

Supplementary Appendix

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

Supplementary Appendix

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Section S1. BPROAD Research Group

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BPROAD Study Sites by Regions

North China (18 study sites)

Province	Study Site	Site PI
Shanxi	Central Hospital of China Railway 12th Bureau Group	Jing Li
	Qingxu County People's Hospital	Xiaoxia Han
	Taiyuan Taihang Hospital	Chunfang Zhang
	Taiyuan Hospital of Traditional Chinese Medicine	Xiaochun Wu
	Pingyao County People's Hospital	Deyu Shang
	The People's Hospital of Shouyang County	Airong Zheng
	The Third People's Hospital of Datong	Yan Liu
	Heji Hospital Affiliated to Changzhi Medical College	Xiaohong Niu
	Xiaoyi People's Hospital	Yifei He
	Hejin People's Hospital	Aifang Hu
	Linfen Liyi Diabetes Hospital	Liyi Su
Hebei	Zhangjiakou First Hospital	Luling Dong
	First Hospital of Qinhuangdao	Qiang Lu
	KaiLuan General Hospital	Qiuyun Li
	Chengde Central Hospital	Fengjie Hao
Beijing	Beijing Jiangong Hospital	Qing Wu
	Beijing Chaoyang Integrative Medicine Emergency Medical Center	Xiaoyun Shi
Inner Mongolia	The Affiliated Hospital of Inner Mongolia Medical University	Zhaoli Yan

Northeast China (31 study sites)

Province	Study site	Site PI
Heilongjiang	The Fourth Hospital of Harbin Medical University, Third Ward	Shuang Yan
	The Fourth Hospital of Harbin Medical University, First Ward	Zhifeng Cheng
	The Second People's Hospital of Yilan County	Yantao Liu
	Bin County People's Hospital	Bojun An
	The First Hospital of Harbin City	Donghong Wu
	Wuchang People's Hospital	Weidong Tang
	Tailai County People's Hospital	Yonghui Zhao
	The Third Affiliated Hospital of Qiqihar Medical University	Li Jin
	Yan County Hospital of Traditional Chinese Medicine	Chunru Lu
	Tieli People's Hospital	Yanbo Niu
	Luobei County People's Hospital	Chunli Gao
Jilin	The Second Hospital of Jilin University	Hanqing Cai
	Jilin Province FAW General Hospital	Chengwei Song
	The Affiliated Hospital to Changchun University of Chinese Medicine	Xi Chen
	Jilin Province People's Hospital	Yadong Sun
	The First Hospital of Jilin University	Guixia Wang
	Baicheng Municipal Hospital	Chunling Li
	The Affiliated Hospital of Baicheng Medical College	Li Shi
	Jilin Municipal People's Hospital	Huanfeng Pan
	Yanji Hospital	Sheng'ai Shen
	Changling County Traditional Chinese Medicine Hospital	Heshu Ma
Liaoning	The First Hospital of China Medical University	Zhongyan Shan
	Affiliated Hospital of Liaoning University of Traditional Chinese Medicine	Tianshu Gao
	The Second Hospital of Dalian Medical University	Haixia Liu
	Dalian Municipal Central Hospital	Zhengnan Gao
	Anshan Central Hospital (Lishan)	Yufang Li

	Anshan Central Hospital	Xiaolu Wang
	The Second Hospital of Chaoyang	Yan Wang
	Chaoyang Central Hospital	Shuli Zuo
	Panjin Central Hospital	Juan Du
	Benxi Central Hospital	Guihong Xing

East China (42 study sites)

Province	Study site	Site PI
Anhui	Lixin Hospital of Traditional Chinese Medicine	Ping Lu
	The People's Hospital of Bozhou	Yusen Zhou
	Maanshan People's Hospital	Weihong Chen
	The Central Hospital of Maanshan City	Hongbo Dang
	Anqing Shihua Hospital of Nanjing Drum Tower Hospital Group	An Wang
	Lai'an Jia Ning Hospital	Shaoping Dai
	Linqun County People's Hospital	Tongqin Yuan
	The Second People's Hospital of Lu'an City	Dongfeng Li
	Guangde County People's Hospital	Shuyun Fan
	The Second People's Hospital, Wuhu	Minmin An
Shandong	The Second Hospital of Shandong University	Shihong Chen
	Shanghe People's Hospital	Zhenfang Guo
	Jinan Central Hospital Affiliated to Shandong First Medical University	Shuguang Pang
	Qilu Hospital of Shandong University	Xinguo Hou
	Shandong Provincial Qianfoshan Hospital	Lin Liao
	Weifang Municipal Official Hospital	Jing Wang
	Weifang Hi-tech Zone People's Hospital	Xiaoliang Zhang
	Yankuang New Journey General Hospital	Ailiang Wang
	Weishan People's Hospital	Xiao'e Li
	The Second Affiliated Hospital of Shandong First Medical University	Xinhuan Zhang
Shanghai	Ruijin Hospital, Shanghai Jiao Tong University School of Medicine	Guang Ning
	Shidong Hospital Affiliated to University of Shanghai for Science and Technology	Suijun Wang

	Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine	Yue Chen
	Zhongshan Hospital, Fudan University	Xiaoying Li
	Shanghai Seventh People's Hospital	Xiaohua Li
	Shanghai Changzheng Hospital	Yongquan Shi
	Shanghai Fifth People's Hospital, Fudan University	Jun Liu
	Shanghai General Hospital (North Campus)	Yufan Wang
	Shanghai General Hospital (South Campus)	Yufan Wang
Jiangsu	Jiangsu Province Hospital on Integration of Chinese and Western Medicine	Chao Liu
	Sir Run Run Hospital of Nanjing Medical University	Yu Liu
	Hai'an People's Hospital	Xiaohua Yang
	Sheyang County Diabetes Hospital	Yuancheng Dai
	Affiliated Hospital of Jiangsu University	Guoyue Yuan
	Wuxi Huishan District People's Hospital	Li Gong
	The Second Affiliated Hospital of Soochow University	Ji Hu
Zhejiang	Ningbo Fenghua District Hospital of Traditional Chinese Medicine	Jieji Zhang
	The First Affiliated Hospital of Ningbo University	Li Li
	Yuhuan Second People's Hospital	Qidong Zheng
Jiangxi	The Third Hospital of Nanchang	Peng Duan
	Second Affiliated Hospital of Nanchang University	Xiaoyang Lai
	Jiangxi Provincial People's Hospital	Yanan Huo

South China (5 study sites)

Province	Study site	Site PI
Guangxi	Nanning Red Cross Hospital	Jian Yang
	The First Affiliated Hospital of Guangxi Medical University	Yingfen Qin
	The First People's Hospital of Yulin	Ping Zhang
Fujian	Fujian Provincial Hospital	Gang Chen
Guangdong	Wuchuan People's Hospital	Xiao Wu

Middle China (34 study sites)

Province	Study site	Site PI
Henan	People's Hospital of Zhengzhou	Qijuan Dong
	Zhengzhou Central Hospital	Zhiqiang Kang
	Ninth People's Hospital of Zhengzhou	Jiangmin Wang
	Xin Mi Hospital of Traditional Chinese Medicine	Shuzeng Cheng
	Zhengzhou Yihe Hospital Affiliated to Henan University	Zhigang Zhao
	Henan Provincial People's Hospital	Huijuan Yuan
	The First People's Hospital of Zhengzhou	Zhihong Wang
	General Hospital of Hebi Coal Industry Group Co. LTD	Fengmei Xu
	The People's Hospital of Hebi	Dekuan Liu
	Xixia County People's Hospital	Lin Wang
	Nanyang First People's Hospital	Yihua Wang
	Jiaozuo People's Hospital	Juzhen Zhao
	Qinyang People's Hospital	Caixia Chen
	General Hospital of Pingmei Shenma Group	Huiqi Zhu
	Pingdingshan The Second People's Hospital	Min Chen
	The People's Hospital of Anyang City	Xiaohu Wang
	Xinxiang Central Hospital	Xiuqin Geng
	Linying County People's Hospital	Peixia Cui
	Zhoukou Central Hospital	Donghui Yang
	The First Affiliated Hospital of Henan University of Science & Technology	Liujun Fu
Xinyang Central Hospital	Xiangyang Guo	
Zhumadian Central Hospital	Lianwei Wang	
Hubei	General Hospital of Central Theater Command	Guangda Xiang
	Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology	Xuefeng Yu
Hunan	The Third Hospital of Changsha	Debin Huang
	People's Hospital of Yuelu	Chunhua Huang
	Xiangya Hospital Central South University	Minxiang Lei
	Changsha Central Hospital	Huige Shao

	The First People's Hospital of Loudi	Tingzhi Li
	The People's Hospital of Liuyang	Xinwen Qiu
	Anhua People's Hospital	Jijun Peng
	Xiangdong Hospital Hunan Normal University	Qing Li
	Xiangxi Autonomous Prefecture People's Hospital	Ziqiang Tan
	The First People's Hospital of Huaihua	Shuibing Yang

Southwest China (12 study sites)

Province	Study site	Site PI
Guizhou	Affiliated Hospital of Guizhou Medical University	Miao Zhang
	The Second People's Hospital of Guiyang	Fei Xiang
	Guihang Guiyang Hospital	Tingting Zhang
	Yunyan District People's Hospital of Guiyang	Yi Zhu
	The First People's Hospital of Guiyang	Wei Lu
	Qiandongnanzhou People's Hospital	Jun Wu
	The Second Affiliated Hospital of Guizhou Medical University	Qian Zhang
	The People's Hospital of QianNan	Qianli Zhang
	The Third Affiliated Hospital of Guizhou Medical University	Xue Yang
Sichuan	The Affiliated Hospital of Southwest Medical University	Qin Wan
	Second People's Hospital of Ya'an City	Jidong He
Chongqing	Xinqiao Hospital, Army Medical University	Hongting Zheng

Northwest China (3 study sites)

Province	Study site	Site PI
Xinjiang	Karamay Central Hospital of Xinjiang	Shengli Wu
Shaanxi	Yanan University Affiliated Hospital	Sheli Li
Gansu	The First Hospital of Lanzhou University	Songbo Fu

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Section S2. Inclusion and Exclusion Criteria

a) Inclusion criteria

1. Men and women aged ≥ 50 years
2. Diabetes defined as:
 - A self-reported previous diagnosis by health care professionals and taking antidiabetic 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
 - Hemoglobin A1c concentration of $\geq 6.5\%$ (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 mm Hg on 0 medication;
 - 130-180 mm Hg on 1 medication;
 - 130-170 mm Hg on up to 2 medications;
 - 130-160 mm Hg on up to 3 medications; or
 - 130-150 mm Hg on up to 4 medications
 - There are no diastolic blood pressure inclusion criteria. If a screenee is otherwise eligible for the trial but presents with a treated blood pressure and/or number of medications that fall outside the inclusion criteria, blood pressure 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 blood pressure lowering medications should have documentation of systolic blood pressure ≥ 140 mm Hg 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 (CVD) (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 electrocardiogram (ECG) change, ECG changes on a graded exercise test, or positive cardiac imaging study
 - Subclinical CVD within 3 years
 - Microalbuminuria
 - $\geq 50\%$ 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/m² or waist circumference ≥ 90 cm (in men) or ≥ 85 cm (in women)
 - Current lipid-lowering medications or low-density lipoprotein cholesterol ≥ 130 mg/dl (3.38 mmol/l)
 - Current lipid-lowering medications or high-density lipoprotein 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 m²

Note: Potential participants were screened according to a standard protocol and using a clinical form. Patients were first asked whether they had a history of clinical CVD or had subclinical CVD. If the patient answered 'yes' to any of the above clinical CVD or subclinical CVD items, he/she was asked to provide medical records of this clinical or subclinical CVD event. Photocopies of the medical records were then uploaded to an electronic data capturing system and reviewed by both study physicians at local sites and personnel at the trial Coordinating Center to verify the events and decide whether the patient satisfied the inclusion criterion of an elevated CVD risk. For a reported microalbuminuria, potential participants would undergo measurements of urine albumin and urine creatinine concentrations at screening to confirm the diagnosis at local sites. For CVD risk factors, potential participants self-reported their smoking status. They would undergo physical examination including height and weight for the calculation of BMI as well as waist circumference. They would undergo measurements of lipids and serum creatinine for the evaluation of eGFR at local sites.

