Supplementary Appendix

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

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A RANDOMIZED TRIAL OF INTENSIVE VERSUS STANDARD BLOOD PRESSURE CONTROL

SUPPLEMENTARY APPENDIX

Table of Contents

	Page
1. SPRINT Research Group	3
2. Inclusion and Exclusion Criteria	12
3. Definition of the study outcomes	15
4. Figure S1. Treatment Algorithm for Intensive Group (Goal SBP < 120 mm Hg)	25
5. Figure S2. Treatment Algorithm for Standard Group (Goal SBP < 140 mm Hg)	26
6. Figure S3. Group Sequential Boundaries and Interim Testing	27
7. Figure S4. Diastolic Blood Pressure	28
8. Figure S5. Forest Plot of Total Mortality by Subgroups	29
9. Table S1. SPRINT Formulary	30
10. Table S2. Utilization of Antihypertensive Medication Classes at Most Recent Visit	31
11. Table S3. Causes of Death	32
12. Table S4. MedDRA Coding of Preferred Terms Occurring in at least 1% of Serious Adverse Events	33
13. Table S5. Serious Adverse Events and Conditions of Interest Classified as Possibly or Definitely Related to the Intervention	34
14. Table S6. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Measures in Participants Over 75	35
15. References	37

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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).

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 (1,2). 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 (1)

	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 (1-3):
+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 (1) and the Universal Definition (4) define positive biomarkers as "the 99th 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 (4). 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 (4).

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 (1); 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 one 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 (5). 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 (6). Brain infarctions will be further sub-typed large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes (7, 8).

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 (9).

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 (10).

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 (10).
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 (11). 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 $\leq$ 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 (1) 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 (1):

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 (1):

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.

It is important to rule out other causes of death. 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:

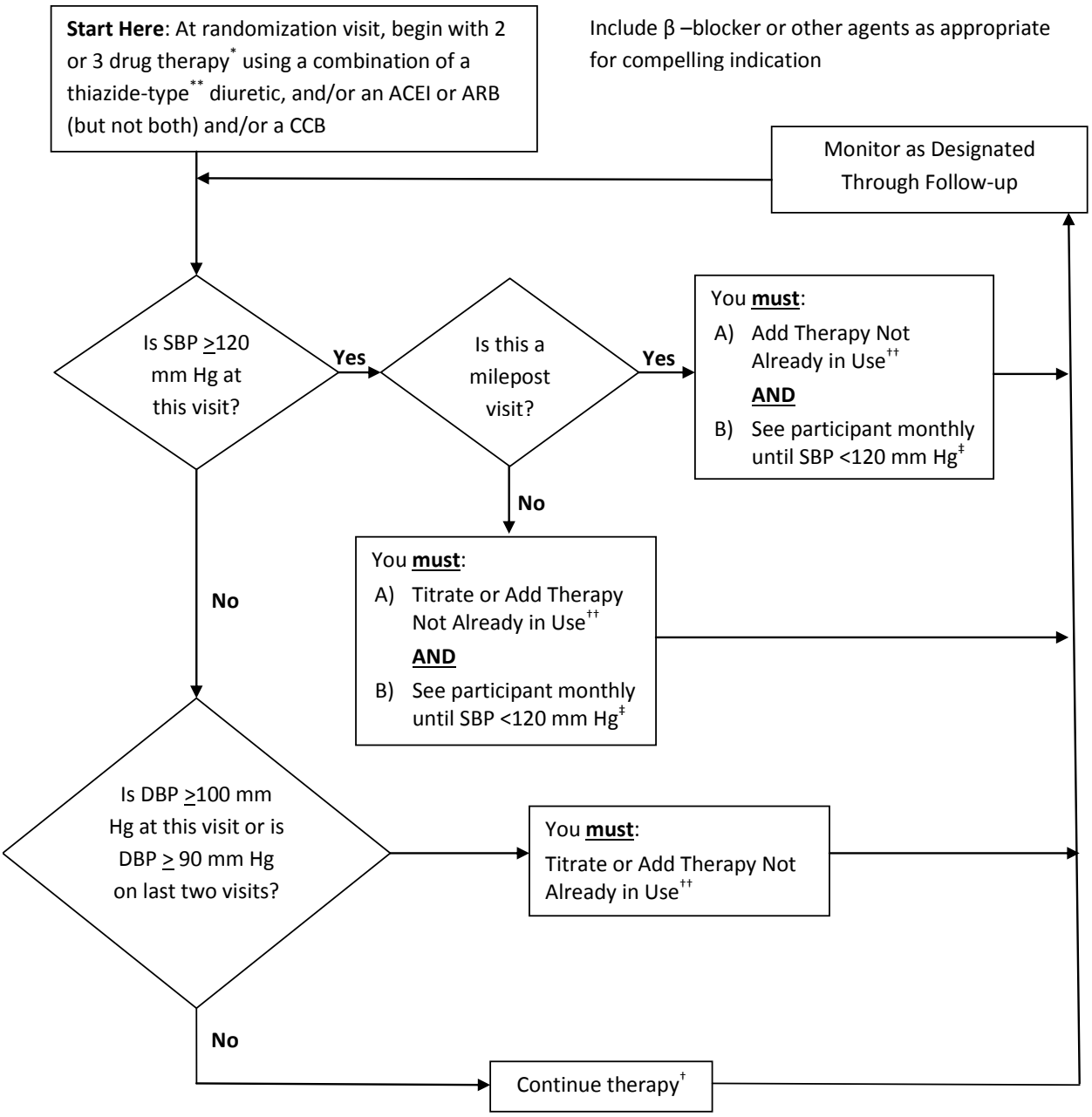
Death after invasive cardiovascular intervention. Death within 28 days of cardiovascular surgery or within 7 days of cardiac cath, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary vascular intervention. Cardiovascular procedures include PAD procedures, including 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.

