# Supplementary Appendix

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

Supplement to: The SPRINT Research Group. Final report of a trial of intensive versus standard blood-pressure control. N Engl J Med 2021;384:1921-30. DOI: 10.1056/NEJMoa1901281

Supplementary appendix

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**Acknowledgments**

The Systolic Blood Pressure Intervention Trial is funded with Federal funds from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS), under Contract Numbers HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals International, Inc.

All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed, and interpreted the data. All aspects of manuscript writing and revision were carried out by the coauthors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government.
We also acknowledge the support from the following CTSAs funded by NCATS:
CWRU: UL1TR000439, OSU: UL1RR025755, U Penn: UL1RR024134& UL1TR000003, Boston: UL1RR025771, Stanford: UL1TR000093, Tufts: UL1RR025752, UL1TR000073 & UL1TR001064, University of Illinois: UL1TR000050, University of Pittsburgh: UL1TR000005, UT Southwestern: 9U54TR000017-06, University of Utah: UL1TR000105-05, Vanderbilt University: UL1 TR000445, George Washington University: UL1TR000075, University of CA, Davis: UL1 TR000002, University of Florida: UL1 TR000064, University of

Michigan: UL1TR000433, Tulane University: P30GM103337 COBRE Award NIGMS. Support was also provided by the Wake Forest University Claude D. Pepper Older Americans Independence Center (P30-AG21332).

Section 2. Inclusion and exclusion criteria

a) Inclusion Criteria

1. At least 50 years old

2. Systolic blood pressure
   SBP: 130 – 180 mm Hg on 0 or 1 medication
   SBP: 130 – 170 mm Hg on up to 2 medications
   SBP: 130 – 160 mm Hg on up to 3 medications
   SBP: 130 – 150 mm Hg on up to 4 medications

3. There are no diastolic blood pressure (DBP) inclusion criteria, since risk is more related to SBP than DBP in the age and risk population anticipated for SPRINT. If a screenee is otherwise eligible for SPRINT but presents with a treated BP and/or number of medications that fall outside the SPRINT 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 for SPRINT. A screenee who presents on no BP medications should have documentation of SBP ≥130 mm Hg on 2 visits within 3 months prior to the randomization visit in order to be eligible for the trial.

4. Risk (one or more of the following):
   a) Presence of clinical* or subclinical** cardiovascular disease other than stroke
   b) CKD, defined as eGFR 20 – 59 ml/min/1.73m$^2$ based on the 4-variable Modification of Diet in Renal Disease (MDRD) equation and latest lab value, within the past 6 months. (If the serum creatinine is unstable within the last 6 months, enrollment into SPRINT could be delayed until the serum creatinine has been stabilized and the eGFR is still within the allowed range.)
   c) Framingham Risk Score for 10-year CVD risk ≥ 15% based on laboratory work done within the past 12 months for lipids
   d) Age ≥ 75 years.

* Clinical CVD (other than stroke)
   a) Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), carotid endarterectomy (CE), carotid stenting
   b) Peripheral artery disease (PAD) with revascularization
   c) Acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test (GXT), or positive cardiac imaging study
   d) At least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery
   e) Abdominal aortic aneurysm (AAA) ≥5 cm with or without repair

** Subclinical CVD
   a) Coronary artery calcium score ≧ 400 Agatston units within the past 2 years.
   b) Ankle brachial index (ABI) ≤0.90 within the past 2 years.
   c) Left ventricular hypertrophy (LVH) by ECG (based on computer reading), echocardiogram report, or other cardiac imaging procedure report within the past 2 years.

b) Exclusion Criteria

1. An indication for a specific BP lowering medication (e.g., beta-blocker following acute myocardial infarction) that the person is not taking and the person has not been documented to be intolerant of the medication class. (If a screenee has a non-hypertension indication for a BP-lowering medication (e.g., beta-blocker post-MI, renin angiotensin system (RAS) blocker for CVD prevention, or alpha blocker for benign prostatic hypertrophy (BPH)), the screenee should be on the appropriate dose of such medication before assessing whether he/she meets the SPRINT inclusion criteria. If the investigator believes that a potential participant has such an indication but is not receiving appropriate treatment, he/she should encourage the potential participant's primary care provider to consider placing the patient on the appropriate therapy prior to proceeding with the screening process.)
2. Known secondary cause of hypertension that causes concern regarding safety of the protocol.
3. One minute standing SBP < 110 mm Hg. Not applicable if unable to stand due to wheelchair use.
4. Proteinuria in the following ranges (based on a measurement within the past 6 months)
   (a) 24 hour urinary protein excretion ≥1 g/day, or
   (b) If measurement (a) is not available, then 24 hour urinary albumin excretion ≥ 600 mg/day, or
   (c) If measurements (a) or (b) are not available, then spot urine protein/creatinine ratio ≥ 1 g/g creatinine, or
   (d) If measurements (a), (b), or (c) are not available, then spot urine albumin/creatinine ratio ≥ 600 mg/g creatinine, or
   (e) If measurements (a), (b), (c), or (d) are not available, then urine dipstick ≥ 2+ protein
5. Arm circumference too large or small to allow accurate blood pressure measurement with available devices
6. Diabetes mellitus. Participants taking medications for diabetes at any time in the last 12 months are excluded. Participants are also excluded if there is documentation of: FPG at or above 126 mg/dL, A1C ≥6.5 percent, a two-hour value in an OGTT (2-h PG) at or above 200 mg/dL or a random plasma glucose concentration ≥200 mg/dL. 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 (eg, FPG and A1C) 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.
7. History of stroke (not CE or stenting)
8. Diagnosis of polycystic kidney disease
9. Glomerulonephritis treated with or likely to be treated with immunosuppressive therapy
10. eGFR < 20 ml/min /1.73m$^2$ or end-stage renal disease (ESRD)
11. Cardiovascular event or procedure (as defined above as clinical CVD for study entry) or hospitalization for unstable angina within last 3 months
12. Symptomatic heart failure within the past 6 months or left ventricular ejection fraction (by any method) < 35%
13. A medical condition likely to limit survival to less than 3 years, or a cancer diagnosed and treated within the past two years that, in the judgment of clinical study staff, would compromise a participant's ability to comply with the protocol and complete the trial. Exceptions to the exclusion for diagnosed cancer would include, for example, non-melanoma skin cancer, early-stage prostate cancer, localized breast cancer.

14. Any factors judged by the clinic team to be likely to limit adherence to interventions. For example,
    (a) Active alcohol or substance abuse within the last 12 months
    (b) Plans to move outside the clinic catchment area in the next 2 years without the ability to transfer to another SPRINT site, or plans to be out of the study area for more than 3 months in the year following enrollment.
    (c) Significant history of poor compliance with medications or attendance at clinic visits
    (d) Significant concerns about participation in the study from spouse, significant other, or family members
    (e) Lack of support from primary health care provider
    (f) Residence too far from the study clinic site such that transportation is a barrier including persons who require transportation assistance provided by the SPRINT clinic funds for screening or randomization visits
    (g) Residence in a nursing home. Persons residing in an assisted living or retirement community are eligible if they meet the other criteria.
    (h) Clinical diagnosis of dementia, treatment with medications for dementia, or in the judgment of the clinician cognitively unable to follow the protocol
    (i) Other medical, psychiatric, or behavioral factors that in the judgment of the Principal Investigator may interfere with study participation or the ability to follow the intervention protocol
15. Failure to obtain informed consent from participant
16. Currently participating in another clinical trial (intervention study). Note: Patient must wait until the completion of his/her activities or the completion of the other trial before being screened for SPRINT.
17. Living in the same household as an already randomized SPRINT participant
18. Any organ transplant
19. Unintentional weight loss > 10% in last 6 months
20. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not using birth control

## Section 3. Definition of Study Outcomes

The primary outcome measure for SPRINT will be major CVD events, defined as the composite endpoint comprised of the first occurrence of a myocardial infarction (MI), non-MI acute coronary syndrome (non-MI ACS), stroke, heart failure (HF), or death attributable to cardiovascular disease (CVD).

SPRINT previously reported primary results with follow-up and events through August 20, 2015(1), the date that the decision was made to terminate the study intervention early for benefit. Those results represented the data available in October 2015. Because of the rapidity of that publication, the ascertainment and adjudication of trial phase events were incomplete, and we continued to collect data and adjudicate potential events through post-intervention close-out. Note that adjudication methods and blinding of adjudication were the same during the trial period and the post-trial observational period.

**MI DEFINITION:** Generally defined as 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. The definition includes MI that occurred during surgery/procedure and MI aborted by thrombolytic therapy or procedure, as well as due to demand ischemia (2,3). 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).

**Table 1. SPRINT Classification of MI (2)**

| | Positive biomarker findings | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cardiac symptoms or signs present | | | | Cardiac symptoms or signs absent | | | |
| ECG Findings** | 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 indicates 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*** (2-4):
+Diagnostic = At least 1 positive biomarker (at least 1 value at least twice the upper limit of normal) 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. Troponin will take precedence over CK-MB, and CK-MB will take precedence

over CK if both are available. Enzymes following CPR are non-interpretable; cardiac ablation, pacing and defibrillator shocks are causes of myocardial injury not related to ischemia (2).

The 2003 AHA Scientific Statement (2) and the Universal Definition (5) define positive biomarkers as "the 99$^{th}$ percentile of the distribution in healthy populations, or the lowest level at which a 10% coefficient of variation can be demonstrated for that laboratory" assay.

***Cardiac symptoms and signs***

**Cardiac symptoms.** 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. More general, atypical symptoms, such as fatigue, nausea, vomiting, diaphoresis, faintness, and back pain, should not be used.

**Cardiac signs.** These can be used for determination of MI, and include acute HF or cardiogenic shock in the absence of non-CHD causes. These can be especially helpful when the patient is unable to provide a history on presentation.

***ECG Criteria***

**Evolving:** evolution of a new diagnostic Q wave; OR equivocal Q wave and evolution of major ST depression or elevation or T wave inversion
**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
**Nonspecific:** evolving minor Q wave alone or evolving non-ST elevation non-Q wave pattern (including evolving ST depression alone)
**Negative for evolving ischemia:** Normal ECG(s), or findings other than those described in the above categories

***Aborted MI***

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

***Procedure Related MI***

**For PTCA**, levels of CK- MB or troponin above 3 times the ULN within 48 hours of the procedure will be characterized as positive (5). Similarly for **CABG**, levels of troponin or MB above 5 times the ULN within 48 hours of the procedure will be categorized as positive. Total CK will not be used for post-CABG enzymes (5).

A revascularization procedure performed for the treatment of acute ischemia (e.g., angioplasty following the presentation of acute coronary syndrome/MI) should *not* be considered as procedure-related (2); however, the occurrence of a second MI with the revascularization procedure will be recorded. The procedure-related MI category is intended to identify MIs that occurred only after the procedure, and were not already in evolution.

**NON-MI ACS Definition:** Defined as hospitalization for evaluation and treatment of an accelerating or new symptom pattern consistent with coronary artery insufficiency without meeting the definition of MI, but requiring evaluation to rule-out MI on clinical presentation. Non-MI ACS will also require objective findings of coronary ischemia.

Non-MI ACS will be defined by one of 3 clinical presentations:

1. New cardiac symptoms and positive ECG findings with normal biomarkers not meeting criteria for MI, or
2. A changing symptom pattern and positive ECG findings with normal biomarkers not meeting criteria for MI, or
3. New or changing cardiac symptoms with normal biomarkers and ECGs but with further confirmatory evidence of CAD (eg 70% cross-sectional obstruction in at least on major coronary artery or branch on angiography at or near the time of admission, treatment with revascularization; prior documented CAD – prior CABG, PTCA, etc- positive exercise test at or near the time of admission, perfusion defect documented on stress scintigraphy or echo). Stress testing within approximately one month prior to admission or occurring during admission will be accepted as related to a particular hospital admission for possible non-MI ACS.

Non-MI ACS requires an **unscheduled admission** that must have begun **within 24 hours** of the most recent symptoms. Escalation of pharmacotherapy such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of non-MI ACS.

**STROKE DEFINITION:** Stroke is generally defined as neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours (6). Stroke will be classified as brain infarction, subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, other type, or unknown type.