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 blood pressure < 110 mm Hg
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. Alanine transaminase (ALT) or aspartate transferase (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 m² 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 clinical 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 clinical 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

Section S3. Blood Pressure Measurement and Treatment

1. Blood Pressure Measurement

Blood pressure was measured according to a standard protocol recommended by the American Heart Association. Participants were advised to avoid alcohol, cigarettes, coffee/tea, and exercise for at least 30 minutes before their blood pressure 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 was used and 1 of 3 cuff sizes (pediatric, regular adult, or large) was chosen on the basis of each participant's arm circumference. Blood pressure was 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) was used as it offered reduced potential for observer biases and decreased demand on staff in terms of effort in data collection. The mean of the 3 measurements was used.

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 participant 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. Participants were required to 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. A minimum period of 3 days (ie, 12 readings) before scheduled visit (monitoring conducted over consecutive days is ideal) were required and participants were advised to record blood pressure readings and report to his/her study physician. 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.

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. This protocol change was also approved immediately by the institutional review board at Ruijin Hospital. The response plan and details for home blood pressure monitoring were attached at the end of the *Study Protocol*.

2. Blood Pressure Treatment

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

changes or other clinical issues.

- **Intensive-treatment group (Figure S1)**

The systolic blood pressure 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. For most participants in the intensive-treatment group, a two- or three-drug regimen of a diuretic and either an angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) and/or a calcium channel blocker (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 were on 0-1 antihypertensive medications and had baseline systolic blood pressure <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 blood pressure ≥ 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 blood pressure goal. Therefore, milepost visits were used in the intensive treatment group in the ACCORD and SPRINT trials to assist in reaching goal systolic blood pressure. In BPROAD, milepost visits were every 6 months throughout follow-up in the intensive-treatment group, beginning at the 6-month visit. If the systolic blood pressure was not <120 mm Hg at a milepost visit, then an antihypertensive drug from a class different from what was being taken should be added, unless there were compelling reasons to wait. A 'Milepost Exemption Form' were completed whenever a new drug was not added at a milepost visit in which the participant's systolic blood pressure was 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 had been prescribed 5 drugs at maximally tolerated doses, if the blood pressure remained above goal at subsequent milepost visits, it would 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 blood pressure in some participants. Medication adherence was 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 S2)**

The systolic blood pressure 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. The standard treatment protocol was designed to achieve a systolic blood pressure 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) was 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 was a compelling indication for another drug class. An ACEI or ARB was preferred in diabetes with albuminuria.

At the randomization visit, standard-treatment group participants on previous antihypertensive drug therapy could be converted to the trial medications or no medications, depending on what the study physician believes was most likely to achieve a systolic blood pressure level between 135-139 mmHg. Because we expected a decrease in average systolic blood pressure 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 blood pressure ≥ 160 mmHg or there was a compelling reason to add medication. Following the randomization visit, medication dose titration or addition of another drug was indicated if systolic blood pressure was ≥ 160 mmHg at a single visit or was ≥ 140 mmHg at two successive visits.

Because it is not known if lowering systolic blood pressure 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) was allowed for participants in the standard-treatment group. Down-titration was not permitted in the Hypertension Optimal Treatment (HOT) Trial if diastolic blood pressure was well below the goal for a participant – this likely contributed to the small differences in achieved blood pressure between the three randomized groups and limited the study's ability to detect differences in outcomes. Therefore, down-titration was included in the ACCORD and SPRINT standard blood pressure protocols and was successful in generating the planned differences in blood pressure between treatment arms. Down titration could be carried out in BPROAD standard-treatment group if the systolic blood pressure was <130 mmHg at a single visit or <135 mmHg at two consecutive visits.

3. Training for standardized implementation

We organized both face-to-face training and online-video training sessions during the entire study period for the study personnel at clinical sites to implement standard procedures including blood pressure measurement and treatment. For face-to-face training, we organized training sessions at different regions across mainland China. All relevant staff members from all clinical sites in the relevant region were convened in a 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. For online-video

training, we uploaded training videos 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. In addition, the trial Coordinating Center organized yearly refresher training sessions to the study personnel of all study sites. During trial conduct, a blood pressure management team of physicians with blood pressure treatment expertise at the trial Coordinating Center would connect with study physicians at local sites to review blood pressure control of participants and make recommendations on changes of treatment regimens if targets were not met.

Section S4. Outcome Definitions and Criteria for Event Adjudication

The current study included the primary composite cardiovascular outcome, secondary outcomes, kidney outcomes, and safety outcomes.

The primary outcome measure for BPROAD is major cardiovascular events, defined as the composite endpoint of the first occurrence of nonfatal stroke, nonfatal myocardial infarction (MI), treated or hospitalized heart failure (HF), and cardiovascular death. Secondary outcomes included individual components of the composite primary outcome, all-cause death, and an expanded outcome of the primary endpoint and all-cause death.

The kidney outcomes include progression of chronic kidney disease (CKD), development of CKD, and incident albuminuria. CKD progression is defined as the composite of a 50% decrease in eGFR, or eGFR <15 ml/min/1.73 m², or development of end-stage renal disease in patients with CKD at baseline. CKD development is defined as a >30% decrease in eGFR and eGFR <60 ml/min/1.73 m² among patients without CKD at baseline. Incident albuminuria is defined as a doubling of urinary albumin-to-creatinine ratio from a value of <10 mg/g to a value of ≥10 mg/g in all participants with or without CKD. Development of end-stage renal disease is defined as the initiation and maintenance of chronic dialysis or receipt of a kidney transplantation and centrally adjudicated according to the medical records. For kidney outcome assessment, the blood and first-morning spot urine samples were collected at baseline and annual visits and shipped in dry ice to the central laboratory at the trial Coordinating Center, which is accredited by the College of American Pathologists. All biochemical tests were performed at the central clinical laboratory using validated and standardized protocols to assess serum creatinine, urine albumin, and urine creatinine concentrations to evaluate kidney outcomes. The decrease in eGFR and the increase in urinary albumin-to-creatinine ratio required a confirmatory value in the next available official study laboratory check.

The safety outcomes include serious adverse events and selected adverse events leading to emergency department visits including arrhythmia, electrolyte abnormality, injurious fall, symptomatic hypotension, syncope, and acute renal failure. Participants were asked if they had been hospitalized or had visited emergency rooms due to conditions of interest since the last clinical visit. If the answer was 'yes', clinical documents such as hospital discharge records or emergency room visit records had to be provided. Study physicians then reviewed the documents and reported adverse events.

Study data were collected locally according to a standard protocol and standardized procedures to ensure uniformity of data quality across sites. For clinical outcome assessment, clinical documents, including admission and discharge summaries, laboratory measurements, imaging and procedures, *etc.*, were collected by blinded physicians in charge of outcome data collection at local sites. Photocopies of the documents were uploaded to an electronic data capturing system and staff at the trial Coordinating Center then reviewed and requested for additional documents if necessary. After all necessary clinical documents were acquired and reviewed, they would go into

the outcome adjudication process, during which an independent outcome adjudication committee would review the clinical documents and make judgements according to standard outcome adjudication criteria. Clinical events occurring during follow-up were ascertained equally in both treatment groups through review of self-reported events and medical record data collected by the study staff. Centrally adjudicated clinical outcomes included MI, stroke, treated or hospitalized HF, all deaths, and development of end-stage renal disease. All reported angina, all cardiovascular revascularization procedures, and transient ischemic attack were also adjudicated to avoid missing MI or stroke. The independent Outcome Adjudication Committee masked to treatment assignments reviewed all supporting materials and judgements were made independently by two adjudicators specialized in the field. Adjudicators for MI, angina, cardiovascular revascularization procedures, and treated or hospitalized HF were cardiologists or geriatricians with expertise in diagnosis and evaluation for coronary heart disease and related conditions. Adjudicators for stroke and transient ischemic attack were neurologists with expertise in the diagnosis and evaluation for cerebrovascular disease. Development of end-stage renal disease was adjudicated by nephrologists or geriatricians with knowledge and experience in chronic kidney disease. The underlying causes of all deaths were first adjudicated by internal medicine physicians, and if they were considered as coronary heart disease (CHD)-related, stroke-related, HF-related, or kidney-related deaths, the death cases were further assigned to the specialist adjudicators for final adjudication.

Adjudicators signed into an online password-protected BPROAD adjudication system and reviewed scanned medical documents, as well as additional pertinent information, including death certificates. The adjudicators made their judgement and entered their responses into an adjudication form in the adjudication system. Each event was independently adjudicated by at least two adjudicators and disagreements were determined by discussion with senior members of the Outcome Adjudication Committee. All adjudicators underwent training based on the event adjudication protocol. Adjudication criteria for potential outcomes were made according to relevant guidelines and international multicenter cardiovascular outcome clinical trials¹⁻⁶. The details are described as follows.

1. MI

MI is 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 used standard case definitions for both fatal and nonfatal MI based on the combination of symptoms, elevation in biomarkers, and/or ECG findings. MI was ascertained 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 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. The definition includes MI that occurred during surgery/procedure and MI aborted by thrombolytic therapy or procedure. The study adjudicators were guided by specific, pre-specified definitions and operational rules.

Adjudicators used 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 outcome¹. 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 criteria².

- **Classification of MI According to SPRINT criteria²**

ECG Findings**	Positive biomarker findings							
	Cardiac symptoms or signs present				Cardiac symptoms or signs absent			
	Diagnostic ⁺	Equivocal ⁺	Missing ⁺	Normal ⁺	Diagnostic	Equivocal	Missing	Normal
Evolving diagnostic	Def	Def	Def	Def	Def	Def	Def	Def
Positive	Def	Prob	Prob	No	Def	Prob	Poss	No
Nonspecific	Def	Poss	No	No	Def*	Poss	No	No
Negative for evolving ischemia	Def	Poss	No	No	Def*	No	No	No

*In absence of diagnostic troponin, downgrade to possible.

**Def = Definite, definite MI; Prob = Probable, probable MI; Poss = Possible, possible MI; and No = no MI. Classification of case is at highest level allowed by combinations of 3 characteristics (cardiac signs and symptoms, ECG findings, biomarkers).

