe variability: Normal distribution data will be described by standard deviation, and skewed distribution data will be described by interquartile range.
2) Descriptive statistics for categorical variables: Number of participants and proportion will be used to describe categorical variables.
3) Comparison between groups: Based on the distribution of continuous variables, the independent sample T-test or Wilcoxon rank sum test will be used to compare the quantitative data between treatment groups. The Chi-square test or Fisher's exact test will be used to compare the qualitative data between treatment groups.

6.3 Outcomes and safety evaluation

6.3.1 Primary endpoint

The primary endpoint is time to first occurrence of a composite outcome of major cardiovascular diseases. The allocated trial treatment at randomization will be used for analysis, and all events which occurred until the trial end will be considered. Time-to-event analysis will be used to compare primary endpoint between the intensive treatment group and the standard treatment group. The calculation of time to events is described in **Section 3.4**.

1) Primary analysis

Primary analysis will be performed according to the intention to-treat principle. All inclusion eligible randomized participants (FAS) will be grouped according to their intervention assignment at randomization, regardless of whether BP goals are achieved.

Description and comparison. Estimates of cumulative event rates will be calculated using the Kaplan-Meier method and differences between two treatment groups will be tested using the log-rank test. The overall two-sided significance level is 0.05.

Effect estimates. Cox proportional hazards regression will be used to compare the time from randomization to the first CVD event between the randomization groups. The model will include an indicator for intervention as its sole predictor variable. Clinical site at randomization will be a stratifying factor. The p-value from the primary analysis will be based on the χ^2 statistic from a likelihood ratio test obtained from proportional hazards models with and without the intervention term. This likelihood ratio test will constitute the primary test of statistical significance (two-sided p-value <0.05) for the primary analysis. Effect estimates (hazard ratios) with confidence intervals (CIs) will be reported.

2) Subgroup analysis

Analyses will be conducted in the following subgroups to determine whether the effects

of intensive BP treatment on primary study outcome (major CVD) are consistent.

- Age at baseline (<65 vs. ≥65 years; <80 vs. ≥80 years)
- Men vs. women
- Previous CVD
- Previous chronic kidney disease (CKD, eGFR<60 ml/min/1.73 m^2)
- Systolic BP levels at baseline (tertiles)
- HbA1c at baseline (tertiles)
- Diabetes duration at baseline (< vs. ≥ the median)
- High BP duration at baseline (< vs. ≥ the median)

The subgroup categories can be pooled, if the number of patients within a category is small. For each subgroup, baseline demographics and other variables will be displayed based on the FAS. Patients with missing information for a subgroup will not be considered in the analysis.

For each subgroup analysis, a proportional hazards model will be used that is the same as the one described for the primary analysis above, but with additional terms identifying subgroup membership and the intervention-by-subgroup interaction. Interactions between treatment effect and pre-specified subgroups will be assessed with a likelihood-ratio test. The p-value for the subgroup-by-treatment interaction, the HR, 95% CI and the corresponding two-sided p-value for the treatment group comparison (intensive vs. standard) for each subgroup category will be obtained from this model.

3) Sensitivity analysis

Cox proportional hazards regression assumptions will be examined by Schoenfeld residual test and plotting log (cumulative hazard) against the follow-up time by treatment groups and checked for parallelism. In case the proportionality assumption for the treatment effect does not hold, an attempt will be undertaken to identify groups of patients for which the proportional assumption holds and a stratified Cox regression and stratified log-rank test will be performed. The HR and corresponding 95% CI will be obtained from the stratified Cox model.

For the primary endpoint, a sensitivity analysis will be done on the PPS, which will be conducted using the same statistical method as the primary analysis.

The Fine and Gray model for the competing risk of death will be used as another sensitivity analysis for the primary endpoint to compare the statistical differences in the risk of composite CVD between the intensive treatment group and the standard treatment group.

6.3.2 Secondary endpoints

Each of the secondary endpoints will be analyzed using a proportional hazards model as described for the primary endpoint analysis. Effects will be reported with HR, 95% CI, and nominal p values without an adjustment for multiple comparisons, since the intent is to articulate a pattern of effects closely related to the primary outcome, rather than to provide additional tests of efficacy.

The Fine and Gray competing risk regression model will be used to compare the statistical differences in the risk of cardiovascular death between the intensive treatment group and the standard treatment group.

HRQoL is assessed by the SF-12, PHQ-9, and EQ-5D at baseline and annual follow up visits. Follow-up scores will be compared using mixed-effects analysis of covariance models. Estimates of the difference in mean levels of the outcome between standard and intensive treatment groups will be obtained using maximum likelihood method. The adjusted least-square means with standard error (SE) per treatment group and the mean difference with SE or 95% CI will be reported for each time point.

6.3.3 Kidney endpoints

The analysis for CKD progression and CKD development will be conducted in patients with and without baseline CKD (eGFR <60 mL/min/1.73m^2), separately. The analysis for incident albuminuria will be conducted in patients with or without CKD. Outcomes will be analyzed using a proportional hazards model as described for the primary endpoint analysis. Effect estimates (HR) with 95% CIs will be reported. Subgroup analysis will follow the same approach as for the primary endpoint.

6.3.4 Cognitive endpoints

1) Primary analysis

The primary endpoint for BPROAD Cognitive Study is time to first identification of all-cause dementia. The primary analysis will be performed the same as that of the primary endpoint of composite CVDs.

Description and comparison

Descriptive analysis of the following cognitive domains measured at baseline will be presented by treatment groups using the FAS.

1) Montreal cognitive assessment (MoCA)

2) Auditory verbal learning test (AVLT)

3) Digit span test (DST)

4) Verbal fluency test (VFT)

5) Trail making test (TMT)

6) Clock drawing test (CDT)

7) Activity of daily living (ADL)

8) Clinical dementia rating (CDR)

Cumulative event rates of all-cause dementia will be calculated using the Kaplan-Meier method and differences between the two treatment groups will be tested using the log-rank test. The overall two-sided significance level is 0.05.

Effect estimates

A cox proportional hazards model as described for the primary endpoint analysis (composite CVDs) will be used to compare the time from randomization to the first identification of dementia between the two treatment groups. Effect estimates (HR) with 95% CIs will be reported.

2) Subgroup analysis

Whether dementia occurs differently between the two treatment groups will also be explored across subgroups. Subgroup analysis will follow the same approach as for the BPROAD primary endpoint of composite CVDs. The following subgroups are prespecified in the BPROAD Cognitive Study.

- Age at baseline (<75 vs ≥75 years)
- Men vs. women
- Previous CVD
- Previous chronic kidney disease (CKD, eGFR<60 ml/min/1.73 m^2)
- Systolic BP levels at baseline (tertiles)
- HbA1c at baseline (tertiles)
- Standing systolic BP (tertiles)
- Apolipoprotein E (APOE) ε4 allele (0, 1, 2)

3) Sensitivity analysis

Cox proportional hazards regression assumptions will be examined by Schoenfeld residual test and plotting log (cumulative hazard) against the follow-up time by treatment groups and checked for parallelism. In case the proportionality assumption for the treatment effect does not hold, the same approach will be used as that of the primary endpoint of composite CVDs.

The Fine and Gray model for the competing risk of death will be used as another sensitivity analysis for the primary endpoint to compare the statistical differences in the risk of all-cause dementia between the intensive and the standard treatment group. A sensitivity analysis will also be done on the PPS, which will be conducted using the same statistical method as the primary analysis.