Brain infarction (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 (7). Brain infarctions will be further sub-typed large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes (8, 9).

Strokes following invasive cardiovascular interventions will also be classified as such. Strokes after cardiovascular invasive interventions will be defined as those associated with the intervention within 7 days. Stroke post non-cardiovascular surgery will be defined as occurring within 7 days of non-cardiovascular surgery or other invasive procedure

Case definitions are based on the World Health Organization definition of stroke, and the updated definition of TIA that is imaging, rather than time, based (10).

Stroke is defined as a rapid onset of focal neurological symptoms, headache, or meningismus

**AND**

Deficit not due to closed head injury, intracranial neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous system infections (encephalitis or meningitis – subacute bacterial endocarditis would be counted as stroke), or other non-vascular cause

**AND**

Lesion on brain imaging consistent with symptoms

***OR***

Evidence of central or branch retinal artery occlusion

***OR***

Death within 24 hours without resolution of symptoms

Subarachnoid Hemorrhage (SAH)

Sudden onset of severe headache, meningismus, depressed consciousness or coma, or focal neurological symptoms

**AND**

Bloody spinal fluid within a few minutes or hours of onset

***OR***

Xanthochromic spinal fluid after 12 hours

***OR***

CT or MRI findings indicating a blood clot in the Sylvian fissure, between the frontal lobes, in the basal cisterns, or in a ventricle (without associated intraparenchymal hematoma)

AND

SAH is spontaneous and did not occur as a result of trauma or other process.

***OR***

Angiographic identification of a saccular aneurysm as a source of bleeding WITH bloody or xanthochromic spinal fluid

***OR***

Surgical or autopsy evidence of saccular aneurysm in the appropriate clinical setting or with evidence of SAH

Intraparenchymal Hemorrhage (IPH): A focal collection of blood within the brain parenchyma or ventricular system that is not cause by trauma (11).

Sudden onset of focal neurological symptoms or coma

**AND**

An area of increased density indicative of IPH identified by CT or MRI

***OR***

Demonstration of an IPH at autopsy or, surgery

***OR***

Cerebral angiographic, surgical, or autopsy evidence of a vascular mass without evidence of aneurysm or arteriovenous malformation

Other Hemorrhage (OH): subdural and epidural hematomas are *not* considered strokes (11).
Insufficient data to classify SAH or IPH

**AND**

Imaging shows blood in the parenchyma, subarachnoid space, ventricle, or any combination of the above

***OR***

Bloody (nontraumatic) or xanthochromic spinal fluid

***OR***

Surgical or autopsy evidence of blood in the parenchyma, subarachnoid space, ventricle, or any combination

Brain Infarction (INF): An episode of neurological dysfunction caused by focal cerebral or retinal infarction.

Not meeting criteria for SAH, IPH, or OH

**AND**

Sudden onset of focal neurological symptoms or coma leading to death or lasting > 24 hours

**AND**

Consistent imaging findings (i.e. no SAH, IPH), or clinically consistent lesion compatible with infarction or hemorrhagic infarction

***OR***

Autopsy or surgical evidence of a nonhemorrhagic (ischemic) infarct of the brain (cerebral thrombosis or cerebral embolism)

**Brain Infarct Subtypes**

**Large artery atherosclerosis**

**Evident**

Either occlusive, or stenotic vascular disease judged to be due to atherosclerosis in the clinically-relevant extracranial or intracranial arteries

[≥50% diameter reduction *or* <50% diameter reduction with plaque ulceration or thrombosis, or plaque with <50% diameter reduction that is seated at the site of the origin of the penetrating artery supplying the region of an acute lacunar infarct]

**AND**

The absence of acute infarction in vascular territories other than the stenotic or occluded artery

**Probable**

Prior history of one or more transient monocular blindness (TMB), TIA, or stroke in the territory of index artery affected by atherosclerosis within the month preceding the index stroke

***OR***

Evidence of thrombosis, near-occlusive stenosis, or non-chronic complete occlusion judged to be due to atherosclerosis in the clinically-relevant extracranial or intracranial arteries (except for the vertebral arteries)

***OR***

The presence of ipsilateral and unilateral acute internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery

**Possible**

The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis (<50%) in the absence of any detectable plaque ulceration or thrombosis in a clinically-relevant extracranial or intracranial artery and prior history of two or more TMB, TIA, or stroke from the territory of index artery affected by atherosclerosis, at least one event within the last month

**Cardio-aortic embolism**

**Evident**

The presence of a high-risk cardiac source of cerebral embolism (left atrial or ventricular thrombus, atrial fibrillation, sick sinus, atrial flutter, recent MI, rheumatic aortic or mitral disease, prosthetic valve, chronic MI plus EF<28%, symptomatic CHF with EF<30%, dilated cardio myopathy, non-bacterial endocarditis, SBE, papillary elastoma, myxoma)

**Probable**

Evidence of systemic embolism

***OR***

The presence of multiple temporally related acute infarctions within both right and left anterior, or both anterior and posterior, circulations in the absence of non-embolic occlusion or near occlusive stenosis of all relevant vessels

**AND**

Other diseases that can cause multifocal ischemic brain injury such as vasculitides, vasculopathies, and haemostatic or hemodynamic disturbances must not be present

**Possible**

The presence of a cardiac condition with low or uncertain primary risk of cerebral embolism (mitral calcification, PFO, PFO/ASA, left ventricular aneurysm without thrombus, left atrial smoke, aortic athero, other arrhythmias)

**Small artery occlusion**

**Evident**

Imaging evidence of a single and clinically relevant acute infarction less than 20 mm in greatest diameter within the territory of basal or brainstem penetrating arteries

**AND**

Absence of any focal other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, etc.)

**Probable**

The presence of stereotypic lacunar transient ischemic attacks within the last week

***OR***

The presence of a lacunar syndrome (pure motor, pure sensory, sensorimotor, ataxic hemiparesis, dysarthria-clumsy hand)

**Possible**

Presenting with a classical lacunar syndrome in the absence of imaging that is sensitive enough to detect small infarctions

**Other uncommon etiology**

**Evident**

The presence of a specific disease process that involves clinically-appropriate brain arteries

**Probable**

A specific disease process that has occurred in clear and close temporal or spatial relationship to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, and cardiovascular interventions

**Possible**

Evidence for an evident other cause in the absence of complete diagnostic investigation for mechanisms listed above

**Undertermined Cause**

**Unknown**

Cryptogenic embolism:

Angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal appearing intracranial arteries

***OR***

Imaging evidence of complete recanalization of previously occluded artery

***OR***

Presence of multiple acute infarctions that have occurred closely-related in time without detectable abnormality in the relevant vessels

Other cryptogenic

Those not fulfilling the criteria for cryptogenic embolism

Incomplete evaluation

The absence of diagnostic tests that, up to the examiner`s judgment, their presence would have been essential to uncover the underlying etiology

**Unclassified**

The presence of more than one possible or evident mechanism where there is either probable evidence for each, or no probable evidence to be able to establish a single cause

Other Stroke (OS)

Not meeting criteria for SAH, IPH, OH, or INF (e.g. cerebral sinus thrombosis with IPH, dissection)

Unknown Stroke Type (UNK)

Insufficient data to classify as SAH, IPH, OH, INF, or OS (e.g. no data available)

**HEART FAILURE DEFINITION**: 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 (12). The SPRINT 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 cases may also be adjudicated as chronic stable HF but this is not considered a SPRINT outcome. 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.

In order to consider an ED only visit as either definite or possible decompensated HF, the medical record must contain specific, clear, and unequivocal documentation that IV therapy was administered, regardless of the strength of the history, physical exam, and evaluations. Intravenous therapy must consist of a loop diuretic or an inotropic agent.

Right sided heart failure due to lung disease with no component of left sided heart failure is very unlikely to respond to SPRINT interventions. Right sided heart failure will not be considered a SPRINT outcome and will not be adjudicated as such.

Evidence of signs and symptoms that may indicate new or decompensated heart failure include evidence of increasing or new onset shortness of breath, increasing or new onset edema, increasing or new onset paroxysmal nocturnal dyspnea, increasing or new onset orthopnea, increasing or new onset hypoxia; and evidence in the doctor's notes that the reason for this hospitalization, or ED visit, was heart failure. Avoid assigning a classification of definite or possible decompensated heart failure if the symptoms include edema without respiratory symptoms unless there is other compelling evidence of heart failure.

**Definite decompensated heart failure**, i.e., decompensation clearly present based on available data (satisfies criteria for decompensation).

**Possible decompensated heart failure,** i.e., decompensation possibly but not definitively present. A typical case of "possible" rather than "definite" would be due to the presence of co-morbidity that could account for the acute symptoms (COPD exacerbation, for example). In general, prefer "possible" whenever the evidence for decompensation (symptoms, signs, imaging) is subtle.

**Chronic stable heart failure** i.e., no decompensation but participant has chronic heart failure. "Stable" also denotes "compensated" heart failure (not necessarily asymptomatic, but that patient's chronic HF symptoms are controlled with therapy and there is no evidence of augmentation of therapy for worsening HF during the hospitalization.) Note: This includes

participants with asymptomatic LV dysfunction (evidence of LV systolic dysfunction, i.e., EF ≤ 50%, and no heart failure symptoms).

HF unlikely should generally be chosen if the patient is on chronic dialysis and symptoms are due to inadequate dialysis with no evidence of cardiac systolic or diastolic dysfunction or history of clinical heart failure. Patients with ESRD on dialysis may be classified as "possible decompensated HF" (or possibly "definite") when there is appropriate supporting evidence for heart failure and the primary cause of the exacerbation is unlikely due to inadequate or missed dialysis. Patients with ESRD and low LVEF who had inadequate dialysis as the cause of volume overload should be classified as HF unlikely.

**DEATH DEFINITIONS**: Causes of death include:

- **Underlying cause** of death is the disease or injury that initiated the event resulting in death
- **Contributory causes** of death include other conditions that contributed to the fatal process, but were not the underlying cause.
- **Immediate cause** of death is the final disease or condition resulting in death and if different from the underlying cause is not recorded.

In SPRINT the adjudicator will only record the main underlying cause of death.

**SPRINT-related outcomes**

Definite CVD death 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. Probable coronary heart disease (CHD) death (2) 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. 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.

Case classification of fatal CHD events for hospitalized patients (2):

Definite fatal MI

1. Death within 28 days of hospital admission in definite MI cases
2. Postmortem findings consistent with MI within 28 days

Probable fatal MI

1. Death within 28 days of hospital admission in cases defined in probable MI cases
2. Death within 6 hours of hospital admission with cardiac symptoms and/or signs. Other confirmatory data (biomarkers, ECG) are absent or not diagnostic.

Possible fatal coronary event

1. Death within 28 days of hospital admission for possible MI, unstable angina or chronic stable angina
2. Postmortem findings show old infarct and/or ≥50% atherosclerotic narrowing of coronary arteries.

Case classification of out-of-hospital CHD death (2):

Definite fatal MI:

1. Documented definite or probable MI in the previous 28 days and
2. No evidence of a noncoronary cause of death, or
3. Autopsy evidence of recent coronary occlusion or MI <28 days old.

Definite fatal CHD:

1. A history of CHD and/or documented cardiac pain within 72 hours before death and
2. No evidence of a noncoronary cause of death, or
3. Autopsy evidence of chronic CHD, including coronary atherosclerosis and myocardial scarring.

Possible fatal CHD:

An ICD code (underlying cause) for CHD death (ICD 9*: 410 to 414, 427.5, 429.2; ICD 10: I20 to 25 and I46) and no evidence of a noncoronary cause of death

Stroke: Death occurring or following cases meeting criteria for stroke.

Sudden cardiac death: death occurring within 1 hour of onset of symptoms, and suggestive of an arrhythmic event

* Sudden cardiac death must occur within one hour of symptom onset of a cardiac etiology and witnessed loss of consciousness with no other lethal non-atherosclerotic cause. Do not select this choice for unwitnessed deaths.