- Biomarker criteria:

Diagnostic = At least 1 positive biomarker in an adequate set of biomarkers showing a rising or falling pattern in the setting of clinical cardiac ischemia and the absence of noncardiac causes of biomarker elevation. An adequate set is at least 2 measurements of the same marker taken at least 6 hours apart.

Equivocal = Present but not diagnostic.

Missing = Not available for the time of the event.

Normal = Normal.

According to the 2003 AHA Scientific Statement, positive biomarkers are defined as above the 99th percentile upper reference limit ¹. Troponin takes precedence over CK-MB, and CK-MB will take precedence over CK if both are available.

- Cardiac symptoms or signs:

Cardiac symptoms include symptoms suggestive of an ischemic cause and include (but are not limited to) acute chest, neck, jaw, arm pain, or epigastric pain, or discomfort or pressure without apparent non-cardiac cause. Cardiac signs can be used for determination of MI and include acute HF or cardiogenic shock in the absence of non-CHD causes.

- ECG Criteria:

(1) Evolving: Evolution of a new diagnostic Q wave; OR equivocal Q wave and evolution of major ST depression or elevation or T wave inversion.

(2) Positive: Evolving ST elevation alone; OR evolving equivocal Q wave and evolving ST or T wave depression or inversion; OR new left bundle branch block.

(3) Nonspecific: Evolving minor Q wave alone or evolving non-ST elevation non-Q wave pattern (including evolving ST depression alone).

(4) Negative for evolving ischemia: Normal ECG(s), or findings other than those described in the above categories.

- **Procedure Related MI**

MIs are also classified according to whether they were medical procedure-related, that is, occurring within 28 days after a medical procedure. Cardiac events up to 28 days after a medical procedure (e.g., general surgery) that meet the criteria for definite, probable, and possible MI described above were assessed for whether they were procedure-related.

- **Aborted MI**

Aborted MI is defined as positive signs/symptoms and positive ECG, but the enzymes remain below the upper limit of normal and the participant received emergent treatment for cardiac ischemia (thrombolytic or revascularization).

2. Stroke

We used standard case definitions for both fatal and nonfatal stroke. Stroke is defined based on all available data, including symptoms and signs, imaging of the brain and large vessels, and cardiac testing, e.g., echocardiography. Adjudicators used their clinical judgment based on the available evidence to classify each case and were 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 hours³. 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 is classified as ischemic stroke, subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, other type, or unknown type.

- **Ischemic stroke:** 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 (sudden onset of focal neurological symptoms or coma) that lasted for more than 24 hours⁴.
- **Subarachnoid hemorrhage:** Typical clinical syndrome of sudden onset headache, with or without depressed consciousness or coma, or focal neurological symptoms, and CT or cerebrospinal fluid evidence of bleeding primarily in the subarachnoid space. Non traumatic subarachnoid hemorrhage documented by imaging is considered a hemorrhagic stroke.

- **Intraparenchymal hemorrhage:** Sudden onset of focal neurological symptoms or coma with CT/MRI evidence of cerebral hemorrhage. (Note: Does not include hemorrhage secondary to cerebral infarct, post-traumatic intracerebral hemorrhage, hemorrhage into a tumor, and hemorrhage into a vascular malformation)
- **Other hemorrhage:** Definite hemorrhage with insufficient data to classify subarachnoid hemorrhage or intraparenchymal hemorrhage, and imaging shows blood in the parenchyma, subarachnoid space, ventricle, or any combination of the above.
- **Stroke, other type:** Not meeting criteria for ischemic stroke, subarachnoid hemorrhage, intraparenchymal hemorrhage, or other hemorrhage (e.g., cerebral sinus thrombosis with intraparenchymal hemorrhage, dissection)
- **Stroke, unknown type:** Definite stroke that does not meet the above criteria for cerebral infarction or hemorrhage (CT scan or MRI not done).

3. Treated or hospitalized HF

HF is 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 is 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 is not considered a BPROAD HF outcome. Adjudication used the ARIC study adjudication system⁵. No identification of HF should rely on a single piece of data, such as the presence of dyspnea or edema, a low ejection fraction, or an increased brain natriuretic peptide (BNP) value. The identification and classification of HF cases relies on multiple pieces of key clinical data as follows:

- **Heart failure symptoms:** Dyspnea, decreased exercise tolerance, fatigue, worsened end-organ perfusion, and other symptoms of volume overload.
- **Heart failure signs:** Peripheral edema, increasing abdominal distention or ascites (in the absence of primary hepatic disease), pulmonary rales/crackles/crepitations, increased jugular venous pressure and/or hepatojugular reflux.
- **Laboratory evidence of HF:** Increased BNP or NT-proBNP concentrations, radiological evidence of pulmonary congestion, noninvasive or invasive diagnostic evidence of HF.
- **HF hospitalization or intravenous HF treatment:** Acute HF as the primary reason for hospital admission or for emergency department visit where HF was diagnosed and intravenous treatment was given.

HF outcome includes definite or possible acute decompensation, including HF with preserved left ventricular ejection fraction as well as HF with reduced ejection fraction. Adjudicators used both the available data and clinical judgment to distinguish between “definite” and “possible” decompensated HF. “Definite” decompensated HF is assigned when decompensation is clearly present based on available data (satisfies criteria for decompensation). “Possible” decompensation is 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).

4. Death

The fact, date, and cause of death were confirmed using all available information, including death certificate, records of the last hospitalization preceding death, final adjudicated outcome, medical history, and descriptions provided by relatives, contacts, or witnesses regarding the circumstances and manifestations of death. Adjudicators only recorded the main underlying cause of death. If the death is due to an event in one of the above categories, the case was further assigned to the specialist adjudicator for final adjudication according to the relevant criteria. The underlying causes of death are adjudicated as the following causes:

- **Cardiovascular death:** Cardiovascular death includes death due to CHD, stroke, HF, and other cardiovascular causes. We use standard case definitions for classification of CVD death.
 - CHD related death: Defined as any death due to MI or other consequences of coronary atherosclerosis (e.g., angina), which was adjudicated by the CHD adjudication team. Definite fatal MI is defined as death within 28 days of hospital admission in definite MI cases or postmortem findings consistent with MI within 28 days for inpatient death, and death within 28 days of a definite or probable MI and no evidence of a non-coronary cause of death, or autopsy evidence of recent coronary occlusion or MI < 28 days old for participants dying as an outpatient. Probable CHD death is 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 death⁶. Possible fatal CHD is adjudicated based on death certificate information consistent with an underlying CHD cause and no evidence of a non-coronary cause.
 - Stroke related: Defined as death occurring or following cases meeting criteria for stroke, which was adjudicated by the stroke adjudication team. In cases where the final underlying cause of death is identified as stroke, the adjudicators will use specific information contained in the case to identify 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.
 - HF related: Death due to clinical, radiologic, or postmortem evidence of HF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock included).
 - Other CVD death: Other cardiac death includes death thought to be due to other CVD (e.g., valvular heart disease, non-ischemic cardiomyopathy, primary arrhythmia, ruptured abdominal aortic aneurysm, acute limb ischemia, and sudden cardiac death).

- **Cancer death:** Death due to cancer or as a consequence of cancer related treatment complications.
- **Death due to causes other than CVD or cancer:** Defined as any death for which clear evidence of a non-cardiovascular cause or non-cancer cause exists.
 - Kidney disease related: Death due to end-stage renal disease or as a consequence of dialysis procedure.
 - Infectious disease (death related to Covid-19 is coded separately)
 - Gastrointestinal or liver disease
 - Respiratory causes (excluding pneumonia)
 - Neurologic disease
 - Acute diabetes complication
 - Accident/Injury
 - Suicide
 - Others
- **Undetermined death:** Deaths are only classified as being of unknown cause if a cause could not be established (e.g., a death for which there is no information beyond “patient died”, despite best efforts to obtain further details).

5. Development of end-stage renal disease

Development of end-stage renal disease is defined as the initiation and maintenance of chronic dialysis or receipt of a kidney transplantation and centrally adjudicated according to the medical records. Acute dialysis for management of acute kidney injury is not considered an end-stage renal disease outcome. The adjudicators checked whether the participant was currently on dialysis (any modality(ies)), for at least 3 months.

Section S5. Interim Analysis

1. Plan of BPROAD 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 planned 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 are the same as the final analysis.

Let hr^{\wedge} be the observed hazard ratio. The following table 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.

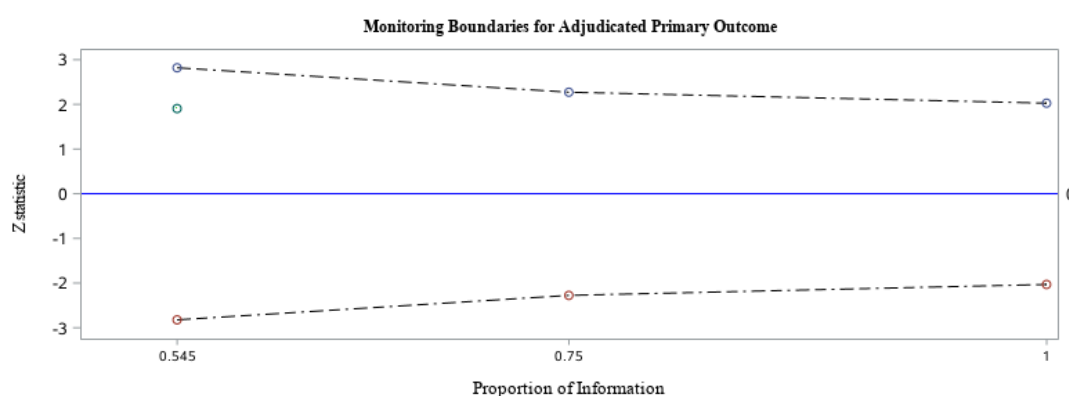
Results of the interim analysis are for the use of the DSMB and will not be revealed to the investigators before the completion of the trial.

Table. Interim analysis for testing $H_0: d=0$ vs. $H_a: d \neq 0$, 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 $hr^{\wedge} > 1.329$ or $hr^{\wedge} < 0.752$, reject H_0 and stop; otherwise continue to the next stage	0.003
2	0.75 (650)	0.185	If $hr^{\wedge} > 1.203$ or $hr^{\wedge} < 0.831$, reject H_0 and stop; otherwise continue to the next stage	0.019
3	1.0 (866)	0.137	If $hr^{\wedge} > 1.147$ or $hr^{\wedge} < 0.872$, reject H_0 and stop; otherwise stop and accept H_0	0.050

2. Conduct of BPROAD Interim Analysis

The 1st interim analysis was conducted when 472 adjudicated events (54.5%) accrued. The followings are the results of the analysis. BPROAD DSMB members reviewed the results and voted unanimously to continue the trial.



Monitoring Results and Boundaries for BPROAD Primary Outcome

Stage	Date	Time	Time scale	Z score	Bounds	One-sided nominal alpha	Cumulative stopping probability under null
1	Feb2023	0.545	472/866	1.908	±2.821	0.0024	0.0048
2		0.750		.	±2.368	0.0089	0.0194
3		1.00		.	±2.015	0.0219	0.0500

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 *Study Protocol*, which prespecifies that the total study length is five years defined by the time between randomization of the 1st participant and study close-out. Therefore, the BPROAD DSMB Chair and DSMB Biostatistician suggested that the second interim analysis would not provide additional information to the DSMB regarding the decision to continue or stop the study. Therefore, the DSMB decided not to conduct the second interim analysis and recommended that the trial proceeds into close-out, continue adjudication, and conduct the final analysis of the primary outcome. The BPROAD Trial Executive Committee followed the DSMB recommendations.