The characteristics of baseline variables and cognitive function will be compared between participants included in the primary analysis versus those excluded due to loss to follow-up or missing information on cognitive function. Sensitivity of results to missing data will be investigated using multiple imputation methods.

4) Secondary analysis

- Mild cognitive impairment

This outcome is defined as time to first identification of MCI. The same analytical approach for dementia will be used for MCI in patients without MCI at baseline.

- A composite of dementia and MCI

This outcome is a composite of all-cause dementia and MCI, defined as time to first

identification of all-cause dementia or MCI. The same analytical approach for dementia will be used for this composite outcome.

- Changes in cognitive performance

This includes cognitive decline in global and specific cognitive domains of learning and memory, complex attention, executive functioning, language, and visuospatial skills. The changes in domain-specific cognitive performance will be calculated as z scores standardized to the baseline mean and SD at each time point. We will use mixed-effects regression models with maximum likelihood estimation to assess between-group differences in changes from baseline to the last visit.

- Changes in brain MRI

This includes the development of cerebral small vessel disease (CSVD), changes in total brain volume, numbers of high signal lesions of white matter, etc. as assessed by brain MRI. The effects of intervention on the occurrence of CSVD will be examined using logistic regression in patients without CSVD at baseline. The effects of intervention on changes in total brain volume and numbers of high signal lesions of white matter will be examined using linear mixed-effects model with maximum likelihood estimation. Fixed effects will include treatment groups and other covariates. Random intercepts and slopes will be included to account for within-individual correlation.

6.3.5 Other efficacy endpoints

For the analysis of other efficacy endpoints including cardiovascular revascularization procedures, hospitalized unstable angina, retinopathy, TIA, LVH, atrial fibrillation or flutter, and cancer, a proportional hazards model as described for the primary CV analysis will be performed to compare the time to the first occurrence of each endpoint between the two treatment groups. For the analysis of cost-effectiveness, the following statistical analysis plan will be used.

Cost-effectiveness

Health effects of the 2 treatments will be measured as life-years gained (LYGs) or quality-adjusted life-years (QALYs). LYGs will be calculated as the additional number of years of life that a participant lives as a result of receiving the intensive treatment over the standard treatment. QALYs adjust LYGs by the quality of the participant's overall HRQoL, as measured by the EQ-5D during these life-years gained. The cost-effectiveness analysis (CEA) and the cost-utility analysis (CUA), which evaluate the incremental cost per LYG and QALY, respectively will be conducted.

All direct medical costs associated with treatment of hypertension and its complications and costs for treating adverse events will be considered. The ratios of cost to health effects such as the LYGs and the QALYs are used to compare cost-effectiveness between the two treatment groups. An incremental cost-effectiveness ratio (ICER) or an incremental cost-utility ratio (ICUR) will be calculated to provide a summary of the cost-effectiveness of the intensive treatment relative to the standard treatment.

ICER = (Difference in costs between the intensive and the standard treatment) / (Difference in LYGs between the intensive and the standard treatment)

ICUR = (Difference in costs between the intensive and the standard treatment) / (Difference in QALYs between the intensive and the standard treatment)

Bootstrap methods will be used to calculate confidence intervals for cost-effectiveness ratios. All costs will be adjusted to the baseline year using the Consumer Price Index. Future costs and outcomes will be discounted by 3%. Estimates of utilization over time will be adjusted for the presence of censored data with variable follow-up. Sensitivity analysis will explore the effect of correlations between costs and outcomes, which will also be empirically examined in the cost and outcome data.

QALYs will be calculated by summing the area under every participant's QALY curve (constructed by plotting the EQ-5D scores for each interview during follow-up). The estimates of mean differences in costs and outcomes – which will be used to create net health benefits and the cost per QALY ratios – will be derived from multivariable regression analyses.

6.3.6 Safety evaluation

The types, frequency of occurrence, and relationship to the study protocol of serious adverse events (SAEs, see section 2.6 'Safety endpoints') will be described. All description of SAEs will be based on the number of patients with SAEs (and not on the number of SAEs). In addition, the numbers and proportions of clinical safety alerts (abnormal serum sodium, abnormal serum potassium, increased serum creatinine, and ECG abnormality) will also be described.

The BPROAD study will focus on SAEs related to BP lowering. The time to first occurrence of an SAE will be compared between the intensive and the standard treatment groups using a cox proportional hazards regression model, the same as that for the BPROAD primary endpoint of composite CVDs, with the use of the intention-to-treat approach on the FAS. A sensitivity analysis will be done on the PPS, which will be conducted using the same statistical method as the primary analysis.

Whether SAEs occur differently between the two treatment groups will also be explored across subgroups. Subgroup analysis will follow the same approach as for the BPROAD primary endpoint of composite CVDs.

6.4 Other analysis

Analyses of biologically plausible subgroups will be explored. Some of these will be further articulation of supporting subgroup analyses described above, such as analysis of continuous baseline factors as continuous variables rather as pre-specified categorical variables. Other analyses will involve baseline variables that are not listed in the pre-specified subgroups, but which may modify treatment effects, such as diastolic blood pressure.

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Blood Pressure Control Target in Diabetes (BPROAD) Trial

Statistical Analysis Plan

Version 5.0

February 2024

CONTENTS

Changes of BPROAD Statistical Analysis Plan Versions 1.0 - 5.0

STATISTICAL ANALYSIS PLAN VERSION 1.0 (June 2019)

STATISTICAL ANALYSIS PLAN VERSION 2.0 (February 2020):

Changes in the BPROAD statistical analysis plan version 2.0 include:

1. Secondary endpoints: 'Total MI including fatal and non-fatal MI', 'ischemic stroke', and 'hemorrhagic stroke' were added as pre-specified 'Secondary endpoints' in the section '2.2 Secondary endpoints'.
2. Cognitive endpoints: A composite of all-cause dementia and mild cognitive function (MCI) was used instead of dementia alone as the primary endpoint of the BPROAD Cognitive Study. Dementia alone and MCI alone were two secondary outcomes, among others. The statistical power for the BPROAD Cognitive Study was re-calculated using the new primary outcome and updated findings from the SPRINT MIND Study. These changes were made to the sections '4.2 Statistical power for cognitive outcome' and '6.3.4 Cognitive endpoints'.
3. Analysis sets: Per protocol set and all analyses using per protocol set were removed. 'inclusion eligible' was removed from the definition of the full analysis set. Therefore, the primary analysis will be conducted on all randomized subjects. These changes were made to the sections '3.2 Analysis sets' and '6.3 Outcomes and safety evaluation'.
4. Subgroup analysis: It was specified that data from the screening visit will be used to define subgroups, which was added to the section '6.3 Outcomes and safety evaluation'.
5. Interim analysis: Early interim analysis was dropped and the interim analysis will be conducted when the accumulating primary case number is at 50% and 75% of the total anticipated number. These changes were made to the section '5. Interim analysis'.
6. Safety evaluation: Analyses for repeat 'adverse events' were considered in the section '6.3 Outcomes and safety evaluation'.
7. Study extension: The possibility of trial extension was added to the section '4.1 Estimation of sample size'.

STATISTICAL ANALYSIS PLAN VERSION 3.0 (June 2020):

Changes in the BPROAD statistical analysis plan version 3.0 include:

1. Cognitive component of the trial: The BPROAD Data and Safety Monitoring Board (DSMB) is concerned about the accumulation of cognitive events within the planned study period and has suggested to indicate how the trial intends to end the cognitive component of the trial in this SAP. Therefore, we made clarifications in the section '4.2 Statistical power for cognitive outcome'.