CHF: Death due to clinical, radiologic, or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock included)

Not cardiac but other cardiovascular (e.g. ruptured aortic aneurysm): this category is intended for classifications of cardiovascular diseases for which hypertension is a risk factor that are not included in other causes listed above. It includes death due to ruptured thoracic or abdominal aortic aneurysm, and intestinal ischemia due to rupture of atherosclerotic plaque or due to cardioembolic phenomena (e.g. atrial fibrillation). This classification can be selected for participants who die of complications of attempted surgical repair of an aneurysm that did not rupture. Do not select this criterion for pulmonary embolism. Do not select this choice for an acute traumatic rupture of an otherwise normal artery (no aneurysm found), or for complications of arteritis due to known inflammatory conditions. Prefer definitive evidence, such as CT scan showing a ruptured aortic aneurysm, of the presence of this condition.

Death from kidney disease: In the absence of other causes, death within 30 days of withdrawal from chronic dialysis, death from hyperkalemia, death in ESRD patient in whom dialysis not initiated.

<u>It is important to rule out other causes of death.</u> For example, if a patient has terminal cancer and decides to withdraw from dialysis, the cause of death should be classified as death from malignancy, rather than uremia.

Death related to dialysis: Death related to the dialysis procedure, not the result of impaired kidney function. Examples are intradialytic hemolysis or air embolism as a result of extracorporeal circuit malfunctioning, and sepsis as a result of infected hemodialysis catheters or peritoneal dialysis catheters.

Adjudicators will also use specific information available to them in the case to record whether deaths occurred in relationship to an invasive procedure. There are two categories of intervention related events:

Death after invasive <u>cardiovascular</u> intervention. Death within 28 days of cardiovascular surgery or within 7 days of cardiac cath, arrhythmia ablation, angioplasty, atherectomy, stent

deployment, or other invasive coronary vascular intervention. Cardiovascular procedures include PAD procedures, including amputation for ischemia.

**Non-SPRINT related outcomes:** Require documentation of a specific underlying cause in medical records and/or autopsy. Categories include:

Other cardiac/non-ischemic (eg, myocarditis)
Cancer
Accident/injury/homicide
Other non-cardiac, non-stroke death: requires evidence of a non-coronary and non-stroke cause of death exclusive of categories above. Deaths included in this category include those due to specific pulmonary diseases (eg, COPD), infection (eg, sepsis, pneumonia), and gastrointestinal disease (eg, gastrointestinal hemorrhage, pancreatitis).
Unclassifiable: insufficient information to determine whether the death was a CHD death (at any certainty level) or a non-cardiac death. Includes other ill-defined and unknown cause of morbidity and mortality and no evidence of a non-coronary cause

**END STAGE RENAL DISEASE DEFINITION:** One of the clinical outcomes of interest in SPRINT is the initiation of renal replacement therapy for ESRD. In order to meet criteria for SPRINT, a participant must have been on chronic dialysis for at least 3 months and/or received a renal transplant. The adjudicator will examine medical records to confirm whether the participant was currently on dialysis (any modality(ies)), and had received RRT for at least 3 months continuously, and if so, enter the date of initiation of dialysis (date of first treatment). The adjudicator will also confirm whether the participant received a transplant, and if so, the date of the transplant. Acute dialysis for management of acute kidney injury will not be considered a SPRINT ESRD outcome.

## Section 4. Multiple imputation to assess the influence of missing outcome data

*General Approach*

We used the non-parametric risk-set imputation approach of Hsu and Taylor(13) to investigate the influence of incomplete ascertainment of outcomes, i.e. participants that did not complete any outcome ascertainment during follow-up or those with incomplete follow-up. Briefly, this approach works by fitting two Cox proportional hazards regression models, separately by treatment group, one for the observed event times and the other for the observed censoring times. Let $\boldsymbol{X} = \{X_1, X_2, \ldots, X_p\}$ be a set of auxiliary variables, which we assume to be time-independent. If we let $\boldsymbol{\beta_E} = \{\beta_{1E}, \beta_{2E}, \ldots, \beta_{pE}\}$ and $\boldsymbol{\beta_C} = \{\beta_{1C}, \beta_{2C}, \ldots, \beta_{pC}\}$ be the estimated log hazard ratios from the event and censoring models respectively, then define risk-scores from each model as the linear combinations, $\boldsymbol{RS_E} = \boldsymbol{X\beta_E}$ and $\boldsymbol{RS_C} = \boldsymbol{X\beta_C}$. After standardizing the risk-scores by subtracting the mean and dividing by the standard deviation, the scaled risk scores are then used to define a pair-wise distance between participants *j* and *k* as

$$d(j,k) = \sqrt{w\{\boldsymbol{RS_E}(j) - \boldsymbol{RS_E}(k)\}^2 + (1-w)\{\boldsymbol{RS_C}(j) - \boldsymbol{RS_C}(k)\}^2},$$

where *w* is a weight used to account for dependent censoring. The imputing risk set is then a group of *NN* participants with longer follow-up times than subject *j* and the smallest pair-wise distances (or simply the number of participants still at risk if it is less than *NN*). Observations are then imputed by drawing an event time from the Kaplan-Meier estimate of participants in the imputing risk set (14).

*Details of Multiple Imputation Procedure*

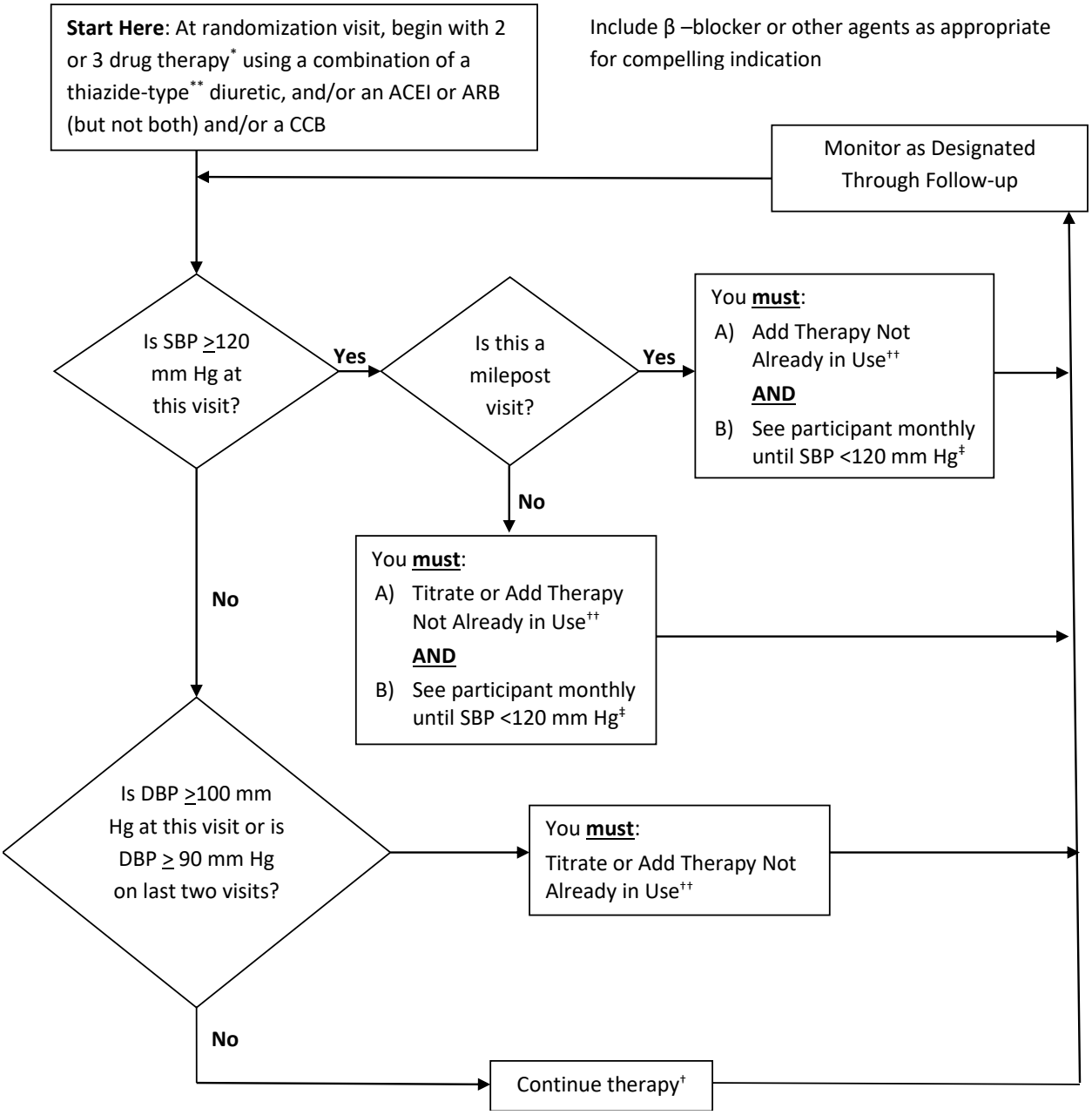
For all scenarios, we used 10 imputed datasets. We varied both the censoring weight (w = 0.2, 0.5, or 0.8) and the size of the imputing risk-set (*NN*=5, 10, 15, or 20). Outcomes were not imputed for participants that either experienced the event of interest, or those with complete follow-up through the extended follow-up visits. For participants that were censored prior to the close-out visit, we set the maximum observation time as the time between July 26, 2016 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 used the following baseline auxiliary variables to define the risk-sets: age, sex, race/ethnicity (White, Black, Hispanic, or Other), education (less than high school education, high school graduate, additional training beyond high school but no college degree, college graduate or higher), smoking status (never, former, or current smoker), polypharmacy (<5 medications, 5 to <10 medications, 10 or more medications), history of cardiovascular disease (CVD, Yes vs No), estimated glomerular filtration rate (eGFR), log urine albumin to creatinine ratio, serum bicarbonate, HDL cholesterol, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), use of aspirin, use of statins, Montreal Cognitive Assessment (MoCA) score, Digit Symbol Coding score, physical and mental component summary scores from the VR-12, and a PHQ-9 score ≥ 10 (yes vs no). There was a small degree of sporadic missing data amongst the baseline auxiliary variables, so we first imputed those variables based on a fully conditional specification as shown in the table below. The base set of predictors for those imputations included the following set of variables with no missing data: age, sex, race/ethnicity, education, history of CVD, smoking status, SBP, DBP, polypharmacy, use of statins, and use of aspirin.

| Auxiliary Variable | No. Missing (%) | Imputation Model | Predictors |
|---|---|---|---|
| Body Mass Index (BMI) | 76 (0.8) | Linear | Base Set |
| HDL Cholesterol (HDL) | 38 (0.4) | Linear | Base Set + BMI |
| Serum Bicarbonate (CO2) | 27 (0.3) | Linear | Base Set + BMI + HDL |
| eGFR | 53 (0.6) | Linear | Base Set + BMI + HDL + CO2 |
| Log Urine Albumin to Creatinine Ratio (log UACR) | 449 (4.8) | Linear | Base Set + BMI + HDL + CO2+ eGFR |
| MoCA Score (MoCA) | 65 (0.7) | Linear | Base Set + BMI + HDL + CO2 + eGFR + log UACR |
| Digit Symbol Coding Score (DSC) | 87 (0.9) | Linear | Base Set + BMI + HDL + CO2 + eGFR + log UACR + MoCA |
| VR-12 Physical Component Summary Score (VR-12 PCS) | 42 (0.4) | Linear | Base Set+BMI+HDL+CO2+eGFR+log UACR+MoCA+DSC |
| VR-12 Mental Component Summary Score (VR-12 MCS) | 48 (0.5) | Linear | Base Set + BMI + HDL + CO2 + eGFR + log UACR + MoCA + DSC + VR-12 PCS |
| PHQ-9 Score ≥ 10 | 47 (0.5) | Logistic | Base Set + BMI + HDL + CO2 + eGFR + log UACR + MoCA + DSC + VR-12 PCS + VR-12 MCS |

The multiple imputation procedure was implemented using *proc mi* and *proc mianalyze* in SAS v9.4 (SAS, Cary, NC), and the *InformativeCensoring* package for the R Statistical Computing Environment (15).

Figure S1. Treatment Algorithm for Intensive Group (Goal SBP < 120 mm Hg).




* May begin with a single agent for participants 75 years old or older with SBP < 140 on 0-1 meds at study entry. A second medication should be added at the 1 Month visit if participant is asymptomatic and SBP > 130.