Section S6. Missing Data

Handling of missing data was prespecified in the *Statistical Analysis Plan*.

1. Missing on baseline characteristics and blood pressure levels

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

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

2. Missing on outcomes

2.1 Multiple imputation for primary outcome and secondary outcomes

We first imputed missing data on baseline characteristics, then we used the imputed dataset with complete baseline information to impute missing outcomes.

a. Imputation of baseline information

We used multiple imputation by fully conditional specification (FCS) with arbitrary missing patterns to make the most use of the available data based on the assumption that data were missing at random⁷. It is generated by estimating each conditional distribution in turn, using observed cases for the variable being considered and imputed values for the other variables at that iteration and imputing missing values. The continuous variables with skewed distributions were log-transformed to normal distributions in the imputation process. The linear regression method was used to impute missing values for continuous variables, and the logistic regression method for binary or ordinal variables. For each variable with missing data, we used the other variables to impute.

We used the following baseline variables with no missing data to define the base set: age, sex, body-mass index, waist circumference, systolic blood pressure, diastolic blood pressure, log-transformed estimated glomerular filtration rate (eGFR), use of aspirin, use of statins, history of clinical CVD (with or without), and subclinical CVD (with or without). With an FCS statement, after the initial filled in, these variables with missing values were imputed sequentially in the order specified in the variable statement lists in each iteration as shown in the following table.

For the imputation of baseline information, 10 replications were generated. The multiple imputation procedure was implemented using *proc mi* in SAS software, version 9.4 (SAS Institute).

Auxiliary Variable	No. Missing (%)	Imputation Model	Predictors
Educational attainment	24(0.2)	Logistic	Base set
Smoking status	28(0.2)	Logistic	Base set + educational attainment
HDL-c	170(1.3)	Linear	Base set + educational attainment + smoking status
LDL-c	176(1.4)	Linear	Base set + educational attainment + smoking status + HDL-c
Triglycerides (TG)	175(1.4)	Linear	Base set + educational attainment + smoking status + HDL-c + LDL-c
Total cholesterol (TC)	173(1.3)	Linear	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG
HbA1c	174(1.4)	Linear	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC
Fasting plasma glucose (FPG)	145(1.1)	Linear	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC + HbA1c
Log Urinary Albumin to Creatinine Ratio (log UACR)	65(0.5)	Linear	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC + HbA1c + FPG
Diabetes duration	67(0.5)	Linear	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC + HbA1c + FPG + log UACR
Hypertension duration	80(0.6)	Linear	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC + HbA1c + FPG + log UACR + diabetes duration
No. of taking antihypertensive drugs	127(1.0)	Logistic	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC + HbA1c + FPG + log UACR + diabetes duration + hypertension duration
Use of insulin	42(0.3)	Logistic	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC + HbA1c + FPG + log UACR + diabetes duration + hypertension duration + No. of taking antihypertensive drugs
No. of taking non-insulin hypoglycemic drugs	41(0.3)	Logistic	Base set + educational attainment + smoking status + HDL-c + LDL-c + TG + TC + HbA1c + FPG + log UACR + diabetes duration + hypertension duration + No. of taking antihypertensive drugs + use of insulin

b. Imputation of outcomes

Outcomes were not imputed for participants that either experienced the event of interest, or those with complete follow-up. For participants that were censored prior to the close-out visit, we set the maximum observation time as the time between May 31, 2024 (last date of primary outcome data collection) and their date of randomization. The lone exception to this was if a participant died during follow-up, then their maximum observation time was the time between their date of death and randomization.

We implemented the outcome imputation method described by Hsu and Taylor⁸. The *InformativeCensoring* package with the method of risk score imputation was used to impute the primary and secondary outcomes, and time to events in R software, version 4.3.3 (R Foundation for Statistical Computing). Based on the 10 imputed datasets with completed baseline information, 5 replications with imputed outcomes were generated for each dataset. At last, 50 (10*5) datasets were obtained. The hazard ratios were calculated by using *proc mianalyze* for combining estimates from multiple datasets according to the Rubin's rules in SAS software, version 9.4 (SAS Institute).

2.2 Multiple imputation by using Pattern-Mixture Models (PMM)

Another sensitivity analysis by using PMM with control-based pattern introduced by Ratitch was conducted⁹.

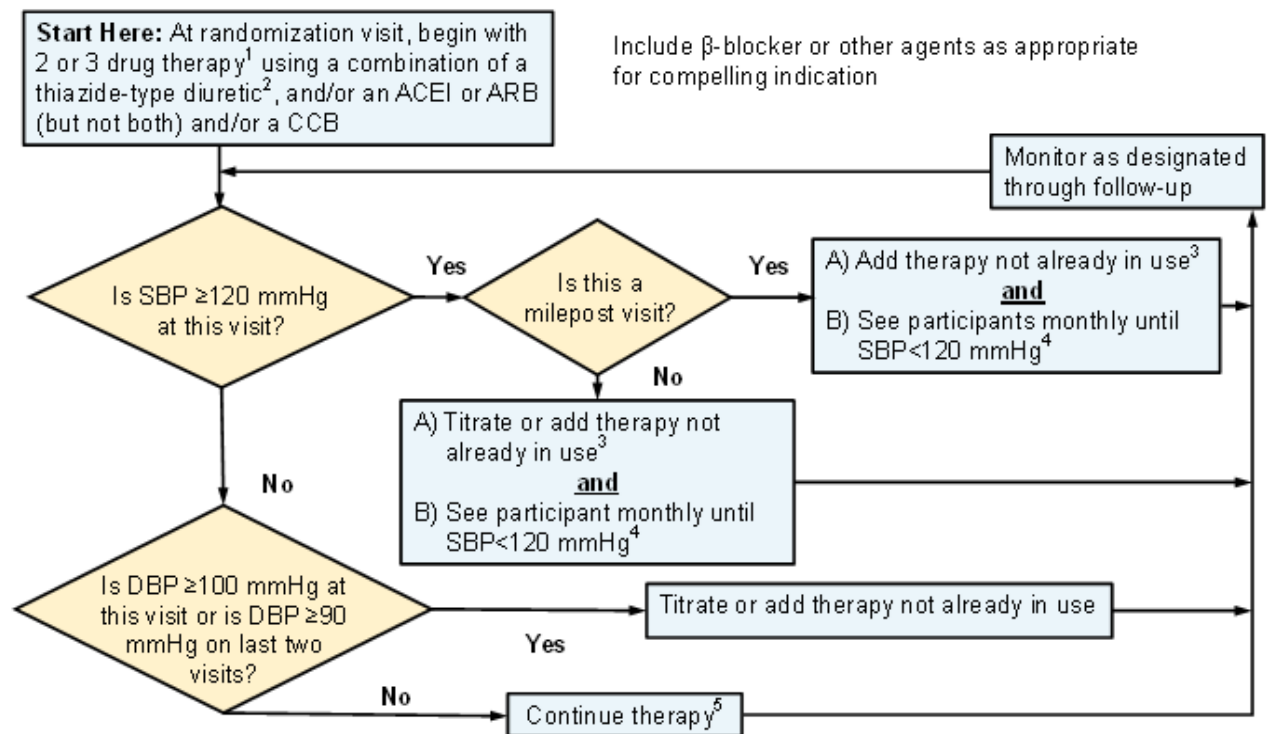
It is natural that subjects stop receiving intensive treatment after discontinuation in the trial. According to this method, it assumes that the discontinued subjects would not take the intensive treatment. Therefore, it might be reasonable to assume that after withdrawal from the study, subjects from the intensive-treatment group will exhibit the same future evolution of the disease as subjects on standard treatment. Subjects that discontinue from the standard-treatment group are assumed to evolve in the same way as standard-treatment subjects that remain in the study. Therefore, in PMM with control-based pattern imputation, the observed data of intensive-treatment group is not used for estimating the imputation model. It builds its imputation model only on data from the standard-treatment group, while it imputes missing data on outcomes in both groups using a single control-based imputation model. Theoretically, such assumptions would tend to move the estimate of the treatment effect, i.e. hazard ratio (HR) that indicated the difference between the intensive and standard treatments, towards a value more close to 1 compared to the analyses using the FCS multiple imputation.

Based on the 10 imputed datasets by using FCS with complete baseline information, we used PMM with control-based pattern imputation strategy to impute the missing outcomes by using aforementioned *InformativeCensoring* package in R. When imputing missing outcomes, the input dataset included all standard-treatment subjects and those subjects from the intensive-treatment group that have outcomes missing. Additionally, the treatment category was not included as an effect in this model. Since subjects from the intensive-treatment group with non-missing values were not included in the input dataset, they would not contribute to the estimation of an imputation model. In this way, subjects from the intensive-treatment group with missing outcomes will be imputed as the same as subjects in the standard-treatment group.

2.3 'Worst case' scenario using opposite imputation approach

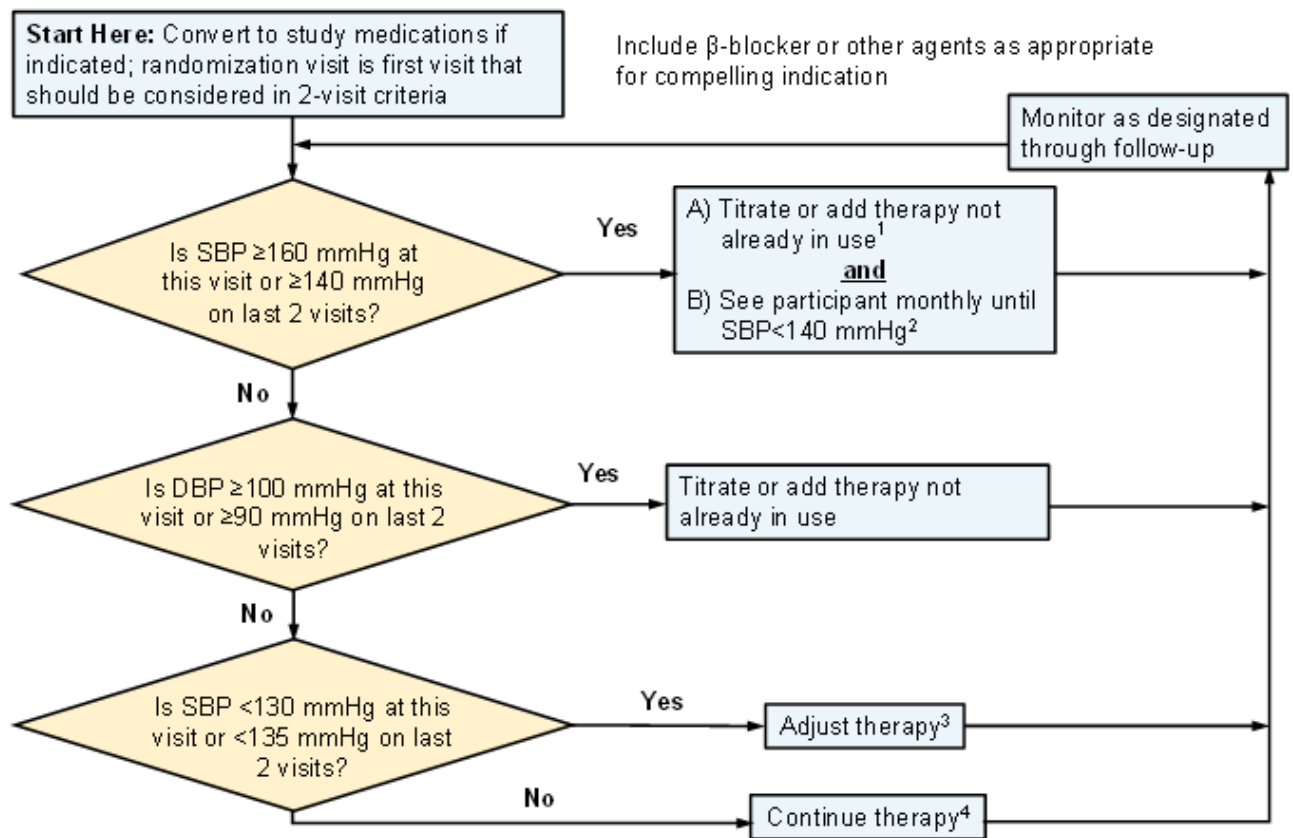
Based on the 10 imputed datasets by using FCS with complete baseline information, we also used a “worst case” strategy to impute the missing outcomes by using aforementioned *InformativeCensoring* package in R. When imputing missing outcomes, the input dataset included all subjects. However, we re-defined the treatment category. For the standard-treatment subjects that have outcomes missing were defined as the intensive-treatment group, while for the intensive-treatment subjects that have outcomes missing were defined as the standard-treatment group. In this way, subjects from intensive-treatment group with missing outcomes will be imputed the same as the standard-treatment subjects, while subjects from standard-treatment group with missing outcomes will be imputed the same as the intensive-treatment subjects.