STATISTICAL ANALYSIS PLAN VERSION 4.0 (October 2022):

Changes in the BPROAD statistical analysis plan version 4.0 include:

1. Stratifying factor for effect estimates: Analyses will stratify by region rather than by clinic. We made changes in the section '6.3.1 Primary endpoint'. The 145 BPROAD study sites and regions to which they belong are listed in the Appendix at the end of this SAP.

STATISTICAL ANALYSIS PLAN VERSION 5.0 (February 2024):

A decision not to conduct the 2nd interim analysis of the BPROAD trial was made and approved by BPROAD Data and Safety Monitoring Board (DSMB) chair and statistician. The signed approval was added to the BPROAD statistical analysis plan version 5.0.

1. Summary of study design

The Blood Pressure Control Target in Diabetes (BPROAD) Trial is a multi-center, open-label, parallel-group, randomized controlled trial. It will test the primary hypothesis of whether an intensive treatment strategy (a systolic blood pressure target of <120 mmHg) is more effective than a standard treatment strategy (a systolic blood pressure target of <140 mmHg) in reducing the risk of major cardiovascular disease (non-fatal stroke, non-fatal myocardial infarction, treated or hospitalized heart failure, and cardiovascular deaths) over a follow-up period of up to 5 years among patients with a history of diabetes and elevated systolic blood pressure. The secondary hypotheses are to compare the intensive blood pressure treatment strategy with the standard treatment strategy on total stroke (fatal and non-fatal ischemic and hemorrhagic stroke), total myocardial infarction (fatal and non-fatal myocardial infarction), treated or hospitalized heart failure, cardiovascular disease mortality, all-cause mortality, cognitive function, kidney outcomes, and quality of life, *etc.*

The trial will recruit 12,702 patients from approximately 150 hospitals within the China Diabetes Clinical Research Network. Eligible criteria include men and women aged ≥50 years; type 2 diabetes mellitus; elevated systolic blood pressure; and a history of clinical cardiovascular disease or increased risk for cardiovascular disease. Main exclusion criteria include known secondary cause of hypertension, symptomatic heart failure, end-stage renal disease, and other serious illness. The proposed trial has 90% statistical power to detect a 20% reduction (hazard ratio of 0.80) in major cardiovascular disease between intensive and standard treatment groups at a 2-sided significance level of 0.05. We further assume an event rate of major cardiovascular disease of 2.0% per year in the control arm based on 3.8-year follow-up data from the China Cardiometabolic Disease and Cancer Cohort (4C) study, 2-year uniform recruitment period, total study length of 5 years, and 2% per year rate of loss to follow-up. The findings from this trial will provide evidence as to whether intensive blood pressure management to achieve a systolic blood pressure target of <120 mmHg has additional benefits over standard management of systolic blood pressure <140 mmHg.

The primary objective of the BPROAD Cognitive Study is to determine whether randomization to an antihypertensive treatment strategy achieving systolic BP <120 mmHg is more effective than a treatment strategy achieving systolic BP <140 mmHg in reducing the risk of a composite of all-cause dementia and mild cognitive impairment (MCI) among patients with diabetes over a follow-up period of up to 5 years. In addition, other objectives are to compare between intensive and standard BP treatment groups: 1) incidence of dementia; 2) incidence of MCI; 3) changes in global and specific cognitive domains including learning and memory, complex attention, executive functioning, language, and visuospatial skills; and 4) changes in total brain volume, incidence of cerebral small vessel disease, *etc.* assessed by brain magnetic resonance imaging (MRI). All BPROAD participants will receive cognitive assessments using cognition scales at the baseline visit and will be reassessed at annual follow-up visits to examine changes in global and domain-specific cognition. In addition, 10-20 study sites will be selected for MRI sub-study and participants recruited in these study sites will receive brain MRI at the baseline visit and at the close-out

visit. The BPROAD Cognitive Study will provide evidence as to whether intensive BP lowering benefits brain health in diabetes.

This Statistical Analysis Plan (SAP) is based on the planned analysis specification as written in BPROAD Study Protocol Chapter 8 "Statistical Considerations". Therefore, SAP readers may consult the protocol for more detailed background information of the trial, e.g., trial objectives, trial design and participants, treatments, endpoints, *etc.*

2. Endpoints

2.1 Primary endpoint

The primary endpoint is time to first occurrence of a composite of non-fatal myocardial infarction (MI), non-fatal stroke, treated or hospitalized heart failure, and death of cardiovascular causes.

2.2 Secondary endpoints

A few secondary endpoints will also be analyzed in BPROAD. These include time to first occurrence of the following:

- An expanded outcome including the composite primary outcome and all-cause mortality
- Macrovascular outcome including the composite primary outcome, hospitalized unstable angina, and all cardiovascular revascularization procedures
- Major coronary artery diseases including non-fatal MI, hospitalized unstable angina, revascularization of coronary arteries, and death due to coronary artery diseases
- Total MI including fatal and non-fatal MI
- Total stroke including fatal and non-fatal stroke
- Ischemic stroke
- Hemorrhagic stroke
- Hospitalized or treated heart failure, or death due to heart failure
- Cardiovascular mortality
- All-cause mortality

In addition, health-related quality of life (HRQoL) is another secondary outcome, which will be assessed by the SF-12, PHQ-9, and EQ-5D at baseline and annual follow-up visits. The HRQoL endpoints are changes in scores of these 3 scales from baseline.

2.3 Kidney endpoints

The kidney related endpoints are time to first occurrence of the following:

- CKD progression: a composite of end-stage renal disease, eGFR<15 ml/min/1.73 m^2, or 50% decline in eGFR from baseline in patients with CKD at baseline

- CKD development: eGFR <60 ml/min/1.73 m^2 and ≥30% decrease from baseline eGFR in patients without CKD
- Incident albuminuria: a doubling of urinary albumin-to-creatinine ratio (ACR) from a value <10 mg/g to a value of >10 mg/g in all patients with or without CKD

2.4 Cognitive endpoints

The primary endpoint in the BPROAD Cognitive Study is time to first identification of a composite of all-cause dementia and MCI. Secondary endpoints include time to first identification of dementia alone, MCI alone, changes in global and specific cognitive domains including learning and memory, complex attention, executive functioning, language, and visuospatial skills, and changes in total brain volume, incidence of cerebral small vessel disease, *etc.* assessed by brain MRI.

2.5 Other efficacy endpoints

- All cardiovascular revascularization procedures including percutaneous transluminal coronary angioplasty (PTCA) with balloon or stent, coronary artery bypass grafting (CABG), carotid angioplasty with stent, carotid endarterectomy, peripheral angioplasty with or without stent, peripheral vascular surgery (including aortic aneurysm repair) and limb amputation including partial or digit amputation due to vascular disease
- Hospitalized unstable angina
- Retinopathy
- Transient ischemic attack (TIA)
- Left ventricular hypertrophy (LVH) diagnosed by ECG
- Atrial fibrillation or flutter
- All cancers
- Cost-effectiveness

2.6 Safety endpoints

Adverse events will be reported if they met criteria of serious adverse events (SAE) defined as an event that is:

- fatal or life-threatening
- result in clinically significant or persistent disability
- require or prolong hospitalization
- important medical events that investigators judge to represent significant hazards or harm to research participants and may require medical or surgical intervention to prevent one of the other outcomes listed above

In addition, a selected list of other important events which lead to emergency room visits will also be reported in BPROAD:

- symptomatic hypotension
- arrhythmia

- acute kidney failure
- electrolyte abnormalities
- injurious falls
- syncope

3. General analysis definitions

3.1 Treatments

Participants eligible for the trial will be randomized to one of two treatment groups:

- Systolic BP <120 mmHg for the intensive treatment group
- Systolic BP <140 mmHg for the standard treatment group

3.2 Analysis sets

1) **Screened Set (SS):** This will include all patients who signed the informed consent.