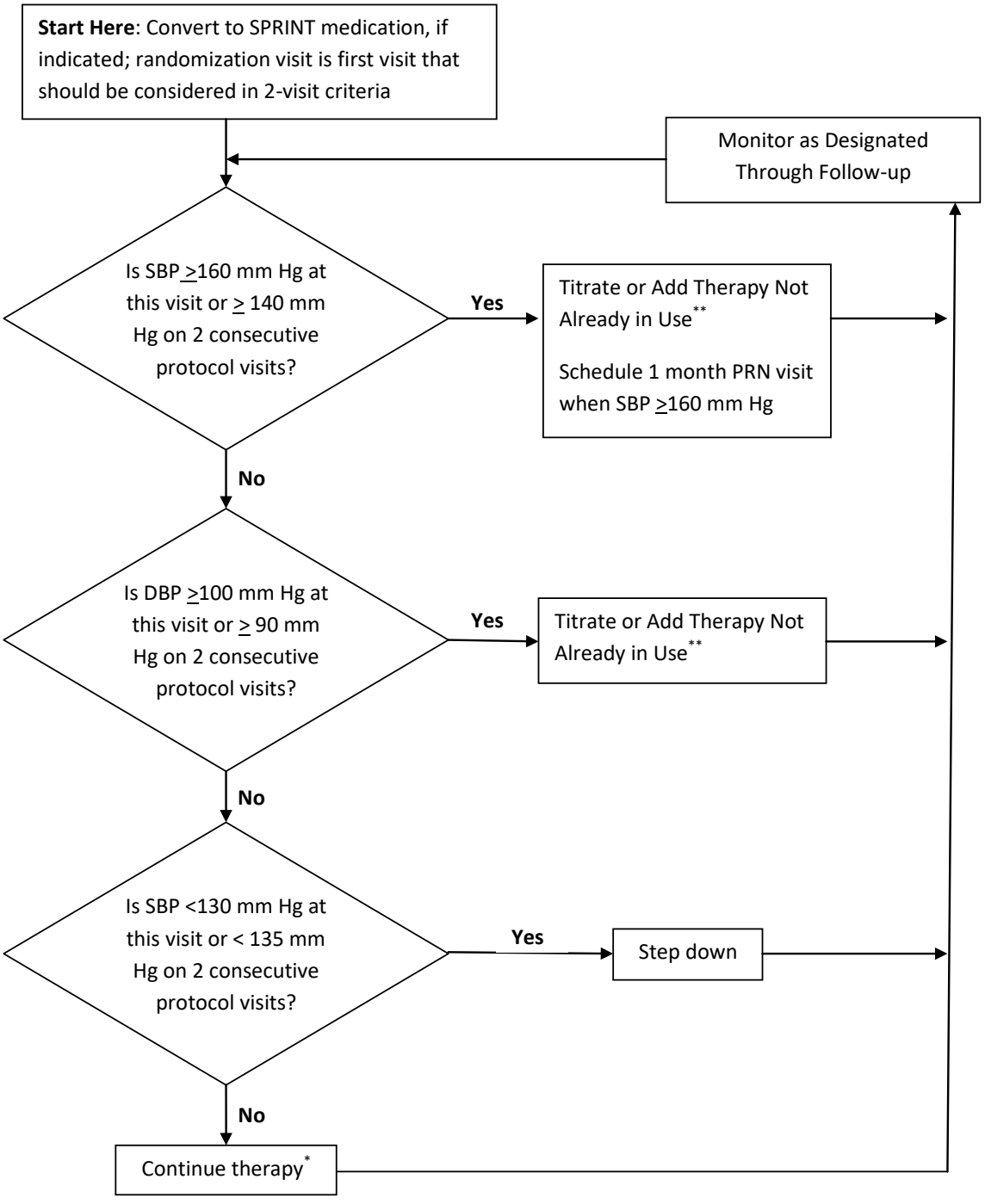
** May use loop diuretic for participants with advanced CKD

† Unless side effects warrant change in therapy

†† Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication

‡ Or until clinical decision made that therapy should not be increased further

Figure S2. Treatment Algorithm for Standard Group (Goal SBP < 140 mm Hg).




Include β –blocker or other agents as appropriate for compelling indications
* Unless side effects warrant change in therapy
** Consider consulting with the Clinical Center Network before adding a fifth anti-hypertensive medication