Figure S1. Treatment Algorithm for Intensive-Treatment Group (Goal Systolic Blood Pressure < 120 mm Hg)



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.

Figure S2. Treatment Algorithm for Standard-Treatment Group (Goal Systolic Blood Pressure < 140 mm Hg)



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.

Figure S3. Number of Clinic and Telephone Interviews across the Trial Period

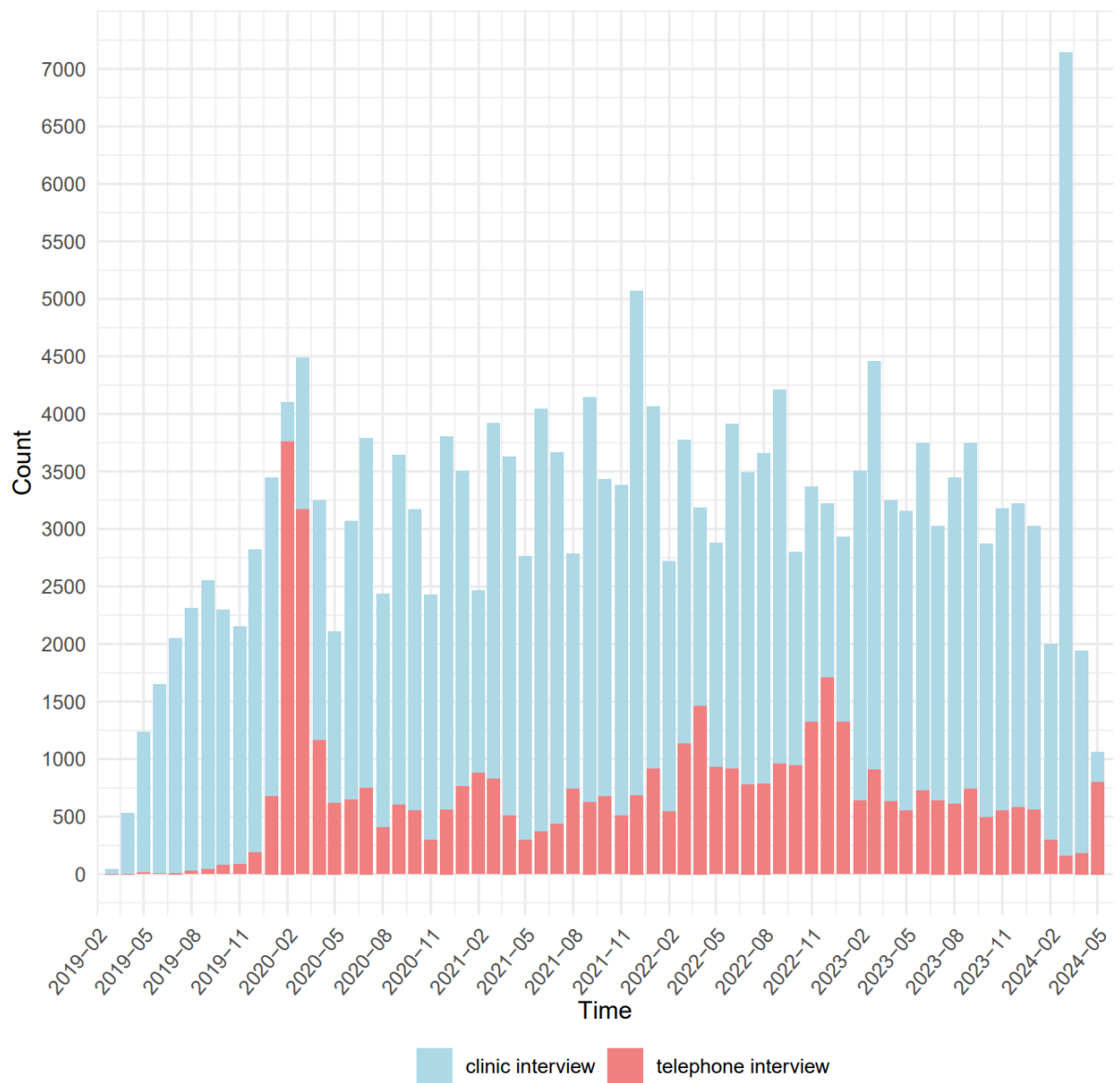


Figure S4. Schoenfeld Residuals Over Time for the Proportional Hazards Assumption

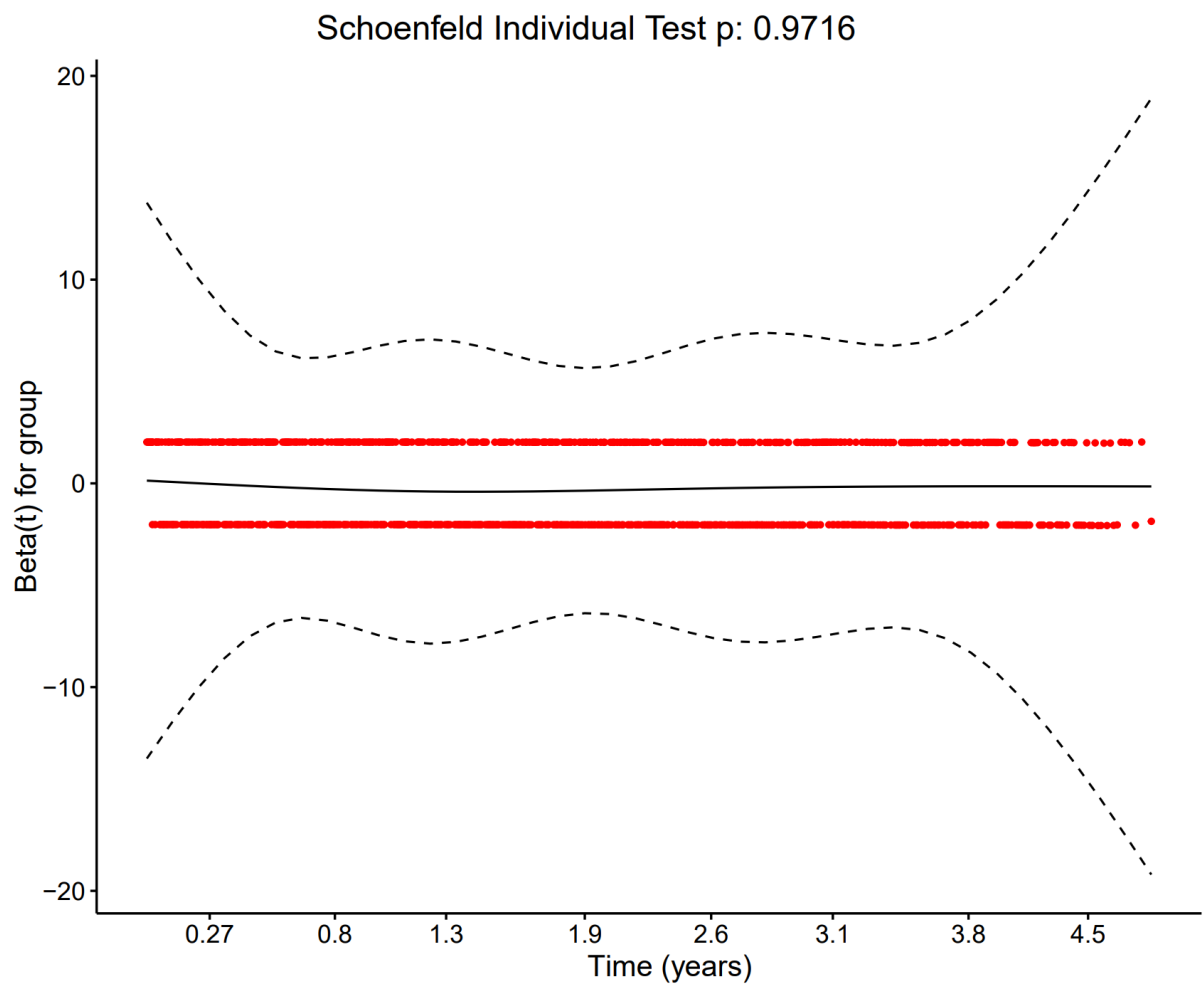
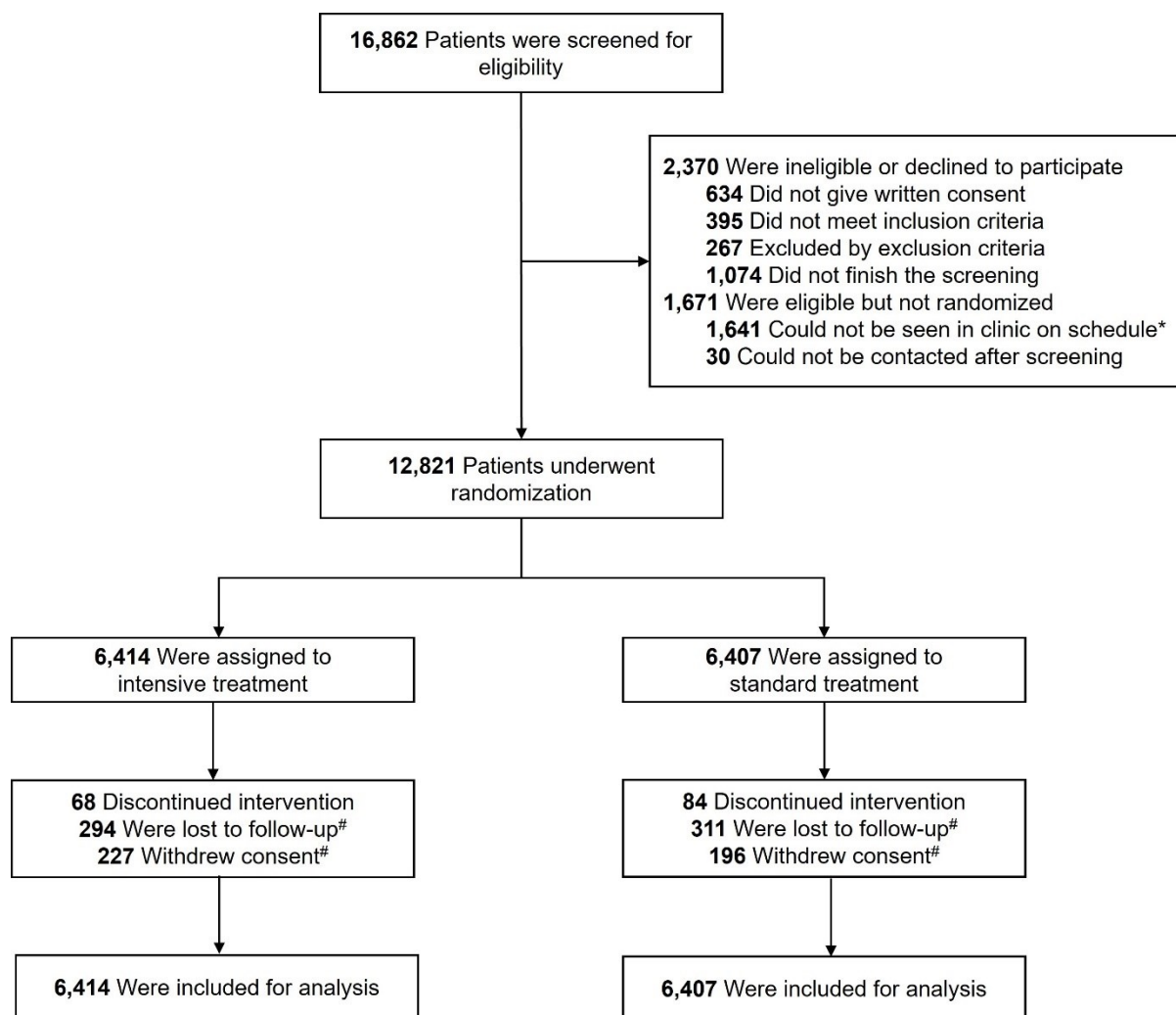