2) **Randomized Set (RS):** All screened patients who were randomized, including those who violated inclusion criteria.

3) **Full Analysis Set (FAS):** According to the Intention to Treatment (ITT) principle, all randomized subjects will be included into the full analysis set and will be grouped according to their intervention assignment at randomization, whether BP goals achieved or not. The FAS is the main data set for outcomes and safety analysis.

Table 1 specifies the patient set for each planned analysis.

Table 1. Specifying patient sets for analysis

	SS	RS	FAS
Disposition	X	X	
Demographic and baseline characteristics			X
Outcome and safety endpoints			X

3.3 Missing data

3.3.1 Missing on baseline characteristics and BP levels

Every effort will be made to collect data as complete as possible. Missing data on baseline information will not be replaced in the patients' baseline characteristics displayed. Patients with baseline missing information for a subgroup definition will not be included in the respective subgroup analysis.

BP levels will be assessed at every visit during the study. The mean and median of the BP levels at each visit will be calculated and compared between the two treatment groups. Missing data on BP levels during the study will not be imputed. Patients with missing BP measurements will not be included in calculation.

3.3.2 Missing on endpoints

The principles given below are the planned methods for imputation depending upon the type of the endpoints.

For each time to event analysis, patients who are lost to follow-up and who do not have a particular endpoint will be censored. In the case that only the year is documented, the day and month will be imputed as 01 January unless the subsequently derived date is before randomization; in this case the date of randomization will be used as the censoring date. If year and month is present, the day will be imputed as first of the month unless the subsequently derived date is before randomization; in this case the date of randomization will be used.

For continuous endpoints such as eGFR, UACR, HRQoL scores, cognitive function scores, and total brain volume, all available data will be considered. Missing data will not be replaced. All subjects with a non-missing baseline value and at least one non-missing post-baseline value will be included in these analyses. Subjects with a missing baseline value or without a non-missing post-baseline value will not contribute to the analyses.

For participants lost to follow-up, all available information until the time of death or loss to follow-up will be used. We will assume missing-at-random (MAR) for the primary analysis. In a sensitivity analysis, we will investigate whether loss to follow-up is related to the outcome being analyzed. The magnitude of this problem will be investigated by using measurements taken at previous visits to predict loss to follow-up. Variables determined to predict loss to follow-up will be included in our predictive models. In addition, we will examine several "worst-case" scenarios, including opposite and pooled imputation approaches. These types of scenarios are members of a broad class that can be parameterized as pattern mixture models and allow for examination of sensitivity of conclusions to missing-not-at-random (MNAR) mechanisms. Finally, the multiple imputation techniques will be used in the sensitivity analyses of the primary and secondary outcomes.

3.4 Time to event

The time to occurrence of primary and secondary endpoints, as well as safety events has to be calculated for analysis. This section describes the calculation of the time to event and the time that patients without an event in the trial (under risk).

The respective time intervals determine the start and end for the derivation of occurrence of a specific event.

For patients with an event, the time to event is calculated as:

<date of event> - < start date> + 1

For patients without an event, the time at risk is calculated as:

<date of censoring> - < start date > + 1

1) Start date

In general, the time to event will be derived from the date of randomization for outcomes and safety events.

2) Date of event

For composite outcomes, e.g. the primary composite endpoint, the earliest onset date of the corresponding components will be used. For fatal MI, fatal stroke, and fatal heart failure, the onset date of the event is used. While for other cardiovascular (CV) deaths, the date of death is used. A patient with at least one event in any of the components of the composite will be considered to have an event and the date of the first event will be used for the composite endpoint.

The dates determined by the outcome adjudication committee will be used; these can be different from the investigator reported dates. For the endpoints of time to CV death and time to all-cause mortality and other endpoints only based on a fatal component, the respective death date will be used.

For events with multiple episodes, such as adverse events (AE), the onset date of the first episode will be used.

The time to first occurrence of endpoints based on laboratory data or performance test, e.g. 'time to incident albuminuria' is determined by the date of the first laboratory measurement, in this example urinary albumin measurement, that fulfils this condition.

3) Censoring

Primary and other endpoints (except for the stand-alone endpoints of CV death, all-cause mortality):

The underlying principle is that the censoring date should be the date at which the patient

was last known to be free of the endpoint event (e.g. free of each component of the primary composite outcome).

Patients without occurrence of a specific endpoint (composite endpoint or individual components) will be considered censored at the individual day of trial completion, which is defined as the date of last visit or the date of last contact if lost to follow-up.

For patients who died during the study, the date of death will be used for censoring.

Endpoints of CV or all-cause mortality:

For CV mortality, a patient who did not die or died from causes other than cardiovascular diseases will be censored at the individual day of trial completion (if alive) or date of death (if died from another event).

For all-cause mortality, a patient will be censored at the individual day of trial completion.

Endpoints based on laboratory data

Patients who already fulfil the respective condition at baseline are generally not considered in the number of patients at risk for this endpoint.

If a baseline laboratory measurement is not available for the parameter of interest, it is assumed that the patient did not experience the condition corresponding to the endpoint at baseline and the patient is included in the patients at risk for this endpoint.

Patients without an event and available post-baseline laboratory measurements will be considered censored at the date of last laboratory sampling of the corresponding parameter.

3.5 Loss to follow-up

If a patient could not be followed up at study termination for primary endpoint or other endpoints, this patient will be considered as loss to follow-up (LTFU) for primary endpoint or respectively as LTFU for other endpoints. Study termination is defined by the start of the close-out period. The number of patients and frequency will be provided.

Patients with an adjudicated event for the primary endpoint are not regarded as LTFU for primary endpoint. Patients who died are not regarded as LTFU for all endpoints.

4. Sample size and statistical power

4.1 Estimation of sample size

The proposed trial has a single primary outcome (a composite of major cardiovascular diseases) and several key secondary outcomes. The sample size calculation is based on the primary outcome and use of the following assumptions:

- Event rate of composite major CVD of 2.0% per year among patients with diabetes and elevated BP (based on the 4C Study 3.8-year follow-up data)
- 20% effect size for the intervention (hazard ratio of 0.80)
- 2-year uniform recruitment period and total study length of 5 years
- 2% per year loss to follow-up
- Two-sided significance test at the 5% level, and a statistical power of 90%

The calculated size of samples is 12,702 and the expected total number of events is 866. In addition, we analyzed statistical powers for various assumptions (**Table 2**). If annual event rate of composite major CVD is only 1.8%, we will still have 87% statistical power to detect a 20% risk reduction. However, if the observed number of primary outcome cases is lower than the anticipated number due to secular trends that might reduce the CVD event rate, e.g. use of SGLT-2 inhibitors, extension of the intervention and trial will be considered after consulting the DSMB.