Figure S3. Eligibility, randomization, and follow-up

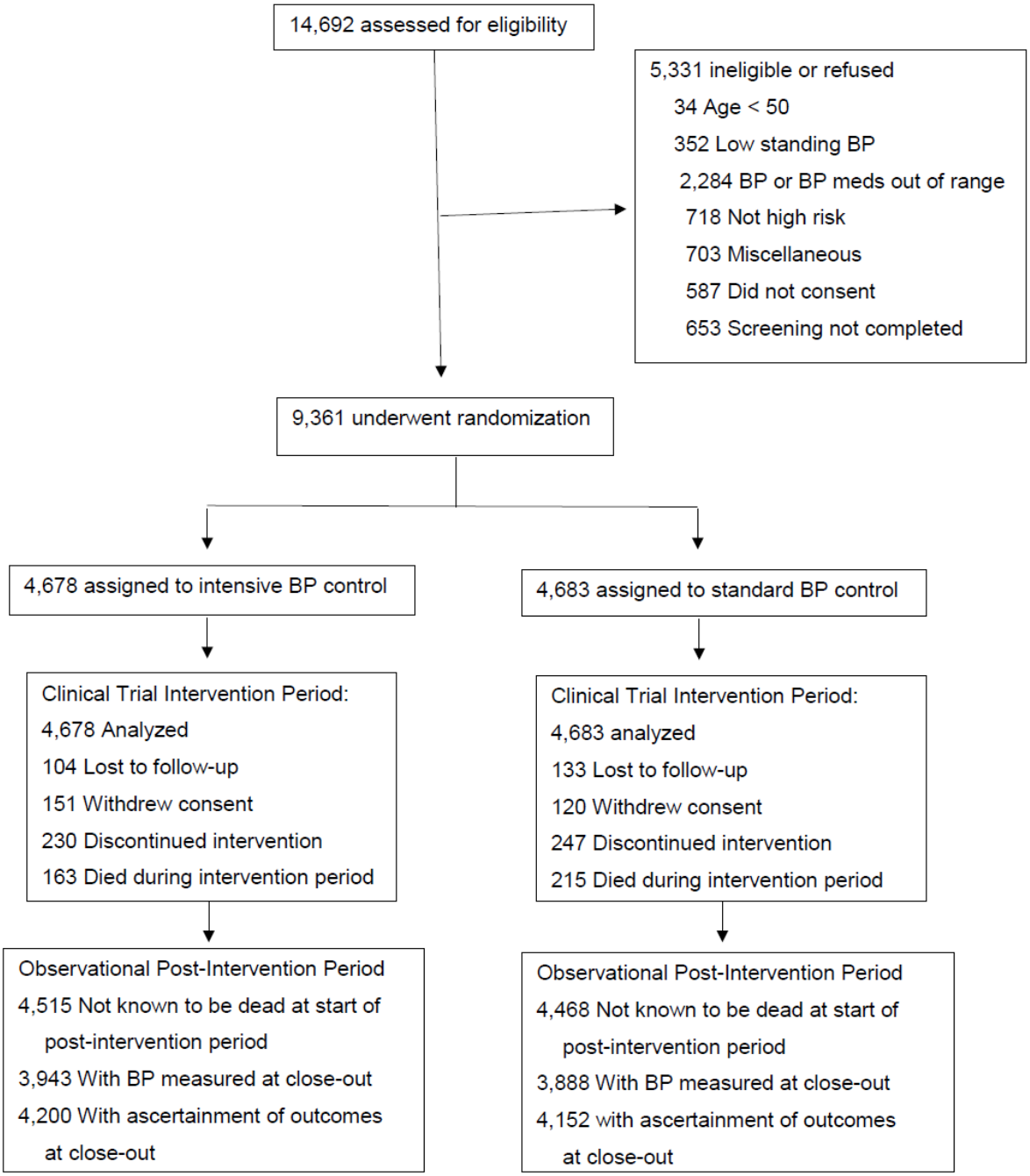


Figure S4. Mean Systolic BP through August 20, 2015

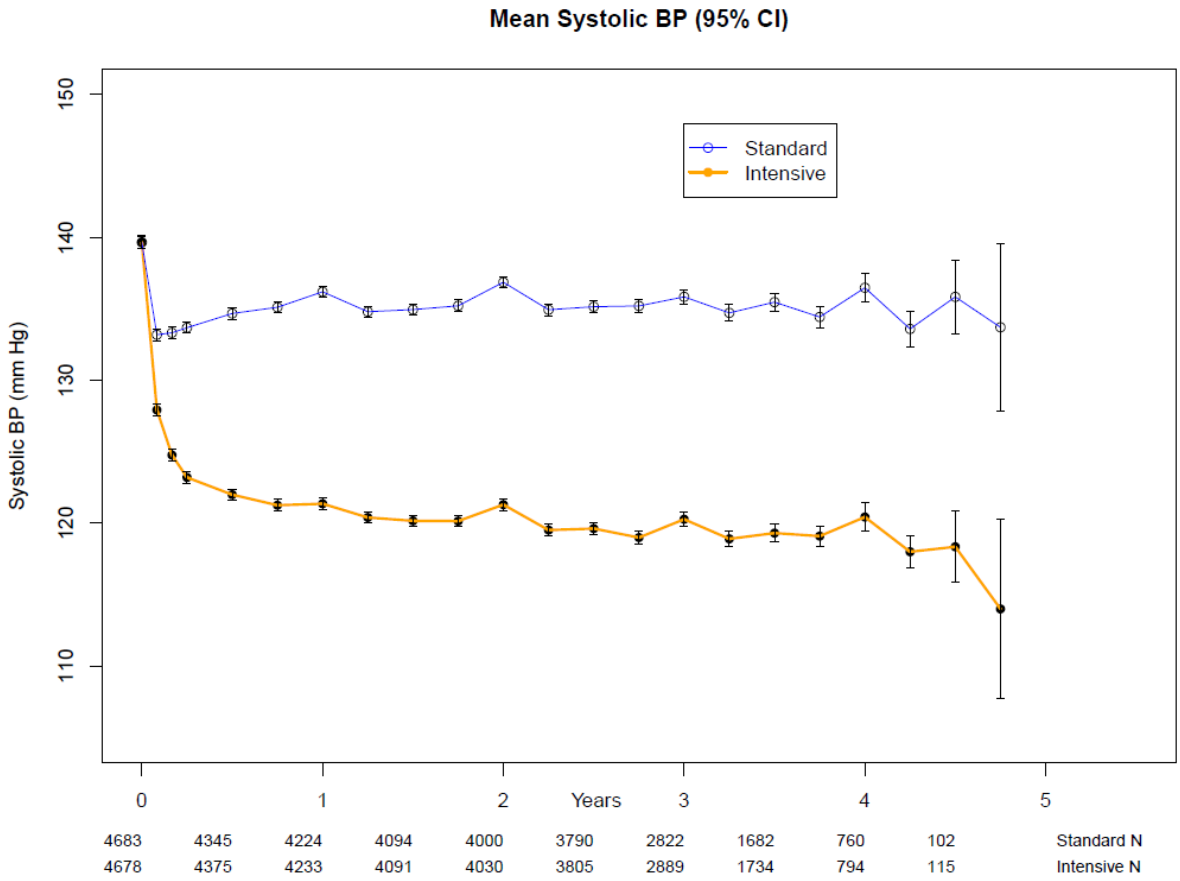


Figure S5. Mean systolic BP through July 29, 2016

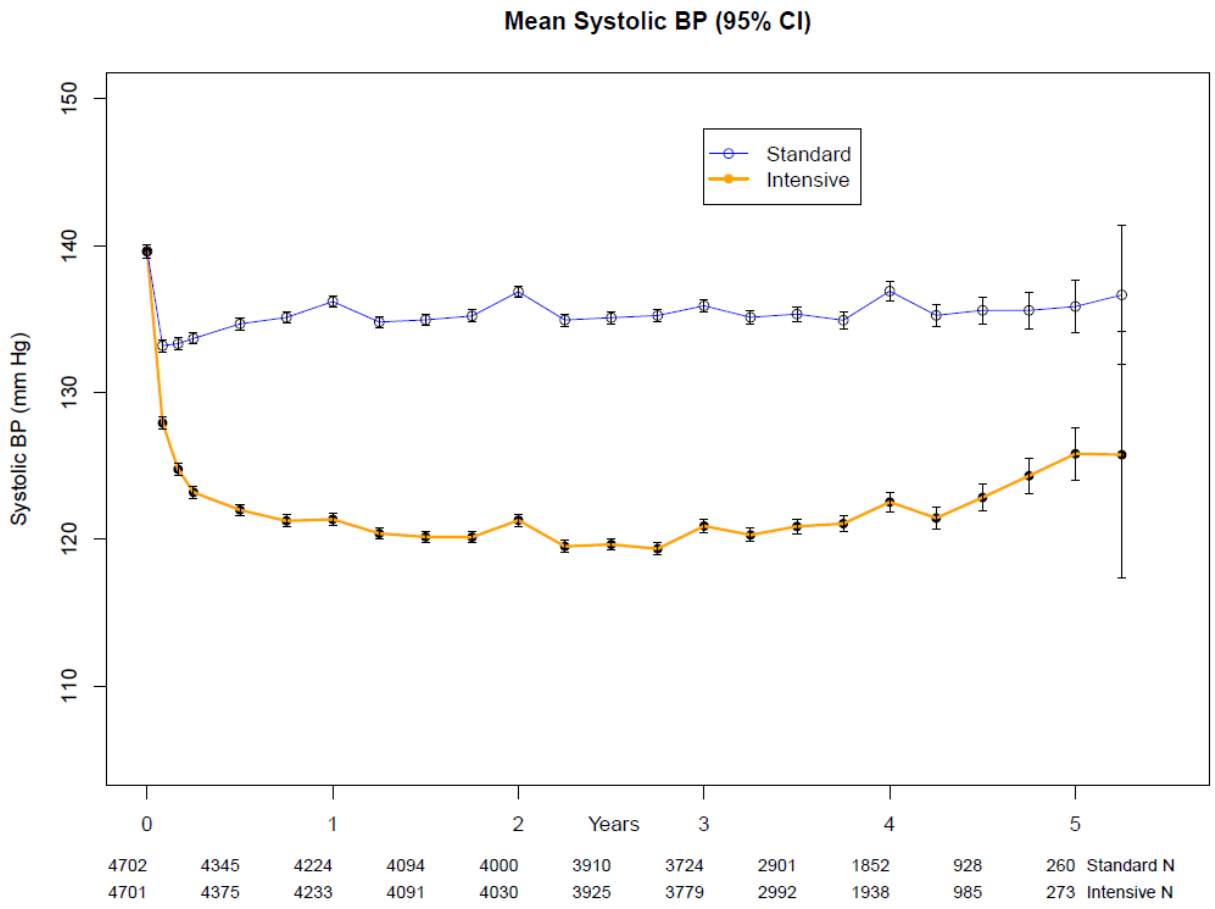


Figure S6. All-cause mortality cumulative hazards through August 20, 2015

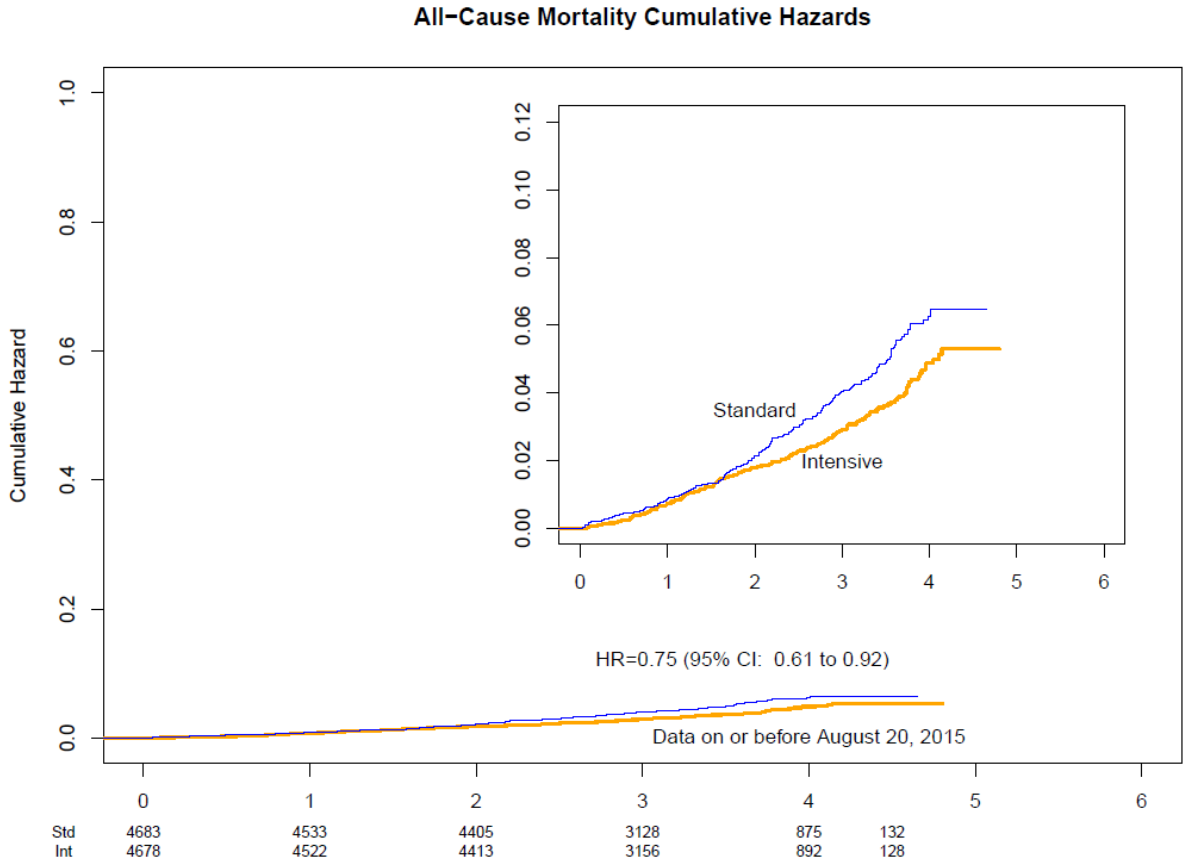
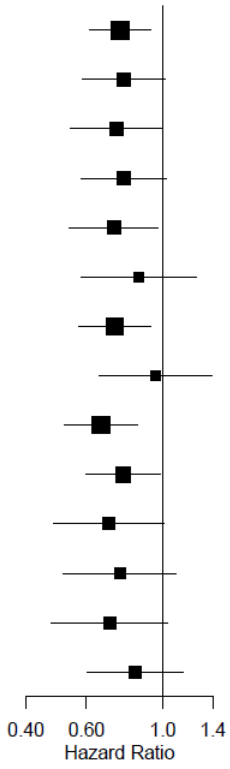


Figure S7. Forest Plot of Total Mortality by Subgroups in Intervention Phase (on or before August 20, 2015).

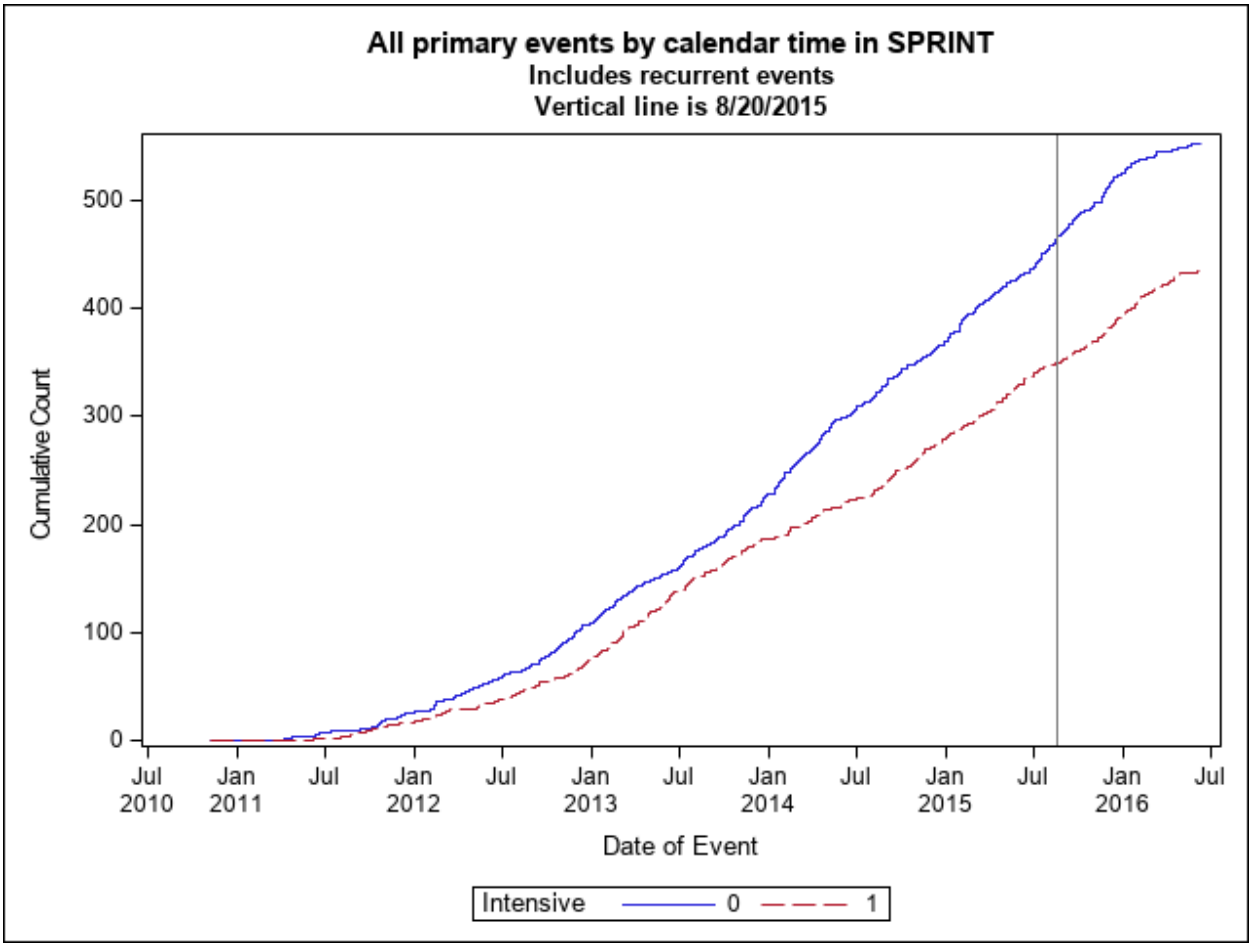
Overall event rates and percentages are reported for each subgroup by treatment. Estimated hazard ratios and 95% confidence intervals were estimated separately within subgroups. Unadjusted p-values for the tests of the interactions between treatment and the subgroups are reported in the right-most column. The solid line for a hazard ratio equal to 1 represents no effect. The box sizes are proportional to the precision of the estimates. HR denotes hazard ratio, Int P denotes interaction P value, CKD denotes chronic kidney disease, CVD denotes cardiovascular disease, and SBP denotes systolic blood pressure. Note that the 'No Prior CKD' group includes some participants with unknown CKD status at baseline, and African-American includes Hispanic African-Americans and African-American as part of a multiracial identification. Interaction p values are adjusted for multiple comparisons.

| Subgroup | Intensive | Standard | HR | Int P |
|---|---|---|---|---|
| Overall | 163/4678 (3.48) | 215/4683 (4.59) | 0.75 (0.61,0.92) | |
| No Prior CKD | 88/3349 (2.63) | 116/3367 (3.45) | 0.77 (0.58,1.02) | 0.77 |
| Prior CKD | 75/1329 (5.64) | 99/1316 (7.52) | 0.74 (0.54,1.00) | |
| Age < 75 | 84/3361 (2.50) | 107/3364 (3.18) | 0.77 (0.58,1.03) | 0.77 |
| Age ≥ 75 | 79/1317 (6.00) | 108/1319 (8.19) | 0.72 (0.53,0.97) | |
| Female | 49/1684 (2.91) | 56/1648 (3.40) | 0.85 (0.58,1.25) | 0.49 |
| Male | 114/2994 (3.81) | 159/3035 (5.24) | 0.72 (0.57,0.92) | |
| African−American | 54/1454 (3.71) | 57/1493 (3.82) | 0.95 (0.65,1.39) | 0.09 |
| Non African−American | 109/3224 (3.38) | 158/3190 (4.95) | 0.66 (0.52,0.84) | |
| No Prior CVD | 111/3738 (2.97) | 143/3746 (3.82) | 0.77 (0.60,0.98) | 0.74 |
| Prior CVD | 52/940 (5.53) | 72/937 (7.68) | 0.70 (0.48,1.01) | |
| SBP ≤ 132 | 48/1583 (3.03) | 65/1553 (4.19) | 0.75 (0.51,1.09) | 0.72 |
| 132 < SBP < 145 | 44/1489 (2.96) | 65/1549 (4.20) | 0.70 (0.47,1.03) | |
| SBP ≥ 145 | 71/1606 (4.42) | 85/1581 (5.38) | 0.83 (0.60,1.14) | |




P-values adjusted for multiple subgroups tested.