Figure S5. Screening, Randomization, and Follow-up of Study Participants

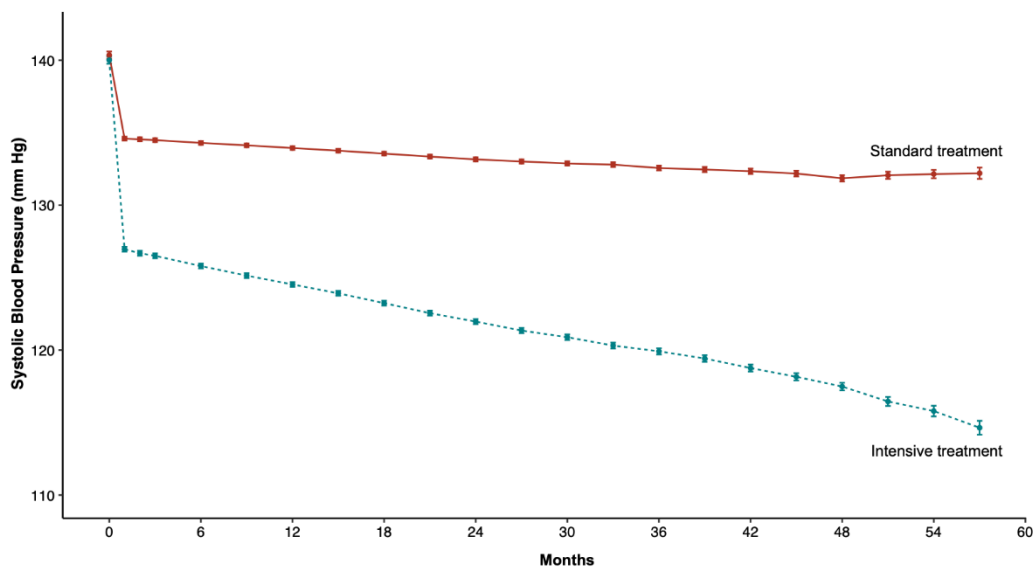


* According to the protocol, patients have to be randomized within 1 month of screening for eligibility.

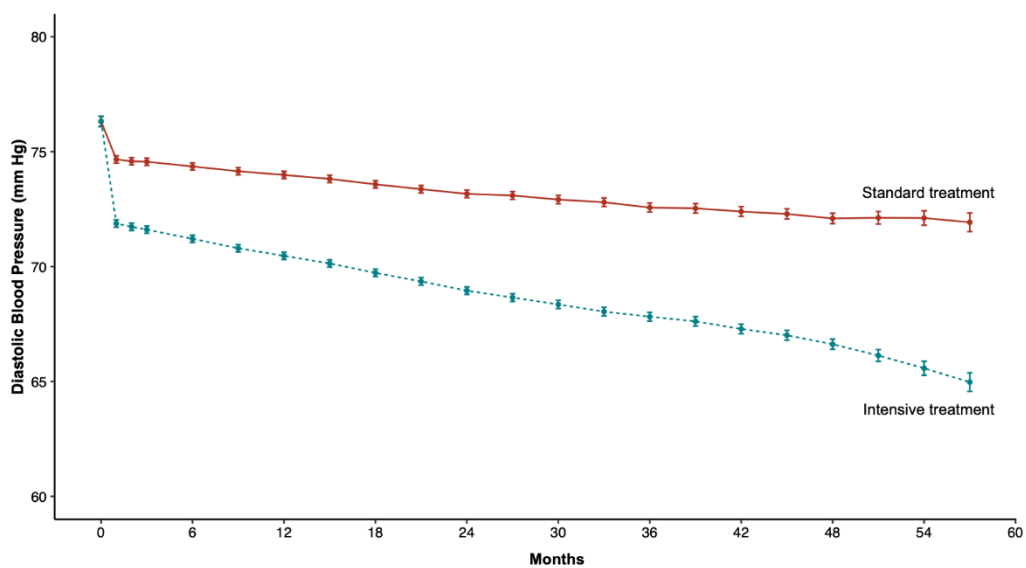
During two large waves of Covid-19 infection in mainland China, there were 133 participants who were lost to follow-up (62 in the intensive-treatment group and 71 in the standard-treatment group) and 142 participants who withdrew consent (84 in the intensive-treatment group and 58 in the standard-treatment group).

Figure S6. Predicted Mean (95% CI) Systolic and Diastolic Blood Pressure by the Joint Model during Follow-up

A. Predicted mean (95% confidence interval) systolic blood pressure by the joint model



B. Predicted mean (95% confidence interval) diastolic blood pressure by the joint model

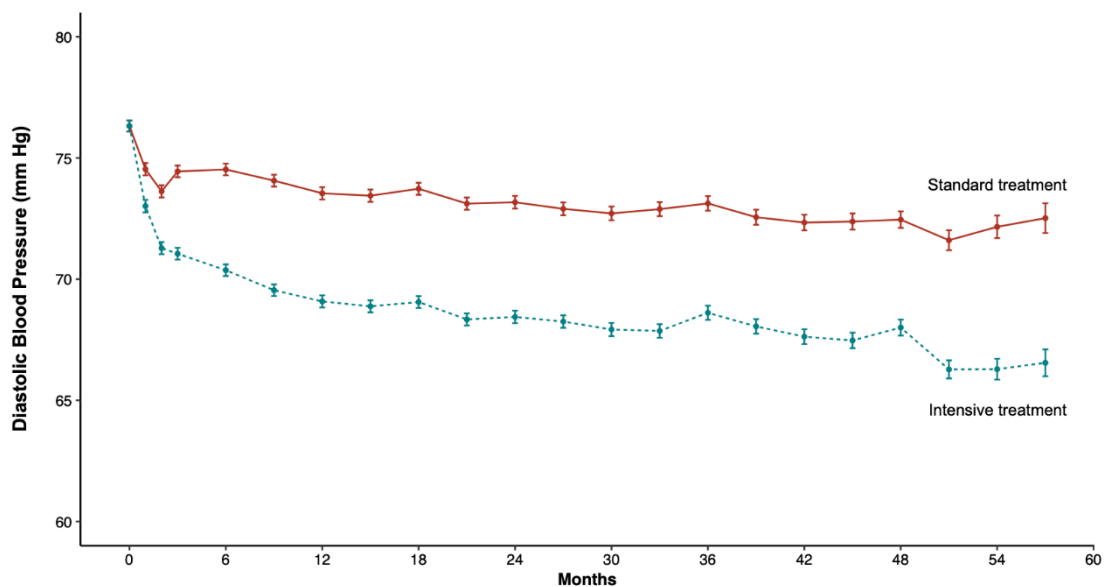


The predicted means and 95% confidence intervals of systolic and diastolic blood pressure were generated by the joint model with the *JMbayes2* package in R considering mortality as a competing risk.^{10,11}

Error bars represent 95% CI.

Abbreviation: CI, confidence interval.

Figure S7. Mean (95% CI) Diastolic Blood Pressure during Follow-up



No. with Data

Standard treatment	6407	5885	5663	5555	5257	4535	4091	3550	3187	1597
Intensive treatment	6414	5858	5612	5474	5244	4541	4119	3573	3198	1622

Mean No. of Medications Prescribed

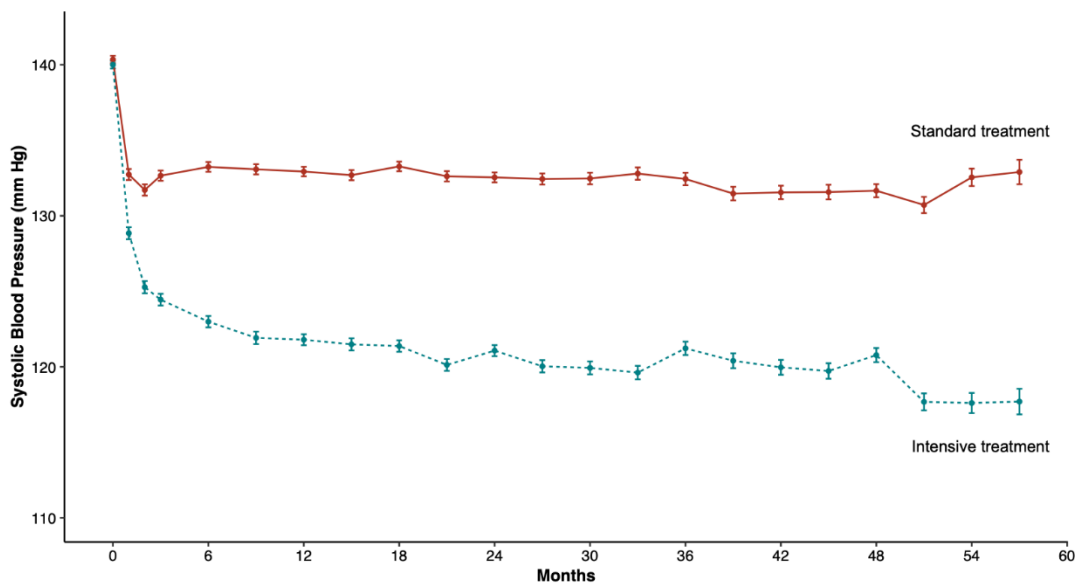
Standard treatment	1.6	1.5	1.5	1.5	1.5	1.4	1.4	1.4	1.4	1.3
Intensive treatment	1.7	2.0	2.1	2.1	2.2	2.2	2.2	2.2	2.2	2.1

Error bars represent 95% CI.