Table 2. Power for the primary outcome (composite major cardiovascular disease)

Sample size/ Hazard ratio	Annual event rate								
	1.8%			*2.0%*			*2.2%*		
	0.75	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*	*0.75*	*0.80*	*0.85*
12000	96.8	84.9	60.0	98.0	88.3	64.3	98.7	91.0	68.3
12250	97.0	85.7	60.8	98.2	88.9	65.2	98.9	91.5	69.2
12500	97.3	86.3	61.6	98.3	89.5	66.0	99.0	92.0	70.0
12750	**97.5**	**87.0**	**62.5**	**98.5**	**90.1**	**66.9**	**99.1**	**92.5**	**70.9**
13000	97.7	87.6	63.3	98.7	90.7	67.7	99.2	93.0	71.7
13250	97.9	88.2	64.1	98.8	91.2	68.6	99.3	93.4	72.5
13500	98.1	88.8	65.0	98.9	91.7	69.4	99.4	93.8	73.3

4.2 Statistical power for cognitive outcome

All BPROAD participants will be included in the BPROAD Cognitive Study. According to the SPRINT MIND findings, we assume a 2.4% per year event rate for the cognitive study primary outcome (a composite of all-cause dementia and MCI) in the standard treatment group, a 15% effect size for the intervention (hazard ratio of 0.85), a two-year uniform recruitment period, a total study length of 5 years, a 2.0% per year loss to follow-up, and a two-sided test at the 5% level. With these assumptions and the sample size of 12,702 participants, the statistical power for the cognitive study primary outcome is 74%.

It should be noted that because of the greater lag in the effects of BP reduction on cognitive effects than on CVD effects, the end of the trial for the cognitive decline and publication of those results will likely occur after the end of the trial and publication of the

CVD results. The annual event rate depends on the age of the final recruited population. Because we may have a study population younger than the SPRINT MIND population, we assume a range between 1.8% to 2.4% per year event rate of the primary outcome in the standard treatment group and calculated the anticipated total event number and statistical power at different annual event rate and total study length shown in **Table 3**. The BPROAD cognitive study will continue until 1374 cases of dementia or MCI (85% power) are observed.

Table 3. The anticipated total cognitive event number (statistical power)

Total Study Length	Event Rate (% per year)						
	1.8	1.9	2.0	2.1	2.2	2.3	2.4
5 years	785 (62%)	827 (65%)	869 (67%)	911 (69%)	952 (71%)	994 (73%)	1035 (74%)
6 years	964 (71%)	1015 (73%)	1066 (76%)	1117 (77%)	1168 (79%)	**1218 (81%)**	**1268 (82%)**
7 years	1137 (78%)	**1197 (80%)**	**1256 (82%)**	**1315 (84%)**	**1374 (85%)**	**1433 (87%)**	**1491 (88%)**

Assumptions: 15% effect size for the intervention (hazard ratio of 0.85); 2-year recruitment with a uniform accrual rate; annual proportion lost to follow-up = 2%; 2-sided significance level = 0.05; and an overall sample size = 12,702

4.3 Statistical power for kidney outcome

For kidney outcome, observational data from the 4C study revealed: 1) an approximately 10% CKD patients (eGFR<60 ml/min/1.73 m^2), 2) an annual event rate of CKD progression of approximately 1.5%, and 3) an annual event rate of CKD development of approximately 1.2% among patients aged ≥50 years with treated diabetes and hypertension at baseline. Statistical powers for kidney outcome are presented in **Table 4** for a range of event rates.

Table 4. Power for the kidney outcome

Hazard Ratio	Event Rate (% per year)						
	1.0	1.1	1.2	1.3	1.4	1.5	1.6
0.80	0.6366	0.6774	0.7144	0.7478	0.7778	0.8047	0.8286
0.81	0.5898	0.6301	0.6673	0.7013	0.7324	0.7608	0.7864
0.82	0.542	0.5811	0.6177	0.6517	0.6832	0.7123	0.7392
0.83	0.4939	0.5312	0.5664	0.5996	0.6308	0.6601	0.6874
0.84	0.4463	0.4811	0.5144	0.5461	0.5763	0.605	0.6321
0.85	0.3997	0.4316	0.4624	0.4922	0.5207	0.5481	0.5743

Assumptions: 2-year recruitment with a uniform accrual rate; annual proportion lost to follow-up = 2%; 2-sided significance level = 0.05; and an overall sample size = 12,702

5. Interim analysis

The interim analyses are based on the stopping boundaries for the primary outcome calculated by the Lan-DeMets method with an O'Brien-Fleming type alpha spending function with the sample size of 12,702. Two interim and one final analyses are planned to be conducted, whereby the interim analysis would occur after approximately 50% and 75% of the total anticipated number of primary endpoint events had been observed and adjudicated. The statistical methods for the interim analysis will be the same as the final analysis (see section 6.3.1 'primary endpoint').

Let hr^ be the observed hazard ratio. **Table 5** lists the stopping efficacy boundaries, which is defined by the log hazard ratio, for the interim analysis. Efficacy boundaries are the threshold for early stop the trial due to significantly effective treatment.

Results of the interim analysis will be for the use of the Data Safety and Monitoring Board (DSMB) and will not be revealed to the investigators.

Table 5. Interim analysis for testing H_0: d=0 vs H_a: d≠0, where d is the log hazard ratio

Stage	Information fraction (Expected number of composite CVD events)	Efficacy boundary value (in log hazard ratio)	Rule	Total type I error achieved
1	0.50 (433)	0.284	If hr^>1.329 or hr^<0.752, reject H_0 and stop; otherwise continue to the next stage	0.003
2	0.75 (650)	0.185	If hr^>1.203 or hr^<0.831, reject H_0 and stop; otherwise continue to the next stage	0.019
3	1.0 (866)	0.137	If hr^>1.147 or hr^<0.872, reject H_0 and stop; otherwise stop and accept H_0	0.050

6. Planned analysis

6.1 Subject disposition

A general overview on patient disposition will include the number of patients screened, randomized, screened but not randomized, randomized and inclusion eligible, randomized but not inclusion eligible. For subjects not randomized and randomized but not inclusion eligible, the number and percentage of subjects by primary reasons will be summarized.

In addition, the number and percentage of randomized subjects who completed planned study visits, and who discontinued the study prematurely by reason for premature discontinuation will be summarized.

6.2 Baseline characteristics

Descriptive analysis of the following characteristics and variables measured at baseline will be presented by treatment groups and in total for the FAS.

1) Demographics and behavior characteristics

- Gender (categorized as men and women), age (continuous and categorized as 50-<60, 60-<70, 70-<75 and ≥75 years), education (categorical), household income (categorical), current working status (categorical)
- height (continuous), weight (continuous), BMI (continuous and categorized as <25, 25-<28 and ≥28 kg/m^2), waist circumference (continuous), hip circumference (continuous), waist-to-hip ratio (continuous)
- Smoking history: current smoking (yes/no), cigarettes smoked per day (continuous), smoking years (continuous), pack-years (continuous), second-hand smoke exposure (yes/no)
- Drinking history: current drinking (yes/no), alcohol consumption per week (continuous)
- Physical activity (continuous and categorized as <600 and ≥600 MET-Mins/week)
- Salt intake (continuous), Dietary Approaches to Stop Hypertension (DASH) score

2) History of cardiovascular disease

- Clinical CVD (yes/no, including stroke, MI, PCI or CABG, carotid endarterectomy or carotid stenting, peripheral artery disease with revascularization, and acute coronary syndrome)
- Subclinical CVD (yes/no, including microalbuminuria; ≥50% stenosis of a coronary artery, a carotid artery, or a lower extremity artery; coronary artery calcium score ≥400 Agatston units; ankle brachial index (ABI) ≤0.90; and left ventricular hypertrophy)

3) Renal function

- Serum creatinine (continuous)
- eGFR (continuous and categorized as <60 or ≥60 mL/min/1.73m², calculated using the CKD-EPI equation)
- UACR (continuous and categorized as <30, 30-<300 and ≥300mg/g)

4) Blood pressure

- Sitting systolic and diastolic BP (continuous and categorized into tertiles)
- Standing systolic and diastolic BP (continuous)

5) Glucose

- Fasting plasma glucose (continuous)
- HbA1c (continuous and categorized as <7.0% and ≥7.0%)

6) Lipid profile

- Fasting total cholesterol (continuous)
- Fasting LDL cholesterol (continuous)
- Fasting HDL cholesterol (continuous)
- Fasting triglycerides (continuous)

7) Other baseline characteristics

- diabetes duration (continuous and categorized as < and ≥ the median)
- hypertension duration (continuous and categorized as < and ≥ the median)
- family history of early onset of CVD (yes/no)
- number of antihypertensive agents (continuous)
- antihypertensive drugs such as ACEI, ARB, CCB, *etc.* (yes/no)
- antidiabetic drugs such as insulin, metformin, GLP-1 receptor agonist, SGLT-2 inhibitors, *etc.* (yes/no)
- statin (yes/no)
- aspirin (yes/no)
- sitting and standing heart rate (continuous)

The following principles will be used to describe the baseline characteristics.