Figure S8. Cumulative counts of all SPRINT primary events by randomized treatment assignment group, including events occurring during the intervention phase (through August 20, 2015, left of vertical line) and the post-interventional follow-up phase (August 21, 2015 through July 29, 2016, right of vertical line).




Intensive treatment goal (1) compared to standard treatment goal (0)
Plot includes all SPRINT primary events, fatal and non-fatal, as well as multiple events per person.

Table S1. SPRINT Formulary

| Class | Drug | Available Strengths | Usual Dose Range/Day | Usual Daily Frequency |
|---|---|---|---|---|
| Diuretics | Chlorthalidone | 25mg | 12.5 – 25mg | 1 |
| | Furosemide | 20mg, 40mg, 80mg | 20 – 80mg | 2 |
| | Spironolactone | 25mg | 25-50 mg | 1 |
| | Triamterene/HCTZ | 75/50mg | 37.5/25mg – 75/50 mg | 1 |
| | Amiloride | 5 mg | 5-10 mg | 1-2 |
| Ace Inhibitors | Lisinopril | 5mg, 10mg, 20mg, 40mg | 5 – 40mg | 1 |
| Angiotensin Receptor Blockers | Losartan | 25mg, 50mg, 100mg | 25 – 100 mg | 1-2 |
| | Azilsartan | 40mg, 80mg | 40 – 80 mg | 1 |
| | Azilsartan/Chlorthalidone | 40/12.5mg, 40/25mg | 40/12.5 – 40/25 mg | 1 |
| Calcium Channel Blockers | Diltiazem | 120mg, 180mg, 240mg, 300mg | 120 – 540 mg | 1 |
| | Amlodipine | 2.5mg, 5mg, 10mg | 2.5 – 10 mg | 1 |
| Beta Blockers | Metoprolol Tartate | 25mg, 50mg, 100mg | 50 – 200 mg | 1-2 |
| | Atenolol | 25mg, 50mg, 100mg | 25 – 100 mg | 1 |
| | Atenolol/Chlorthalidone | 50/25mg | 50/25 mg | 1 |
| Vasodilators | Hydralazine | 25mg, 50mg, 100mg | 50 – 200 mg | 2 |
| | Minoxidil | 2.5mg, 10mg | 2.5 – 80 mg | 1-2 |
| Alpha 2 Agonists | Guanfacine | 1mg, 2mg | 0.5 – 2 mg | 1 |
| Alpha Blockers | Doxazosin | 1mg, 2mg, 4mg, 8mg | 1 – 16 mg | 1 |
| Potassium Supplements | KCL tablets | 20mEq | 20 – 80 mEq | 1-2 |
| | KCL oral solution (10%) | 20mEq/15ml | 20 – 80 MEq | 1-2 |
| Additional medications are included in a restricted use formulary (below). These medications will be provided by the study and may be prescribed for individual participants only after consultation with and approval from a designated representative for each CCN. | | | | |
| **Class** | **Drug** | **Available Strengths** | **Usual Dose Range in mg/day** | **Usual Daily Frequency** |
| Ace Inhibitors | Lisinopril/HCTZ | 20/12.5mg, 20/25mg | 10 – 40/ 12.5 – 50 mg | 1 |
| Adrenergic inhibitors | Reserpine | 0.1mg, 0.25mg | 0.1 – 0.25 mg | 1 |
| Alpha 2 Agonists | Clonidine patch | 0.1mg, 0.2mg, 0.3mg | 0.1 – 0.3 mg | 1 wkly |
| Beta blockers | Metoprolol ER | 25mg, 50mg, 100mg, 200mg | 50 – 200 mg | 1 |
| Diuretics | Amiloride/HCTZ | 5/50mg | 5/50 mg | 1 |
| Thiazide diuretics | HCTZ | 12.5mg, 25mg | 12.5 – 50 mg | 1 |
| Angiotensin Receptor Blockers | Valsartan | 80mg, 160mg, 320mg | 80 – 320 mg | 1-2 |

Table S2. Baseline characteristics of the study participants.*

| | Intensive Treatment (N=4678) | Standard Treatment (N=4683) |
|---|---|---|
| Inclusion criteria | | |
| Age ≥75 years | 1317 (28.2) | 1319 (28.2) |
| Baseline chronic kidney disease (estimated GFR <60) | 1329 (28.4) | 1316 (28.1) |
| Prior cardiovascular disease | 940 (20.1) | 937 (20.0) |
| Clinical | 779 (16.7) | 783 (16.7) |
| Subclinical | 247 (5.3) | 246 (5.3) |
| 10-year Framingham Risk ≥15% | 3556 (76.0) | 3547 (75.7) |
| Only Framingham Risk ≥15% | 1542 (33.0) | 1546 (33.0) |
| Gender (female) | 1684 (36.0) | 1648 (35.2) |
| Age (years) | 67.9 (9.4) | 67.9 (9.5) |
| Race (4-level category) | | |
| Black | 1379 (29.5) | 1423 (30.4) |
| Hispanic | 503 (10.8) | 481 (10.3) |
| White | 2698 (57.7) | 2701 (57.7) |
| Other | 98 (2.1) | 78 (1.7) |
| Black race† | 1454 (31.1) | 1493 (31.9) |
| Age ≥75 years | 1317 (28.2) | 1319 (28.2) |
| Age among those ≥75 years | 79.8 (3.9) | 79.9 (4.1) |
| Baseline blood pressure, mm Hg | | |
| Systolic | 139.7 (15.8) | 139.7 (15.4) |
| Diastolic | 78.2 (11.9) | 78.0 (12.0) |
| Systolic blood pressure tertile, mm Hg | | |
| SBP ≤ 132 | 1583 (33.8) | 1553 (33.2) |
| 132 < SBP < 145 | 1489 (31.8) | 1549 (33.1) |
| SBP ≥ 145 | 1606 (34.3) | 1581 (33.8) |
| Serum creatinine (mg/dL) | 1.07 (0.34) | 1.08 (0.34) |
| Estimated glomerular filtration rate, ml/min/1.73m2 | | |
| Overall | 71.8 (20.7) | 71.7 (20.5) |

| | Intensive Treatment (N=4678) | Standard Treatment (N=4683) |
|---|---|---|
| Non-CKD cohort | 81.3 (15.5) | 81.1 (15.5) |
| CKD cohort | 47.8 (9.5) | 47.9 (9.5) |
| Urine albumin/creatinine (mg/g) | 44.1 (178.7) | 41.1 (152.9) |
| Total cholesterol (mg/dL) | 190.2 (41.4) | 190.0 (40.9) |
| Fasting HDL-C (mg/dL) | 52.9 (14.3) | 52.8 (14.6) |
| Fasting total triglycerides (mg/dL) | 124.8 (85.8) | 127.1 (95.0) |
| Fasting plasma glucose (mg/dL) | 98.8 (13.7) | 98.8 (13.4) |
| Statin use | 1978 (42.6) | 2076 (44.7) |
| Aspirin use | 2406 (51.6) | 2350 (50.4) |
| Smoking | | |
| Never smoker | 2051 (43.8) | 2072 (44.2) |
| Former smoker | 1977 (42.3) | 1996 (42.6) |
| Current smoker | 639 (13.7) | 601 (12.8) |
| Missing | 11 (0.3) | 14 (0.3) |
| Body mass index (kg/m2) | 29.9 (5.8) | 29.8 (5.7) |
| Number of medication agents entering baseline visit | 1.8 (1.0) | 1.8 (1.0) |
| Not using hypertensive agents | 432 (9.2) | 450 (9.6) |

*Mean (SD) or N (%)

ǂ includes Hispanic and non-Hispanic

Table S3. First occurrence of outcomes in the randomized trial intervention phase as previously reported,* outcomes added in the current report, and the total number after final adjudication of all outcomes.†

| | Intensive Treatment: No. of Participants with Outcomes | | | Standard Treatment: No. of Participants with Outcomes | | |
|---|---|---|---|---|---|---|
| | Previously Reported* | Additional Outcomes Added | Total Outcomes Reported | Previously Reported* | Additional Outcomes Added | Total Outcomes Reported |
| All Participants | N = 4678 | | | N = 4683 | | |
| Primary Outcome‡ | 243 | 21 | 264 | 319 | 35 | 354 |
| Secondary Outcomes | | | | | | |
| Myocardial infarction | 97 | 5 | 102 | 116 | 24 | 140 |
| Acute coronary syndrome | 40 | 2 | 42 | 40 | 1 | 41 |
| Stroke | 62 | 7 | 69 | 70 | 8 | 78 |
| Heart failure | 62 | 6 | 68 | 100 | 5 | 105 |
| Death – cardiovascular | 37 | 4 | 41 | 65 | 6 | 71 |
| Death – any cause | 155 | 8 | 163 | 210 | 5 | 215 |
| Primary outcome or death | 332 | 38 | 370 | 423 | 51 | 474 |
| Participants with CKD at baseline | N = 1330 | | | N = 1316 | | |
| Composite renal outcome§ | 14 | 3 | 17 | 15 | 1 | 16 |
| ≥ 50% reduction in eGFR¶ | 10 | 2 | 12 | 11 | 1 | 12 |
| Long-term dialysis | 6 | 1 | 7 | 10 | 0 | 10 |
| Kidney transplantation | 0 | 0 | 0 | 0 | 0 | 0 |
| Incident albuminuria‖ | 49/526 | 15 | 64 | 59/500 | 26 | 85 |
| Participants without CKD at baseline | N = 3332 | | | N = 3345 | | |
| ≥ 30% reduction in eGFR¶ | 127 | 21 | 148 | 37 | 4 | 41 |
| Long-term dialysis | 0 | 0 | 0 | 0 | 0 | 0 |
| Kidney transplantation | 0 | 0 | 0 | 0 | 0 | 0 |
| Incident albuminuria‖ | 110/1769 | 32 | 142 | 135/1831 | 49 | 184 |

*The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. New Engl J Med 2015;373:2103-16.