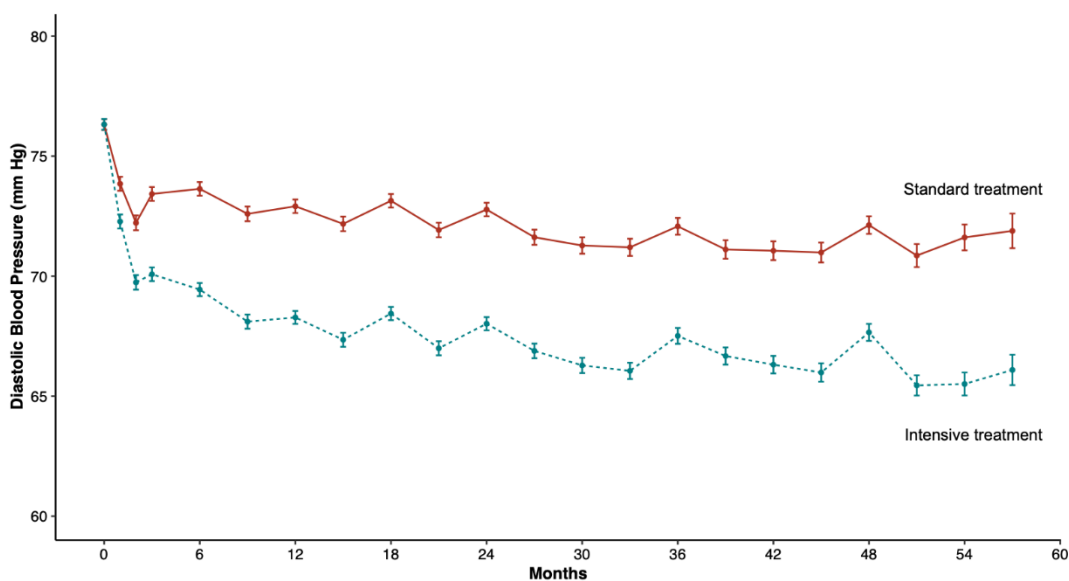
Abbreviation: CI, confidence interval.

Figure S8. Mean (95% CI) Systolic and Diastolic Blood Pressure in Clinic during Follow-up

A. Mean (95% confidence interval) systolic blood pressure in clinic



B. Mean (95% confidence interval) diastolic blood pressure in clinic



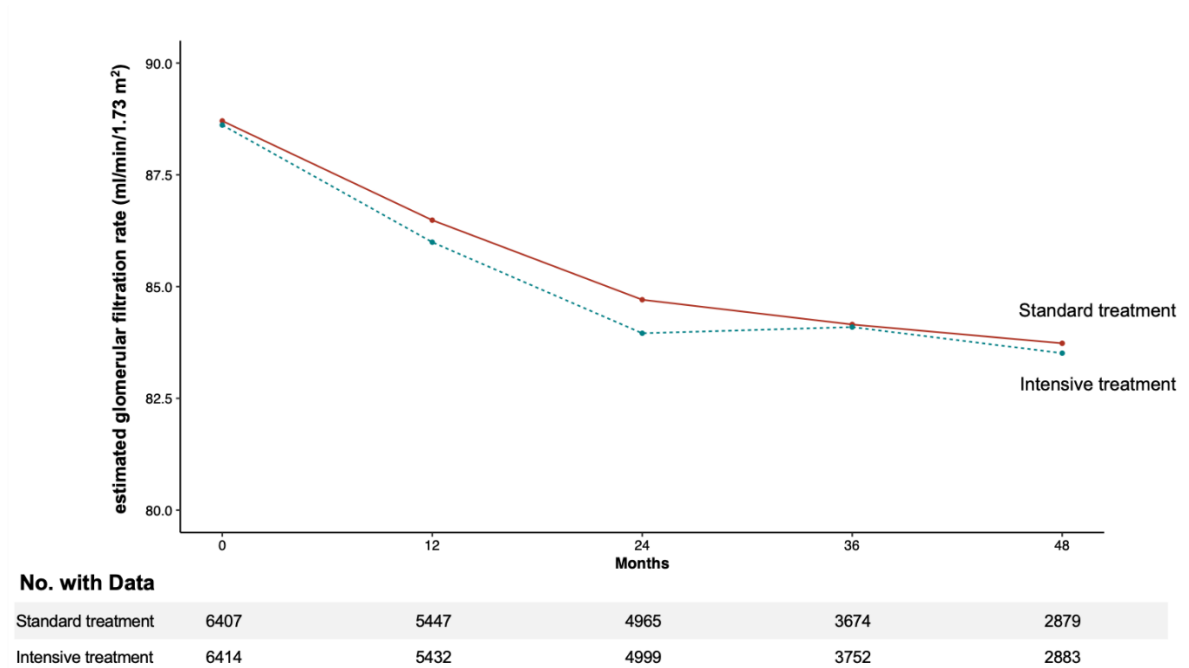
No. with Data

Standard treatment	6407	4592	4909	4587	4727	3265	3206	2562	2870	1299
Intensive treatment	6414	4620	4890	4530	4744	3312	3240	2603	2871	1325

Error bars represent 95% CI.

Abbreviation: CI, confidence interval.

Figure S9. Mean eGFR at Baseline and Annual Visits by Treatment Groups



Abbreviation: eGFR, estimated glomerular filtration rate.

Table S1. Clinic and Telephone Interviews at Protocol Visits by Treatment Groups

Visit	Intensive treatment (n=6414)			Standard treatment (n=6407)		
	No. of clinic interview	No. of telephone interview	Percentage of telephone interview (%)	No. of clinic interview	No. of telephone interview	Percentage of telephone interview (%)
1-month	4887	1122	18.7	4874	1158	19.2
2-month	4164	1685	28.8	4150	1706	29.1
3-month	4544	1423	23.8	4486	1480	24.8
6-month	4620	1238	21.1	4592	1293	22.0
9-month	4019	1663	29.3	4000	1707	29.9
12-month	4890	722	12.9	4909	754	13.3
15-month	4051	1462	26.5	4074	1460	26.4
18-month	4530	944	17.2	4587	968	17.4
21-month	3951	1323	25.1	3973	1389	25.9
24-month	4744	500	9.5	4727	530	10.1
27-month	3695	1311	26.2	3726	1308	26.0
30-month	3312	1229	27.1	3265	1270	28.0
33-month	2930	1285	30.5	2907	1345	31.6
36-month	3240	879	21.3	3206	885	21.6
39-month	2724	1058	28.0	2647	1107	29.5
42-month	2603	970	27.1	2562	988	27.8
45-month	2389	980	29.1	2345	1001	29.9
48-month	2871	327	10.2	2870	317	9.9
51-month	1800	451	20.0	1750	454	20.6
54-month	1325	297	18.3	1299	298	18.7
57-month	746	165	18.1	714	186	20.7
Close-out	4929	626	11.3	4902	646	11.6

Table S2. Clinical and Subclinical CVD at Screening

Characteristics	Intensive treatment (n=6414)	Standard treatment (n=6407)
History of clinical CVD	1480 (23.1)	1408 (22.0)
Stroke	831 (13.0)	776 (12.1)
Myocardial infarction	166 (2.6)	153 (2.4)
PCI or CABG	501 (7.8)	469 (7.3)
Carotid endarterectomy or carotid stenting	18 (0.3)	24 (0.4)
Peripheral artery disease with revascularization	7 (0.1)	8 (0.1)
Acute coronary syndrome	286 (4.5)	260 (4.1)
Subclinical CVD	2173 (33.9)	2251 (35.1)
Microalbuminuria	1814 (28.3)	1875 (29.3)
\geq 50% stenosis of a coronary, carotid, or lower extremity artery	345 (5.4)	352 (5.5)
Coronary artery calcium score \geq 400 Agatston units	3 (0.0)	4 (0.1)
Ankle brachial index \leq 0.90	64 (1.0)	66 (1.0)
Left ventricular hypertrophy	125 (1.9)	123 (1.9)

Data are numbers (percentages).

Abbreviations: CABG, coronary artery bypass grafting; CVD, cardiovascular disease; PCI, percutaneous coronary intervention.

Table S3. Representativeness of Study Participants

Category	
Disease, problem, or condition under investigation	Type 2 diabetes (T2D) with elevated systolic blood pressure
Special considerations related to:	
Sex and gender	Both age-standardized prevalence of diabetes and hypertension was slightly lower in women than in men (diabetes, 10.2% vs. 10.8%; hypertension, 32% vs. 34%) globally ^{12,13} . Men with diabetes generally have higher rates of hypertension ¹⁴ , especially at younger ages, while women with hypertension or diabetes had higher risk of CVD ¹⁵ .
Age	Globally, age presented positive associations with systolic blood pressure and glycemic metrics ¹⁶ . In specific, an older age (≥ 65 years) was associated with a poorer blood pressure control in adults with diabetes in China ¹⁴ .
Race or ethnic group	Age-adjusted prevalence of hypertension was higher in non-Hispanic Black and non-Hispanic White populations, followed by Hispanic and non-Hispanic Asian populations, while that of diabetes was the highest in Hispanic population, followed by non-Hispanic Black, non-Hispanic Asian, and non-Hispanic White populations ¹⁷ , as recorded in NHANES.
Geography	Hypertension was the top modifiable risk factor for CVD in China ¹⁸ and globally ¹⁹ , especially in those with T2D ²⁰ , troubling approximately 2/3 of patients. Currently, China still ranked top in absolute hypertension burden and second in T2D burden worldwide, accounting for 24.7% and 15.2% of global disability-adjusted life years (DALYs), respectively ²¹ . Compared with the global average in T2D including that in the United States ²² , European countries and Asian countries including Japan ²³ and India ²⁴ , China had a lower blood pressure control rate (only 22.2% achieved a blood pressure target of 130/80 mm Hg) ¹⁴ , which was also associated with elevated risk of macrovascular events ²⁵ . Besides, hypertension prevalence ²⁶ (North over East) and related CVD risk ²⁷ (Northeast>Central>Southwest>South) in T2D population also varies by geography across China.
Other considerations	Compared with those without diabetes, T2D patients are characterized by higher risks of adverse cardiovascular and renal outcomes when associated with elevated blood pressure. Current practice and evidence on optimal blood-

	pressure lowering target in T2D patients remain controversial.
Overall representativeness of this trial	<p>The BPROAD study included patients with T2D aged 50 years or older with elevated systolic blood pressure and increased risk of CVD. Women represented about 45.3% of the trial population, which was nearly comparable to the proportion of men, and also matched the global distribution¹³. The mean age of study participants was 63.8 years old and there was also fair representation of participants aged 65 years or older (44.6%) in our study. All participants were of Asian descent, reflecting the ethnicity of interest but not the global diversity of T2D and hypertension. Finally, study participants were enrolled from 145 clinical sites covering all seven geographic regions across mainland China. Hence, this study contributed valuable evidence from China regarding the optimal blood pressure targets for T2D patients, with potential broader generalizability to other populations.</p>