1) Descriptive statistics for continuous variables:
   - The continuous variables will be tested for normal distribution, and statistics will be selected based on the distribution.
   - Describe central tendency: Normal distribution data will be described by means, and skewed distribution data will be described by medians.
   - Describe variability: Normal distribution data will be described by standard deviation, and skewed distribution data will be described by interquartile range.
2) Descriptive statistics for categorical variables: Number of participants and proportion will be used to describe categorical variables.
3) Comparison between groups: Based on the distribution of continuous variables, the independent sample T-test or Wilcoxon rank sum test will be used to compare the quantitative data between treatment groups. The Chi-square test or Fisher's exact test will be used to compare the qualitative data between treatment groups.

6.3 Outcomes and safety evaluation

6.3.1 Primary endpoint

The primary endpoint is time to first occurrence of a composite outcome of major cardiovascular diseases. The allocated trial treatment at randomization will be used for analysis, and all events which occurred until the trial end will be considered. Time-to-event analysis will be used to compare primary endpoint between the intensive treatment group and the standard treatment group. The calculation of time to events is described in **Section 3.4**.

1) Primary analysis

Primary analysis will be performed according to the intention to-treat principle. All inclusion eligible randomized participants (FAS) will be grouped according to their intervention assignment at randomization, regardless of whether BP goals are achieved.

Description and comparison. Estimates of cumulative event rates will be calculated using the Kaplan-Meier method and differences between two treatment groups will be tested using the log-rank test. The overall two-sided significance level is 0.05.

Effect estimates. Cox proportional hazards regression will be used to compare the time from randomization to the first CVD event between the randomization groups. The model will include an indicator for intervention as its sole predictor variable. Seven geographical regions in mainland China, which are North, Northeast, East, South, Middle, Southwest, and Northwest China, will be used as a stratifying factor. The 145 BPROAD study sites and regions to which they belong are listed in the Appendix at the end of this SAP. The p-value from the primary analysis will be based on the χ^2 statistic from a likelihood ratio test obtained from proportional hazards models with and without the intervention term. This likelihood ratio test will constitute the primary test of statistical significance (two-sided p-value <0.05) for the primary analysis. Effect estimates (hazard ratios) with confidence intervals (CIs) will be reported.

2) Subgroup analysis

Analyses will be conducted in the following subgroups to determine whether the effects of intensive BP treatment on primary study outcome (major CVD) are consistent. Subgroups will be defined using data collected at the screening visit except for those not collected, in which case data collected at the baseline visit will be used.

- Age at baseline (<65 vs. ≥65 years; <80 vs. ≥80 years)
- Men vs. women
- Previous CVD
- Previous chronic kidney disease (CKD, eGFR<60 ml/min/1.73 m^2)
- Systolic BP levels at baseline (tertiles)
- HbA1c at baseline (tertiles)
- Diabetes duration at baseline (< vs. ≥ the median)
- High BP duration at baseline (< vs. ≥ the median)

The subgroup categories can be pooled, if the number of patients within a category is small. For each subgroup, baseline demographics and other variables will be displayed based on the FAS. Patients with missing information for a subgroup will not be considered in the analysis.

For each subgroup analysis, a proportional hazards model will be used that is the same as the one described for the primary analysis above, but with additional terms identifying subgroup membership and the intervention-by-subgroup interaction. Interactions between treatment effect and pre-specified subgroups will be assessed with a likelihood-ratio test. The p-value for the subgroup-by-treatment interaction, the HR, 95% CI and the corresponding two-sided p-value for the treatment group comparison (intensive vs. standard) for each subgroup category will be obtained from this model.

3) Sensitivity analysis

Cox proportional hazards regression assumptions will be examined by Schoenfeld residual test and plotting log (cumulative hazard) against the follow-up time by treatment groups and checked for parallelism. In case the proportionality assumption for the treatment effect does not hold, an attempt will be undertaken to identify groups of patients for which

the proportional assumption holds and a stratified Cox regression and stratified log-rank test will be performed. The HR and corresponding 95% CI will be obtained from the stratified Cox model.

The Fine and Gray model for the competing risk of death will be used as another sensitivity analysis for the primary endpoint to compare the statistical differences in the risk of composite CVD between the intensive treatment group and the standard treatment group.

6.3.2 Secondary endpoints

Each of the secondary endpoints will be analyzed using a proportional hazards model as described for the primary endpoint analysis. Effects will be reported with HR, 95% CI, and nominal p values without an adjustment for multiple comparisons, since the intent is to articulate a pattern of effects closely related to the primary outcome, rather than to provide additional tests of efficacy.

The Fine and Gray competing risk regression model will be used to compare the statistical differences in the risk of cardiovascular death between the intensive treatment group and the standard treatment group.

HRQoL is assessed by the SF-12, PHQ-9, and EQ-5D at baseline and annual follow up visits. Follow-up scores will be compared using mixed-effects analysis of covariance models. Estimates of the difference in mean levels of the outcome between standard and intensive treatment groups will be obtained using maximum likelihood method. The adjusted least-square means with standard error (SE) per treatment group and the mean difference with SE or 95% CI will be reported for each time point.

6.3.3 Kidney endpoints

The analysis for CKD progression and CKD development will be conducted in patients with and without baseline CKD (eGFR <60 mL/min/1.73m^2), separately. The analysis for incident albuminuria will be conducted in patients with or without CKD. Outcomes will be analyzed using a proportional hazards model as described for the primary endpoint analysis. Effect estimates (HR) with 95% CIs will be reported. Subgroup analysis will follow the same approach as for the primary endpoint.

6.3.4 Cognitive endpoints

1) Primary analysis

The primary endpoint for BPROAD Cognitive Study is time to first identification of all-cause dementia or mild cognitive impairment (MCI). The primary analysis will be performed the same as that of the primary endpoint of composite CVDs.

Description and comparison

Descriptive analysis of the following cognitive domains measured at baseline will be presented by treatment groups using the FAS.

1) Montreal cognitive assessment (MoCA)

2) Auditory verbal learning test (AVLT)

3) Digit span test (DST)

4) Verbal fluency test (VFT)

5) Trail making test (TMT)

6) Clock drawing test (CDT)

7) Activity of daily living (ADL)

8) Clinical dementia rating (CDR)

Cumulative event rates of all-cause dementia and MCI will be calculated using the Kaplan-Meier method and differences between the two treatment groups will be tested using the log-rank test. The overall two-sided significance level is 0.05.