†CKD denotes chronic kidney disease, eGFR estimated glomerular filtration rate

‡ The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome not resulting in infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Primary outcome components are shown including fatal and non-fatal cases.
§The composite renal outcome for participants with CKD at baseline was the first occurrence of a reduction in eGFR of 50% or more, long-term dialysis, or kidney transplantation.
¶Reductions in eGFR were confirmed by a second laboratory test at least 90 days later.
‖Incident albuminuria was defined by a doubling of the ratio of urinary albumin (in mg) to creatinine (in g) from less than 10 at baseline to greater than 10 during follow-up. The denominators for number of participants represent those without albuminuria at baseline

Table S4. First occurrence of outcomes during clinical trial intervention period and during observational post-intervention periods.

| | **Clinical Trial Intervention Period*** | | | **Observational Post-Intervention Period**** | | | |
|---|---|---|---|---|---|---|---|
| | Intensive Treatment | Standard Treatment | Hazard Ratio (95% CI) | Intensive Treatment | Standard Treatment | Hazard Ratio (95% CI) | Interaction P Value†† |
| **All Participants** | **N = 4678** | **N = 4683** | | **N = 4515** | **N = 4468** | | |
| | % per year | % per year | | % per year | % per year | | |
| Primary outcome‡ | 1.77 | 2.40 | 0.74 (0.63-0.87) | 2.35 | 2.70 | 0.85 (0.61-1.17) | 0.44 |
| Primary outcome without non-fatal heart failure | 1.48 | 1.97 | 0.75 (0.63-0.89) | 1.64 | 2.29 | 0.75 (0.51-1.07) | 0.99 |
| Secondary outcomes | | | | | | | |
| Myocardial infarction | 0.68 | 0.93 | 0.74 (0.57-0.94) | 0.58 | 0.96 | 0.56 (0.30-1.00) | 0.40 |
| Acute coronary syndrome | 0.28 | 0.27 | 0.98 (0.64-1.49) | 0.13 | 0.27 | 0.67 (0.15-2.09) | 0.55 |
| Stroke | 0.45 | 0.52 | 0.85 (0.62-1.17) | 0.44 | 0.81 | 0.63 (0.29-1.24) | 0.42 |
| Heart failure | 0.45 | 0.70 | 0.68 (0.50-0.92) | 1.42 | 0.59 | 1.63 (1.02-2.57) | 0.001 |
| Non-fatal heart failure | 0.43 | 0.67 | 0.69 (0.50-0.93) | 1.42 | 0.59 | 1.67 (1.04-2.64) | <0.001 |
| Death - Cardiovascular | 0.27 | 0.47 | 0.56 (0.38-0.82) | 0.66 | 0.71 | 1.08 (0.57-1.95) | 0.07 |
| Death – any cause | 1.06 | 1.41 | 0.75 (0.61-0.91) | 2.31 | 2.51 | 0.97 (0.69-1.34) | 0.16 |
| Primary outcome or death | 2.47 | 3.20 | 0.78 (0.68-0.88) | 3.90 | 4.20 | 0.92 (0.71-1.18) | 0.22 |
| **Participants with CKD at baseline†** | **N =1330** | **N = 1316** | | **N = 1148** | **N = 1125** | | |
| Composite renal outcome§ | 0.39 | 0.37 | 0.99 (0.50-1.93) | 0.16 | 0.50 | 0.37 (0.02-2.06) | 0.31 |
| ≥ 50% reduction in eGFR†¶ | 0.28 | 0.28 | 1.07 (0.48-2.40) | 0.16 | 0.17 | 0.43 (0.02-2.54) | 0.37 |
| Long-term dialysis | 0.16 | 0.23 | 0.60 (0.22-1.51) | 0.16 | 0.33 | 1.54 (0.08-12.39) | 0.47 |
| Kidney transplantation | 0 | 0 | | 0 | 0.17 | | |
| Incident albuminuria‖ | 3.93 | 5.61 | 0.71 (0.50-0.99) | 2.30 | 4.71 | 0.64 (0.21-1.54) | 0.83 |

| **Participants without CKD at baseline** | **N = 3332** | **N = 3345** | | **N = 2887** | **N = 2967** | | |
|---|---|---|---|---|---|---|---|
| ≥ 30% reduction in eGFR¶ | 1.39 | 0.38 | 3.71 (2.68-5.22) | 0.64 | 0.43 | 1.37 (0.62-2.79) | 0.004 |
| Long-term dialysis | 0 | 0 | | 0 | 0 | | |
| Kidney transplantation | 0 | 0 | | 0 | 0 | | |
| Incident albuminuria‖ | 2.54 | 3.25 | 0.79 (0.63-0.98) | 0.99 | 1.76 | 0.42 (0.19-0.84) | 0.09 |

* Includes additional events not previously reported[1]

† CI denotes confidence interval, CKD chronic kidney disease, eGFR estimated glomerular filtration rate

‡ The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome not resulting in infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Primary outcome components are shown including fatal and non-fatal cases, except where noted for non-fatal heart failure.

§ The composite renal outcome for participants with CKD at baseline was the first occurrence of a reduction in eGFR of 50% or more, long-term dialysis, or kidney transplantation.

¶ Reductions in eGFR ere confirmed by a second laboratory test at least 90 days later.

‖Incident albuminuria was defined by a doubling of the ratio of urinary albumin (in mg) to creatinine (in g) from less than 10 at baseline to greater than 10 during follow-up. The denominators for number of participants represent those without albuminuria at baseline

** Participants not known to be dead as of the beginning of the post-trial observational period included in analyses

†† P values represent comparison using an indicator for on/before or after August 20, 2015, in a time-varying-covariate model. Inferences drawn from these tests may not be reproducible since none of the p-values or 95% confidence intervals are adjusted for multiplicity

Note that there are small differences between models shown in this Table and models shown in Tables 1 and 2. This Table includes data from both the intervention and post-intervention observational periods and uses a time varying covariate model including an interaction term. These small differences in results relate to differences in baseline hazards between the models employed to create these Tables.

Table S5. Medication changes by randomized treatment assignment group comparing the last visit in the intervention phase (through August 20, 2015) to the first post-intervention visit in the observational phase (August 21, 2015 through July 29, 2016) among participants with both types of visits (data presented are N [%]).*‡

| Medication | Standard Intervention N = 4006 | | | Intensive Intervention N = 4055 | | | P value† |
|---|---|---|---|---|---|---|---|
| | Stopped | No change | Added | Stopped | No change | Added | |
| ACE inhibitor | 36 (0.9%) | 3891 (97.1%) | 79 (2.0%) | 47 (1.2%) | 3993 (98.5%) | 15 (0.4%) | **<0.001** |
| Aldosterone receptor blocker | 5 (0.1%) | 3993 (99.7%) | 8 (0.1%) | 17 (0.4%) | 4026 (99.3%) | 12 (0.3%) | 0.22 |
| Combined alpha- and beta-blocker§ | 5 (0.1%) | 3991 (99.6%) | 10 (0.2%) | 3 (0.1%) | 4047 (99.8%) | 5 (0.1%) | 0.53 |
| Alpha-1 blocker | 12 (0.3%) | 3989 (99.6%) | 5 (0.1%) | 20 (0.5%) | 4028 (99.3%) | 7 (0.2%) | 0.38 |
| Angiotensin II receptor blocker | 41 (1.0%) | 3919 (97.8%) | 46 (1.1%) | 39 (1.0%) | 3986 (98.3%) | 30 (0.7%) | 0.26 |
| Central alpha-2 agonists/other centrally acting drugs | 3 (0.1%) | 4001 (99.9%) | 2 (0.0%) | 3 (0.1%) | 4051 (99.9%) | 1 (0.0%) | 0.74 |
| Direct vasodilator | 2 (0.0%) | 3995 (99.7%) | 9 (0.2%) | 21 (0.5%) | 4026 (99.3%) | 8 (0.2%) | **0.002** |
| Potassium sparing diuretic | 11 (0.3%) | 3991 (99.6%) | 4 (0.1%) | 5 (0.1%) | 4048 (99.8%) | 2 (0.0%) | 0.39 |
| Loop diuretic | 14 (0.3%) | 3978 (99.3%) | 14 (0.3%) | 19 (0.5%) | 4016 (99.0%) | 20 (0.5%) | 0.90 |
| Non-dihydropyridine calcium channel blocker | 14 (0.3%) | 3986 (99.5%) | 6 (0.1%) | 6 (0.1%) | 4043 (99.7%) | 6 (0.1%) | 0.15 |
| Beta blocker without intrinsic sympathomimetic activity | 25 (0.6%) | 3947 (98.5%) | 34 (0.8%) | 35 (0.9%) | 3989 (98.4%) | 31 (0.8%) | 0.24 |
| Thiazide-type diuretics | 64 (1.6%) | 3826 (95.5%) | 116 (2.9%) | 105 (2.6%) | 3920 (96.7%) | 30 (0.7%) | **<0.001** |
| Any diuretic | 69 (1.7%) | 3824 (95.5%) | 113 (2.8%) | 103 (2.5%) | 3910 (96.4%) | 42 (1.0%) | **<0.001** |
| Any ACE or ARB | 71 (1.8%) | 3818 (95.3%) | 117 (2.9%) | 71 (1.8%) | 3953 (97.5%) | 31 (0.8%) | **<0.001** |
| Any beta blocker | 25 (0.6%) | 3947 (98.5%) | 34 (0.8%) | 35 (0.9%) | 3989 (98.4%) | 31 (0.8%) | **0.24** |
| Chlorthalidone | 56 (1.4%) | 3864 (96.5%) | 86 (2.1%) | 105 (2.6%) | 3926 (96.8%) | 24 (0.6%) | **<0.001** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hydro-chlorothiazide | 18 (0.4%) | 3950 (98.6%) | 38 (0.9%) | 11 (0.3%) | 4027 (99.3%) | 17 (0.4%) | 0.12 |
| Other thiazide | 0 (0.0%) | 4005 (100.0%) | 1 (0.0%) | 1 (0.0%) | 4054 (100.0%) | 0 (0.0%) | 0.16 |
| Triamterene | 6 (0.1%) | 3996 (99.8%) | 4 (0.1%) | 3 (0.1%) | 4051 (99.9%) | 1 (0.0%) | 0.99 |
| Hydralazine | 2 (0.0%) | 3995 (99.7%) | 9 (0.2%) | 18 (0.4%) | 4029 (99.4%) | 8 (0.2%) | **0.005** |
| Minoxidil | 0 (0.0%) | 4006 (100.0%) | 0 (0.0%) | 3 (0.1%) | 4052 (99.9%) | 0 (0.0%) | 0.09 |

*The first visit in the post-intervention phase could be a close-out visit or a "PRN" visit arranged for follow-up of a specific issue (eg, follow-up for an adverse event)

†P value from 2-sided Cochran-Armitage Trend Test for medication changes in standard vs intensive

§ not available in the SPRINT formulary although some participants may have been prescribed by a SPRINT clinician or by a clinician outside SPRINT

‡ Inferences drawn from these tests may not be reproducible since none of the p-values or 95% confidence intervals are adjusted for multiplicity

ACE, angiotensin converting enzyme; ARB, Angiotensin II receptor blocker

Table S6. Medication changes by randomized treatment assignment group among 55 participants having a heart failure outcome after the intervention phase, comparing the last visit in the intervention phase (through August 20, 2015) to the first post-intervention visit in the observational phase (August 21, 2015 through July 29, 2016) among participants with both types of visits (data presented are N [%]).*

| | Standard Intervention N = 19 | | | Intensive Intervention N= 36 | | |
|---|---|---|---|---|---|---|
| Medication | Stopped | No change | Added | Stopped | No change | Added |
| ACE inhibitor | 0 (0.0%) | 19 (100.0%) | 0 (0.0%) | 2 (5.6%) | 34 (94.4%) | 0 (0.0%) |
| Aldosterone receptor blocker | 0 (0.0%) | 18 (94.7%) | 1 (5.3%) | 0 (0.0%) | 36 (100.0%) | 0 (0.0%) |
| Combined alpha- and beta-blocker | 0 (0.0%) | 17 (89.5%) | 2 (10.5%) | 0 (0.0%) | 36 (100.0%) | 0 (0.0%) |
| Alpha-1 blocker | 0 (0.0%) | 19 (100.0%) | 0 (0.0%) | 0 (0.0%) | 36 (100.0%) | 0 (0.0%) |
| Angiotensin II receptor blocker | 0 (0.0%) | 18 (94.7%) | 1 (5.3%) | 0 (0.0%) | 36 (100.0%) | 0 (0.0%) |
| Any ACE or ARB | 0 (0.0%) | 18 (94.7%) | 1 (5.3%) | 2 (5.6%) | 34 (94.4%) | 0 (0.0%) |
| Direct vasodilator | 0 (0.0%) | 19 (100.0%) | 0 (0.0%) | 1 (2.8%) | 35 (97.2%) | 0 (0.0%) |
| Loop diuretic | 0 (0.0%) | 16 (84.2%) | 3 (15.8%) | 2 (5.6%) | 31 (86.1%) | 3 (8.3%) |
| Non-dihydropyridine calcium channel blocker | 0 (0.0%) | 19 (100%) | 0 (0.0%) | 1 (2.8%) | 35 (97.2%) | 0 (0.0%) |
| Beta blocker without intrinsic sympathomimetic activity | 1 (5.3%) | 18 (94.7%) | 0 (0.0%) | 0 (0.0%) | 34 (94.4%) | 2 (5.6%) |
| Thiazide-type diuretic | 1 (5.3%) | 18 (94.7%) | 0 (0.0%) | 2 (5.6%) | 34 (94.4%) | 0 (0.0%) |
| Any diuretic | 0 (0.0%) | 17 (89.5%) | 2 (10.5%) | 2 (5.6%) | 32 (88.9%) | 2 (5.6%) |
| Any beta blocker | 1 (5.3%) | 18 (94.7%) | 0 (0.0%) | 0 (0.0%) | 34 (94.4%) | 2 (5.6%) |
| Chlorthalidone | 1 (5.3%) | 18 (94.7%) | 0 (0.0%) | 1 (2.8%) | 35 (97.2%) | 0 (0.0%) |
| Other thiazide | 0 (0.0%) | 19 (100%) | 0 (0.0%) | 1 (2.8%) | 35 (97.2%) | 0 (0.0%) |
| Hydralazine | 0 (0.0%) | 19 (100%) | 0 (0.0%) | 1 (2.8%) | 35 (97.2%) | 0 (0.0%) |