Table S4. Numbers and Percentages of Participants with Systolic Blood Pressure Levels Lower than 120 mm Hg at Protocol Visits in the Intensive-Treatment Group

Visit	No. of participants within target	Percentage of participants within target (%)
1-month	1741	29.0
2-month	2312	39.5
3-month	2810	47.1
6-month	3224	55.0
9-month	3350	59.0
12-month	3269	58.3
15-month	3305	59.9
18-month	3259	59.5
21-month	3368	63.9
24-month	3091	58.9
27-month	3152	63.0
30-month	2888	63.6
33-month	2642	62.7
36-month	2415	58.6
39-month	2351	62.2
42-month	2229	62.4
45-month	2160	64.1
48-month	1925	60.2
51-month	1601	71.1
54-month	1145	70.6
57-month	645	70.8

Table S5. Utilization of Antihypertensive and Hypoglycemic Medications, Statin, and Aspirin at 48-Month Visit

Medication classes	Intensive treatment (n=3198)	Standard treatment (n=3187)
Antihypertensive drug treatment – no. (%)	3068 (97.6)	2632 (84.1)
ACEI	339 (10.8)	269 (8.6)
ARB	2062 (65.6)	1407 (45.0)
CCB	2313 (73.6)	1591 (50.8)
Diuretics	831 (26.4)	323 (10.3)
α -receptor blocker	71 (2.3)	18 (0.6)
β -receptor blocker	939 (29.9)	623 (19.9)
Others	41 (1.3)	17 (0.5)
Hypoglycemic drug treatment – no. (%)	3062 (98.6)	3054 (98.8)
Insulin	1547 (49.9)	1530 (49.5)
Metformin	1980 (63.8)	1977 (63.9)
TZD	76 (2.4)	78 (2.5)
Sulfonylurea	376 (12.1)	399 (12.9)
α -glucosidase inhibitor	959 (30.9)	890 (28.8)
GLP-1 receptor agonist	141 (4.5)	143 (4.6)
DPP-4 inhibitor	310 (10.0)	308 (10.0)
SGLT-2 inhibitor	641 (20.7)	676 (21.9)
Statin – no. (%)	1774 (57.2)	1773 (57.3)
Aspirin – no. (%)	1435 (46.3)	1459 (47.2)

Missing values: n=114 for antihypertensive drug treatment and antihypertensive drug classes (56 in intensive treatment group and 58 in standard treatment group); n=189 for hypoglycemic drug treatment and hypoglycemic drug classes (94 in intensive treatment group and 95 in standard treatment group) except for insulin n=190 (95 in intensive treatment group and 95 in standard treatment group); n=191 for statin treatment (96 in intensive treatment group and 95 in standard treatment group); n=194 for aspirin treatment (98 in intensive treatment group and 96 in standard treatment group).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose transport protein-2; TZD, thiazolidinedione.

Table S6. Risk Factor Levels of the Study Participants at 48-Month Visit

Risk factors	Intensive treatment (n=3198)	Standard treatment (n=3187)
BMI – kg/m ²	26.3 ± 3.3	26.3 ± 3.3
Waist circumference – cm	94.3 ± 8.6	94.2 ± 8.6
HbA1c – %	7.6 ± 1.4	7.6 ± 1.4
Total cholesterol – mg/dl	178.9 ± 52.5	177.7 ± 53.1
LDL cholesterol – mg/dl	91.7 ± 37.0	90.5 ± 36.9
HDL cholesterol – mg/dl	43.1 ± 12.0	42.9 ± 11.7
Triglycerides – mg/dl	148.8 (103.6-219.7)	144.8 (101.9-222.3)

Data are means ± standard deviations or medians (interquartile ranges).

Missing values: n=658 for BMI (334 in intensive treatment group and 324 in standard treatment group); n=689 for waist circumference (350 in intensive treatment group and 339 in standard treatment group); n=719 for HbA1c (365 in intensive treatment group and 354 in standard treatment group); n=718 for total cholesterol (365 in intensive treatment group and 353 in standard treatment group); n=720 for LDL cholesterol (366 in intensive treatment group and 354 in standard treatment group); n=718 for HDL cholesterol (365 in intensive treatment group and 353 in standard treatment group); n=718 for triglycerides (365 in intensive treatment group and 353 in standard treatment group).

Abbreviations: BMI, body-mass index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table S7. Causes of Death

Causes of death	Overall	Intensive treatment	Standard treatment
CVD Death	139	60	79
CHD related	64	26	38
Stroke related	52	24	28
HF related	10	4	6
Other CVD death	13	6	7
Cancer Death	87	43	44
Death due to causes other than CVD or cancer	88	48	40
Infectious disease	37	19	18
Covid-19 related	10	5	5
Gastrointestinal or liver disease	7	5	2
Respiratory causes (excluding pneumonia)	4	3	1
Neurologic disease	2	2	0
Acute diabetes complication	3	2	1
Accident/Injury	16	7	9
Suicide	4	1	3
Others	15	9	6
Undetermined	34	18	16
Total	348	169	179

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure.

Table S8. Numbers of Participants with eGFR Measurements and Completeness at Annual and Close-out Visits

Visit	Intensive treatment		Standard treatment	
	No. observed	Completeness (%)	No. observed	Completeness (%)
12-month	5432	85.5	5447	85.9
24-month	4999	81.2	4965	80.6
36-month	3752	77.9	3674	76.7
48-month	2883	80.1	2879	80.4
Close-out	4173	72.3	4173	72.5

Abbreviation: eGFR, estimated glomerular filtration rate.

Table S9. Primary and Sensitivity Analysis Using Different Methods for Missing Outcomes

Outcomes	Hazard ratio (95% CI)			
	Multiple imputation assuming missing at random	Loss to follow-up treated as censoring	Multiple imputation using Pattern-Mixture Models	'Worst case' scenario using opposite imputation approach
Primary outcome	0.79 (0.69-0.90)	0.79 (0.69-0.90)	0.81 (0.71-0.93)	0.82 (0.72-0.94)
Secondary outcomes				
Fatal and nonfatal MI	0.84 (0.60-1.16)	0.84 (0.61-1.15)	0.85 (0.61-1.17)	0.85 (0.62-1.18)
Fatal and nonfatal stroke	0.79 (0.67-0.92)	0.79 (0.68-0.92)	0.80 (0.68-0.94)	0.81 (0.69-0.94)
Treated or hospitalized heart failure	0.66 (0.41-1.04)	0.67 (0.43-1.06)	0.68 (0.43-1.07)	0.72 (0.45-1.14)
Cardiovascular death	0.76 (0.55-1.06)	0.76 (0.54-1.06)	0.77 (0.55-1.07)	0.78 (0.56-1.09)
All-cause death	0.95 (0.77-1.17)	0.94 (0.76-1.16)	0.95 (0.77-1.17)	0.95 (0.77-1.17)
Primary outcome and all-cause death	0.83 (0.74-0.94)	0.84 (0.74-0.94)	0.84 (0.75-0.95)	0.85 (0.75-0.96)
CKD outcomes				
CKD progression	1.36 (0.71-2.59)	1.44 (0.76-2.72)	1.33 (0.70-2.54)	1.34 (0.70-2.54)
CKD development	1.11 (0.92-1.34)	1.08 (0.90-1.30)	1.11 (0.92-1.34)	1.11 (0.92-1.34)
Incident albuminuria	0.87 (0.77-0.97)	0.82 (0.73-0.92)	0.87 (0.77-0.97)	0.87 (0.77-0.97)

Confidence intervals have not been adjusted for multiplicity and these intervals may not be used for hypothesis testing.

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; MI, myocardial infarction.

Table S10. Sensitivity Analysis Using the Fine and Gray Model for the Competing Risk

Outcomes	Composites/details	Competing risk	Hazard ratio (95% CI)
Primary outcome	- Nonfatal MI	Non-CVD death	0.79 (0.69-0.90)
	- Nonfatal stroke		
	- Treated or hospitalized HF		
	- Cardiovascular death		
Secondary outcomes			
Fatal and nonfatal MI	—	Non-MI death	0.84 (0.60-1.16)
Fatal and nonfatal stroke	—	Non-stroke death	0.79 (0.68-0.92)
Treated or hospitalized HF	—	Non-HF death	0.66 (0.41-1.05)
Cardiovascular death	—	Non-CVD death	0.76 (0.55-1.06)
All-cause death	—	None	/
Primary outcome and all-cause death	—	None	/
CKD outcomes			
CKD progression	A composite of a 50% decrease in eGFR, or eGFR<15 ml/min/1.73 m ² , or development of end-stage renal disease in patients with CKD at baseline	All-cause death	1.35 (0.73-2.50)
CKD development	A >30% decrease in eGFR and eGFR <60 ml/min/1.73 m ² in patients without CKD at baseline	All-cause death and initiation of chronic renal replacement therapy	1.12 (0.93-1.34)
Incident albuminuria	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	All-cause death	0.87(0.78-0.98)

Confidence intervals have not been adjusted for multiplicity and these intervals may not be used for hypothesis testing.

Abbreviations: ACR, albumin-to-creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction.

Table S11. Sensitivity Analysis for the Primary Outcome Stratified by Clinic Rather Than Region

Outcome	Hazard ratio (95% CI)			
	Multiple imputation assuming missing at random	Loss to follow-up treated as censoring	Multiple imputation using Pattern-Mixture Models	'Worst case' scenario using opposite imputation approach
Primary outcome	0.79 (0.69-0.90)	0.79 (0.69-0.90)	0.81 (0.71-0.92)	0.82 (0.72-0.94)

Confidence intervals have not been adjusted for multiplicity and these intervals may not be used for hypothesis testing.

Abbreviation: CI, confidence interval.

Table S12. Serious Adverse Events

Category of events*	Intensive treatment (n=6414)		Standard treatment (n=6407)		P value †
	No. of events	Percentage	No. of events	Percentage	
Hypertension	38	0.60%	31	0.50%	0.40
Diabetes	723	11.27%	654	10.21%	0.06
Acute diabetes complication	21	0.30%	21	0.30%	1.00
Cerebrovascular disease	549	8.60%	598	9.30%	0.15
Coronary heart disease	526	8.20%	551	8.60%	0.45
Other cardiovascular disease	116	1.80%	98	1.50%	0.22
Chronic kidney disease	29	0.50%	33	0.50%	0.61
Cancer	137	2.10%	158	2.50%	0.22
Gastrointestinal or liver disease	175	2.70%	151	2.40%	0.18
Pneumonia	120	1.87%	111	1.73%	0.55
Covid-19 related	26	0.40%	28	0.40%	0.79
Other infectious disease	144	2.20%	132	2.10%	0.47
Fracture	90	1.40%	96	1.50%	0.66
Other accident	47	0.70%	48	0.70%	0.92
Osteoarthritis	77	1.20%	72	1.10%	0.68
Cataract	44	0.70%	46	0.70%	0.83

* Occurred in at least 0.50% of participants. Participants were only counted once for each category of events. Death cases were not included.

† P values were calculated using chi-square test.

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