Effect estimates

A cox proportional hazards model as described for the primary endpoint analysis (composite CVDs) will be used to compare the time from randomization to the first identification of dementia or MCI between the two treatment groups. Effect estimates (HR) with 95% CIs will be reported.

2) Subgroup analysis

Whether the composite of dementia and MCI occurs differently between the two treatment groups will also be explored across subgroups. Subgroup analysis will follow the same approach as for the BPROAD primary endpoint of composite CVDs. The following subgroups are prespecified in the BPROAD Cognitive Study.

- Age at baseline (<75 vs ≥75 years)
- Men vs. women
- Previous CVD
- Previous chronic kidney disease (CKD, eGFR<60 ml/min/1.73 m^2)
- Systolic BP levels at baseline (tertiles)
- HbA1c at baseline (tertiles)
- Standing systolic BP (tertiles)
- Apolipoprotein E (APOE) ε4 allele (0, 1, 2)

3) Sensitivity analysis

Cox proportional hazards regression assumptions will be examined by Schoenfeld residual test and plotting log (cumulative hazard) against the follow-up time by treatment groups and checked for parallelism. In case the proportionality assumption for the treatment effect does not hold, the same approach will be used as that of the primary endpoint of composite CVDs.

The Fine and Gray model for the competing risk of death will be used as another sensitivity analysis for the primary endpoint to compare the statistical differences in the risk

of a composite outcome of all-cause dementia and MCI between the intensive and the standard treatment group.

The characteristics of baseline variables and cognitive function will be compared between participants included in the primary analysis versus those excluded due to loss to follow-up or missing information on cognitive function. Sensitivity of results to missing data will be investigated using multiple imputation methods.

4) Secondary analysis

- All-cause dementia

This outcome is defined as time to first identification of dementia. The same analytical approach for the primary cognitive endpoint will be used for this outcome.

- Mild cognitive impairment

This outcome is defined as time to first identification of MCI. Two occurrences of an adjudicated classification of MCI will be required for the MCI diagnosis. The 2nd adjudication of MCI need not to be consecutive. Similarly, MCI then a later dementia adjudication is also acceptable for the MCI diagnosis.

The same analytical approach for the primary cognitive endpoint will be used for MCI.

- Changes in cognitive performance

This includes cognitive decline in global and specific cognitive domains of learning and memory, complex attention, executive functioning, language, and visuospatial skills. The changes in domain-specific cognitive performance will be calculated as z scores standardized to the baseline mean and SD at each time point. We will use mixed-effects regression models with maximum likelihood estimation to assess between-group differences in changes from baseline to the last visit.

- Changes in brain MRI

This includes the development of cerebral small vessel disease (CSVD), changes in total brain volume, numbers of high signal lesions of white matter, *etc.* as assessed by brain MRI. The effects of intervention on the occurrence of CSVD will be examined using logistic regression in patients without CSVD at baseline. The effects of intervention on changes in total brain volume and numbers of high signal lesions of white matter will be examined using linear mixed-effects model with maximum likelihood estimation. Fixed effects will include treatment groups and other covariates. Random intercepts and slopes will be included to account for within-individual correlation.

6.3.5 Other efficacy endpoints

For the analysis of other efficacy endpoints including cardiovascular revascularization procedures, hospitalized unstable angina, retinopathy, TIA, LVH, atrial fibrillation or flutter, and cancer, a proportional hazards model as described for the primary CV analysis will be performed to compare the time to the first occurrence of each endpoint between the two treatment groups. For the analysis of cost-effectiveness, the following statistical analysis plan

will be used.

Cost-effectiveness

Health effects of the 2 treatments will be measured as life-years gained (LYGs) or quality-adjusted life-years (QALYs). LYGs will be calculated as the additional number of years of life that a participant lives as a result of receiving the intensive treatment over the standard treatment. QALYs adjust LYGs by the quality of the participant's overall HRQoL, as measured by the EQ-5D during these life-years gained. The cost-effectiveness analysis (CEA) and the cost-utility analysis (CUA), which evaluate the incremental cost per LYG and QALY, respectively will be conducted.

All direct medical costs associated with treatment of hypertension and its complications and costs for treating adverse events will be considered. The ratios of cost to health effects such as the LYGs and the QALYs are used to compare cost-effectiveness between the two treatment groups. An incremental cost-effectiveness ratio (ICER) or an incremental cost-utility ratio (ICUR) will be calculated to provide a summary of the cost-effectiveness of the intensive treatment relative to the standard treatment.

ICER = (Difference in costs between the intensive and the standard treatment) / (Difference in LYGs between the intensive and the standard treatment)

ICUR = (Difference in costs between the intensive and the standard treatment) / (Difference in QALYs between the intensive and the standard treatment)

Bootstrap methods will be used to calculate confidence intervals for cost-effectiveness ratios. All costs will be adjusted to the baseline year using the Consumer Price Index. Future costs and outcomes will be discounted by 3%. Estimates of utilization over time will be adjusted for the presence of censored data with variable follow-up. Sensitivity analysis will explore the effect of correlations between costs and outcomes, which will also be empirically examined in the cost and outcome data.

QALYs will be calculated by summing the area under every participant's QALY curve (constructed by plotting the EQ-5D scores for each interview during follow-up). The estimates of mean differences in costs and outcomes – which will be used to create net health benefits and the cost per QALY ratios – will be derived from multivariable regression analyses.

6.3.6 Safety evaluation

The types, frequency of occurrence, and relationship to the study protocol of serious adverse events (SAEs, see section 2.6 'Safety endpoints') will be described. All description of SAEs will be based on the number of patients with SAEs (and not on the number of SAEs). In addition, the numbers and proportions of clinical safety alerts (abnormal serum sodium, abnormal serum potassium, increased serum creatinine, and ECG abnormality) will also be described.

The BPROAD study will focus on SAEs related to BP lowering. The time to first occurrence of an SAE will be compared between the intensive and the standard treatment

groups using a cox proportional hazards regression model, the same as that for the BPROAD primary endpoint of composite CVDs, with the use of the intention-to-treat approach on the FAS.

Additionally, considering possible recurrence of adverse events in the same patient, we will use the Counting Process Approach for data layout and use the cox proportional hazards model and robust estimation technique to calculate the estimates (HR and 95% CI).

Whether SAEs occur differently between the two treatment groups will also be explored across subgroups. Subgroup analysis will follow the same approach as for the BPROAD primary endpoint of composite CVDs.

6.4 Other analysis

Analyses of biologically plausible subgroups will be explored. Some of these will be further articulation of supporting subgroup analyses described above, such as analysis of continuous baseline factors as continuous variables rather as pre-specified categorical variables. Other analyses will involve baseline variables that are not listed in the pre-specified subgroups, but which may modify treatment effects, such as diastolic blood pressure.