*includes medications or medication classes with any change between intervention period compared to post-intervention period

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

Table S7. Medication changes by randomized treatment assignment group comparing the last visit in the intervention phase (through August 20, 2015) to the first post-intervention visit in the observational phase (August 21, 2015 through July 29, 2016) among participants with both types of visits (data presented are N [%]): Among all participants and among participants with a heart failure outcome after the intervention phase.*

| All Participants | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Standard Intervention N = 4006 | | | | Intensive Intervention N = 4055 | | | |
| | Stopped | No Change | Added | Added and Stopped | Stopped | No Change | Added | Added and Stopped |
| Any Medication | 143 (3.6%) | 3552 (88.7%) | 244 (6.1%) | 67 (1.7%) | 204 (5.0%) | 3688 (90.9%) | 96 (2.4%) | 67 (1.7%) |
| Participants with Heart Failure Outcome After Intervention Phase | | | | | | | | |
| | Standard Intervention N = 19 | | | | Intensive Intervention N = 36 | | | |
| | | | | | | | | |
| Any Medication | 0 (0.0%) | 14 (73.7%) | 3 (15.8%) | 2 (10.5%) | 3 (8.3%) | 29 (80.6%) | 1 (2.8%) | 3 (8.3%) |

*includes medications or medication classes with any change between intervention period compared to post-intervention period

Table S8. First occurrence of outcomes combining clinical trial intervention period with observational post-intervention period, through July 29, 2016.*

| | Intensive Treatment | | Standard Treatment | | | |
|---|---|---|---|---|---|---|
| **All Participants** | N = 4678 | | N = 4683 | | Hazard Ratio (95%CI) | P value‖ |
| | No. of Participants (%) | % per year | No. of Participants (%) | % per year | | |
| Primary outcome† | 315 (6.7) | 1.84 | 411 (8.8) | 2.43 | 0.76 (0.65-0.88) | <0.001 |
| Primary outcome without non-fatal heart failure | 258 (5.5) | 1.50 | 342 (7.3) | 2.01 | 0.75 (0.64-0.88) | <0.001 |
| Secondary outcomes | | | | | | |
| Myocardial infarction | 115 (2.5) | 0.66 | 161 (3.4) | 0.94 | 0.71 (0.56-0.90) | 0.005 |
| Acute coronary syndrome | 45 (1.0) | 0.26 | 47 (1.0) | 0.27 | 0.95 (0.63-1.43) | 0.81 |
| Stroke | 79 (1.7) | 0.45 | 96 (2.0) | 0.55 | 0.82 (0.61-1.10) | 0.18 |
| Heart failure - all | 100 (2.1) | 0.57 | 118 (2.5) | 0.68 | 0.84 (0.64-1.09) | 0.19 |
| Heart failure - nonfatal | 98 (2.1) | 0.56 | 114 (2.4) | 0.66 | 0.85 (0.65-1.11) | 0.23 |
| Death – cardiovascular | 56 (1.2) | 0.32 | 87 (1.9) | 0.50 | 0.65 (0.46-0.90) | 0.01 |
| Death – any cause | 216 (4.6) | 1.23 | 272 (5.8) | 1.55 | 0.79 (0.66-0.94) | 0.009 |
| Primary outcome or death | 455 (9.7) | 2.66 | 563 (12.0) | 3.32 | 0.80 (0.70-0.90) | <0.001 |
| **Participants with CKD at baseline** | N = 1330 | | N = 1316 | | | |
| Composite renal outcome‡ | 18 (1.4) | 0.36 | 19 (1.4) | 0.39 | 0.90 (0.47-1.73) | 0.76 |
| ≥ 50% reduction in eGFR§ | 13 (1.0) | 0.26 | 13 (1.0) | 0.27 | 0.96 (0.44-2.10) | 0.92 |
| Long-term dialysis | 8 (0.6) | 0.16 | 12 (0.9) | 0.25 | 0.65 (0.26-1.59) | 0.35 |
| Kidney transplantation | 0 | | 1 (0.1) | 0.02 | 0.00 | 0.26 |
| Incident albuminuria¶ | 69/526 (13.1) | 3.74 | 94/500 (0.19) | 5.51 | 0.70 (0.50-0.97) | 0.03 |
| **Participants without CKD at baseline** | N = 3332 | | N = 3345 | | | |
| ≥ 30% reduction in e GFR§ | 158 (4.7) | 1.29 | 48 (1.4) | 0.39 | 3.34 (2.44-4.66) | <0.001 |
| Long-term dialysis | 0 | | 0 | | | |
| Kidney transplantation | 0 | | 0 | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Incident albuminuria¶ | 150/1769 (8.5) | 2.35 | 198/1831 (10.8) | 3.07 | 0.75 (0.61-0.93) | 0.009 |

* Includes additional events not previously reported;[1] CI denotes confidence interval, CKD chronic kidney disease, eGFR estimated glomerular filtration rate

†The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome not resulting in infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Primary outcome components are shown including fatal and non-fatal cases, except where noted for non-fatal heart failure‡ The composite renal outcome for participants with CKD at baseline was the first occurrence of a reduction in eGFR of 50% or more, long-term dialysis, or kidney transplantation.

§ Reductions in eGFR ere confirmed by a second laboratory test at least 90 days later.

¶ Incident albuminuria was defined by a doubling of the ratio of urinary albumin (in mg) to creatinine (in g) from less than 10 at baseline to greater than 10 during follow-up. The denominators for number of participants represent those without albuminuria at baseline

‖ P value for between group differences; inferences drawn from these tests may not be reproducible since none of the p-values or 95% confidence intervals are adjusted for multiplicity

Table S9. Sensitivity analysis for missing data using risk-set multiple imputation* on primary outcome combining clinical trial period with observational post-intervention period through July 29, 2016.

| | | Hazard ratio (95% CI) | P value |
|---|---|---|---|
| Primary Outcome Observed† | | 0.76 (0.65-0.88) | <0.001 |
| NN | W | | |
| 5 | 0.2 | 0.76 (0.65-0.87) | <0.001 |
| | 0.5 | 0.75 (0.65-0.87) | <0.001 |
| | 0.8 | 0.75 (0.65-0.87) | <0.001 |
| 10 | 0.2 | 0.75 (0.65-0.87) | <0.001 |
| | 0.5 | 0.75 (0.65-0.88) | <0.001 |
| | 0.8 | 0.75 (0.65-0.87) | <0.001 |
| 15 | 0.2 | 0.76 (0.66-0.88) | <0.001 |
| | 0.5 | 0.76 (0.65-0.89) | <0.001 |
| | 0.8 | 0.75 (0.65-0.87) | <0.001 |
| 20 | 0.2 | 0.75 (0.65-0.87) | <0.001 |
| | 0.5 | 0.76 (0.65-0.88) | <0.001 |
| | 0.8 | 0.76 (0.65-0.88) | <0.001 |

*The methods used for multiple imputation are described in Supplementary Appendix Section 4

† See Table S8

Table S10. Serious adverse events, conditions of interest, and monitored clinical events combining data collected during the clinical trial intervention period and observational post-intervention period, through July 29, 2016¶

| Variable | Intensive Treatment | | Standard Treatment | | | |
|---|---|---|---|---|---|---|
| | N = 4678 | | N = 4683 | | | |
| | No. of participants (%) | % per year | No. of participants (%) | % per year | Hazard ratio (95% CI) | P Value |
| Serious adverse event* | 1962 (41.9) | 14.4 | 1924 (41.1) | 14.0 | 1.03 (0.97-1.10) | 0.36 |
| Conditions of interest | | | | | | |
| Serious adverse event only | | | | | | |
| Hypotension | 112 (2.4) | 0.6 | 63 (1.3) | 0.4 | 1.78 (1.31-2.44) | <0.001 |
| Syncope | 107 (2.3) | 0.6 | 84 (1.8) | 0.5 | 1.27 (0.96-1.70) | 0.10 |
| Bradycardia | 91 (1.9) | 0.5 | 80 (1.7) | 0.5 | 1.13 (0.84-1.53) | 0.41 |
| Electrolyte abnormality | 156 (3.3) | 0.9 | 116 (2.5) | 0.7 | 1.35 (1.06-1.72) | 0.01 |
| Injurious fall† | 126 (2.7) | 0.7 | 115 (2.5) | 0.7 | 1.09 (0.85-1.41) | 0.50 |
| Acute kidney injury or acute renal failure‡ | 222 (4.7) | 1.3 | 131 (2.8) | 0.8 | 1.70 (1.37-2.12) | <0.001 |
| Emergency department visit or serious adverse event | | | | | | |
| Hypotension | 163 (3.5) | 0.9 | 85 (1.8) | 0.5 | 1.93 (1.49-2.51) | <0.001 |
| Syncope | 163 (3.5) | 0.9 | 114 (2.4) | 0.7 | 1.43 (1.13-1.83) | 0.003 |
| Bradycardia | 108(2.3) | 0.6 | 89 (1.9) | 0.5 | 1.21 (0.92-1.61) | 0.18 |
| Electrolyte abnormality | 189 (4.0) | 1.1 | 141 (3.0) | 0.8 | 1.35 (1.08-1.68) | 0.007 |
| Injurious fall† | 383 (8.2) | 2.3 | 349 (7.5) | 2.1 | 1.10 (0.95-1.27) | 0.22 |
| Acute kidney injury or acute renal failure‡ | 229 (4.9) | 1.3 | 136 (2.9) | 0.8 | 1.69 (1.37-2.10) | <0.001 |
| Monitored clinical events | | | | | | |
| Adverse laboratory measure§ | | | | | | |
| Serum sodium < 130 mmol/liter | 204 (4.4) | 1.2 | 113 (2.4) | 0.7 | 1.82 (1.45-2.30) | <0.001 |
| Serum sodium > 150 mmol/liter | 6 (0.1) | 0.0 | 0 (0.0) | 0 | - | 0.004 |
| Serum potassium < 3.0 mmol/liter | 129 (2.8) | 0.7 | 86 (1.8) | 0.5 | 1.50 (1.15-1.98) | 0.003 |
| Serum potassium > 5.5 mmol/liter | 206 (4.4) | 1.2 | 195 (4.2) | 1.1 | 1.06 (0.87-1.28) | 0.59 |

* A serious adverse event was defined as an event that was fatal or life threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalization, or was an important medical event that

the investigator judged to be a significant hazard or harm to the participant that may have required medical or surgical intervention to prevent one of the other events listed above.
† Injurious fall was defined as any fall that resulted in evaluation in an emergency department or resulted in hospitalization, regardless of injury
‡ Acute Kidney Injury and Acute renal failure were coded if the diagnosis was listed in the hospital discharge summary and was felt to be one of the top 3 reasons for admission or continued hospitalization. Although acute kidney injury was not reportable as a condition of interest if it resulted only in evaluation in an emergency department, it was noted in a few cases in which the participant presented to an emergency department for one of the other conditions of interest.
§ Adverse laboratory measures were detected on routine or unscheduled tests; routine labs were performed at one month, then quarterly during the first year, then every 6 months.
¶ Inferences drawn from these tests may not be reproducible since none of the p-values or 95% confidence intervals are adjusted for multiplicity

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