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.

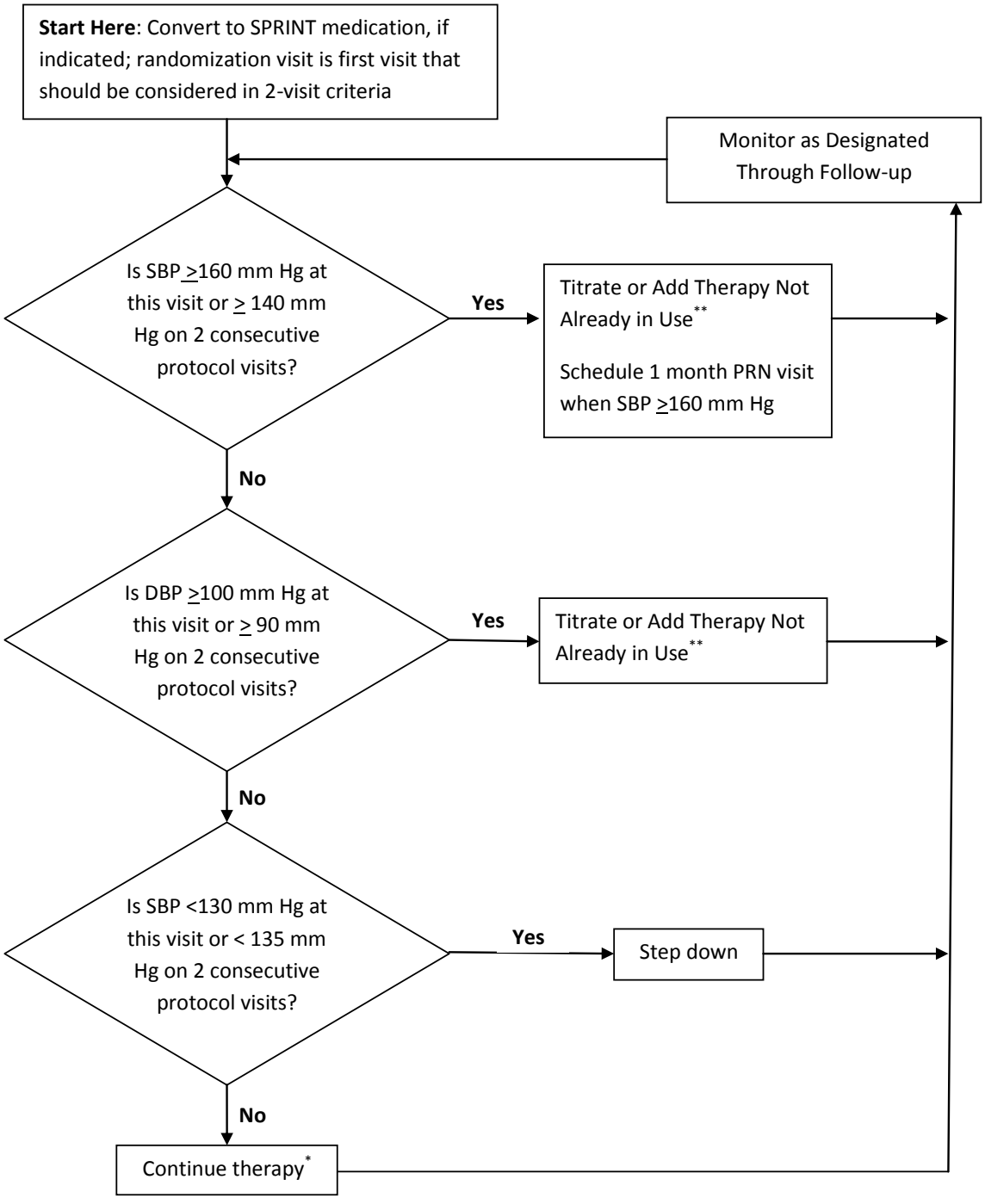
** May use loop diuretic for participants with advanced CKD