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APPENDIX 1: list of BPROAD study sites by regions

North China (18 study sites)

Province	**Study Site**
Shanxi	Central Hospital of China Railway 12th Bureau Group
	Qingxu County People's Hospital
	Taiyuan Taihang Hospital
	Taiyuan Hospital of Traditional Chinese Medicine
	Pingyao County People's Hospital
	The People's Hospital of Shouyang County
	The Third People's Hospital of Datong
	Heji Hospital Affiliated to Changzhi Medical College
	Xiaoyi People's Hospital
	Hejin People's Hospital
	Linfen Liyi Diabetes Hospital
Hebei	Zhangjiakou First Hospital
	First Hospital of Qinhuangdao
	KaiLuan General Hospital
	Chengde Central Hospital
Beijing	Beijing Jiangong Hospital
	Beijing Chaoyang Integrative Medicine Emergency Medical Center
Inner Mongolia	The Affiliated Hospital of Inner Mongolia Medical University

Northeast China (31 study sites)

Province	**Study site**
Heilongjiang	The Fourth Hospital of Harbin Medical University, Third Ward
	The Fourth Hospital of Harbin Medical University, First Ward
	The Second People's Hospital of Yilan County
	Bin County People's Hospital
	The First Hospital of Harbin City, First Ward of the Endocrinology Department

	Wuchang People's Hospital
	Tailai County People's Hospital
	The Third Affiliated Hospital of Qiqihar Medical University
	Yian County Hospital of Traditional Chinese Medicine
	Tieli People's Hospital
	Luobei County People's Hospital
Jilin	The Second Hospital of Jilin University
	Jilin Province FAW General Hospital
	The Affiliated Hospital to Changchun University of Chinese Medicine
	Jilin Province People's Hospital
	The First Bethune Hospital of Jilin University
	Baicheng Municipal Hospital
	The Affiliated Hospital of Baicheng Medical College
	Jilin People's Hospital
	Yanji Hospital
	Changling County Traditional Chinese Medicine Hospital
Liaoning	The First Hospital of China Medical University
	Affiliated Hospital of Liaoning University of Traditional Chinese Medicine
	The Second Hospital of Dalian Medical University
	Dalian Municipal Central Hospital
	Anshan Central Hospital (Lishan)
	Anshan Central Hospital
	The Second Hospital of Chaoyang
	Chaoyang Central Hospital
	Panjin Central Hospital
	Benxi Central Hospital

East China (42 study sites)

Province	**Study site**
Anhui	Lixin Hospital of Traditional Chinese Medicine

	The People's Hospital of Bozhou
	Maanshan People's Hospital
	The Central Hospital of Maanshan City
	Anqing Shihua Hospital of Nanjing Drum Tower Hospital Group
	Lai'an Jia Ning Hospital
	Linquan County People's Hospital
	The Second People's Hospital of Lu'an City
	Guangde County People's Hospital
	The Second People's Hospital, Wuhu
Shandong	The Second Hospital of Shandong University
	Shanghe People's Hospital
	Jinan Central Hospital
	Qilu Hospital of Shandong University
	Shandong Provincial Qianfoshan Hospital
	Weifang Municipal Governmental Hospital
	Weifang Hi-tech Zone People's Hospital
	Yankuang New Journey General Hospital
	Weishan People's Hospital
	The Second Affiliated Hospital of Shandong First Medical University
Shanghai	Ruijin Hospital, Shanghai Jiao Tong University School of Medicine
	Shidong Hospital Affiliated to University of Shanghai for Science and Technology
	Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine
	Zhongshan Hospital, Fudan University
	Shanghai Seventh People's Hospital
	Shanghai Changzheng Hospital
	Shanghai Fifth People's Hospital, Fudan University
	Shanghai General Hospital (North Campus)
	Shanghai General Hospital (South Campus)
Jiangsu	Jiangsu Province Hospital on Integration of Chinese and Western Medicine
	Sir Run Run Hospital of Nanjing Medical University
	Hai'an City People's Hospital

	Sheyang County Diabetes Hospital
	Affiliated Hospital of Jiangsu University
	Wuxi Huishan District People's Hospital
	The Second Affiliated Hospital of Soochow University
Zhejiang	Ningbo Fenghua District Hospital of Traditional Chinese Medicine
	The First Affiliated Hospital of Ningbo University
	Yuhuan Second People's Hospital
Jiangxi	The Third Hospital of Nanchang
	Second Affiliated Hospital of Nanchang University
	Jiangxi Provincial People's Hospital

South China (5 study sites)

Province	**Study site**
Guangxi	Nanning Red Cross Hospital
	The First Affiliated Hospital of Guangxi Medical University
	The First People's Hospital of Yulin
Fujian	Fujian Provincial Hospital
Guangdong	Wuchuan People's Hospital

Middle China (34 study sites)

Province	**Study site**
Henan	People's Hospital of Zhengzhou
	Zhengzhou Central Hospital
	Ninth People's Hospital of Zhengzhou
	Xin Mi Hospital of Traditional Chinese Medicine
	Zhengzhou Yihe Hospital Affiliated to Henan University
	Henan Provincial People's Hospital
	The First People’s Hospital of Zhengzhou
	General Hospital of Hebi Coal Industry Group Co. LTD
	The People's Hospital of Hebi

	Xixia County People's Hospital
	Nanyang First People's Hospital
	Jiaozuo People's Hospital
	Qinyang People's Hospital
	General Hospital of Pingmei Shenma Group
	Pingdingshan The Second People's Hospital
	The People's Hospital of Anyang City
	Xinxiang Central Hospital
	Linying County People's Hospital
	Zhoukou Central Hospital
	The First Affiliated Hospital of Henan University of Science & Technology
	Xinyang Central Hospital
	Zhumadian Central Hospital
Hubei	General Hospital of Central Theater Command
	Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology
Hunan	The Third Hospital of Changsha
	People's Hospital of Yuelu
	Xiangya Hospital Central South University
	Changsha Central Hospital
	The First People's Hospital of Loudi
	The People's Hospital of Liuyang
	Anhua People’s Hospital
	Xiangdong Hospital Hunan Normal University
	Xiangxi Autonomous Prefecture People's Hospital
	The First People's Hospital of Huaihua

Southwest China (12 study sites)

Province	**Study site**
Guizhou	Affiliated Hospital of Guizhou Medical University

	The Second People's Hospital of Guiyang
	Guihang Guiyang Hospital
	Yunyan District People's Hospital of Guiyang
	The First People's Hospital of Guiyang
	Qiandongnanzhou People's Hospital
	The Second Affiliated Hospital of Guizhou Medical University
	The People’s Hospital of QianNan
	The Third Affiliated Hospital of Guizhou Medical University
Sichuan	The Affiliated Hospital of Southwest Medical University
	Second People's Hospital of Ya'an City
Chongqing	Xinqiao Hospital, Army Medical University

Northwest China (3 study sites)

Province	**Study site**
Xinjiang	Karamay Central Hospital of Xinjiang
Shaanxi	Yanan University Affiliated Hospital
Gansu	The First Hospital of Lanzhou University

APPENDIX 2

Decision on the 2nd Interim Analysis of the BPROAD Trial

February 22, 2024

According to the *BPROAD Statistical Analysis Plan v4.0*, two interim were planned to be conducted before the final analyses; the interim analyses would occur after approximately 50% and 75% of the total anticipated number of primary endpoint events had been observed and adjudicated. The targeted number of primary outcome events is 866; the 1st interim analysis was conducted when 472 adjudicated events (54.5%) accrued.

As of December 31, 2023, 667 adjudicated primary outcome events (77.0%) accrued and more than 180 potential events were in the process of adjudication. Although the 2nd interim analysis could have been conducted, the trial was scheduled to end on February 24, 2024 according to the *BPROAD Study Protocol v4.0*, which prespecifies that the total study length is five years defined by the time between randomization of the 1st participant and study closeout. Therefore, the BPROAD DSMB Chair and DSMB Statistician recommended against performing the 2nd interim analysis as it was unnecessary. The DSMB chair and statistician recommend that the trial proceeds into closeout, continue adjudication, and conduct the final analyses of the primary outcome.

The BPROAD Trial Executive Committee will follow the DSMB recommendations and will not conduct the 2nd interim analysis of the BPROAD trial.

The DSMB has reviewed and approved this document.

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