† Unless side effects warrant change in therapy

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

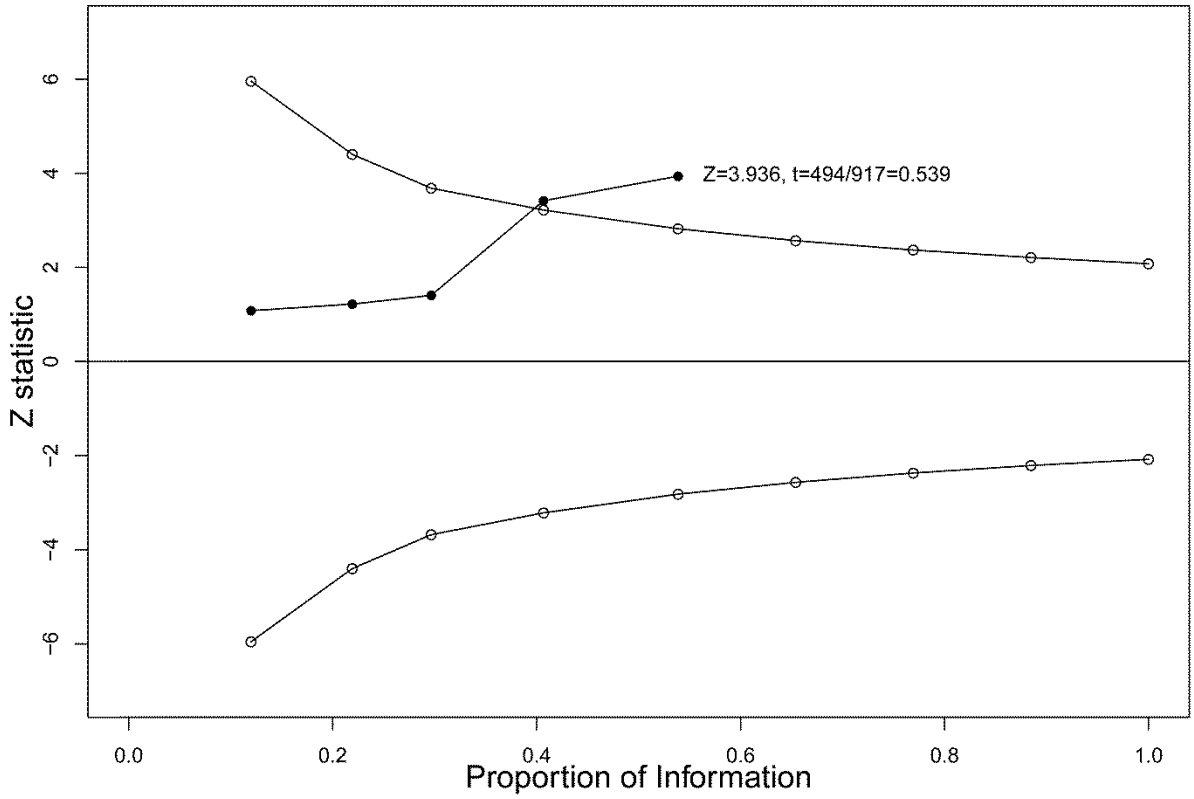
‡ Or until clinical decision made that therapy should not be increased further

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. Group Sequential Boundaries and Interim Testing



Stage	Date	Time	Time scale	Z score	Bounds	One-sided nominal alpha for bound	Cumulative stopping probability under null
1	Oct 2013	0.12	110/917	1.08	±5.956	<.0001	<.0001
2	Mar 2014	0.219	201/917	1.219	±4.402	<.0001	<.0001
3	Oct 2014	0.297	272/917	1.405	±3.681	0.0001	0.0002
4	Mar 2015	0.407	373/917	3.413	±3.217	0.0006	0.0014
5	**Aug 2015**	**0.539**	**494/917**	3.936	±2.819	0.0024	0.0053

Figure S4. Diastolic Blood Pressure. Error bars represent 95% confidence intervals.

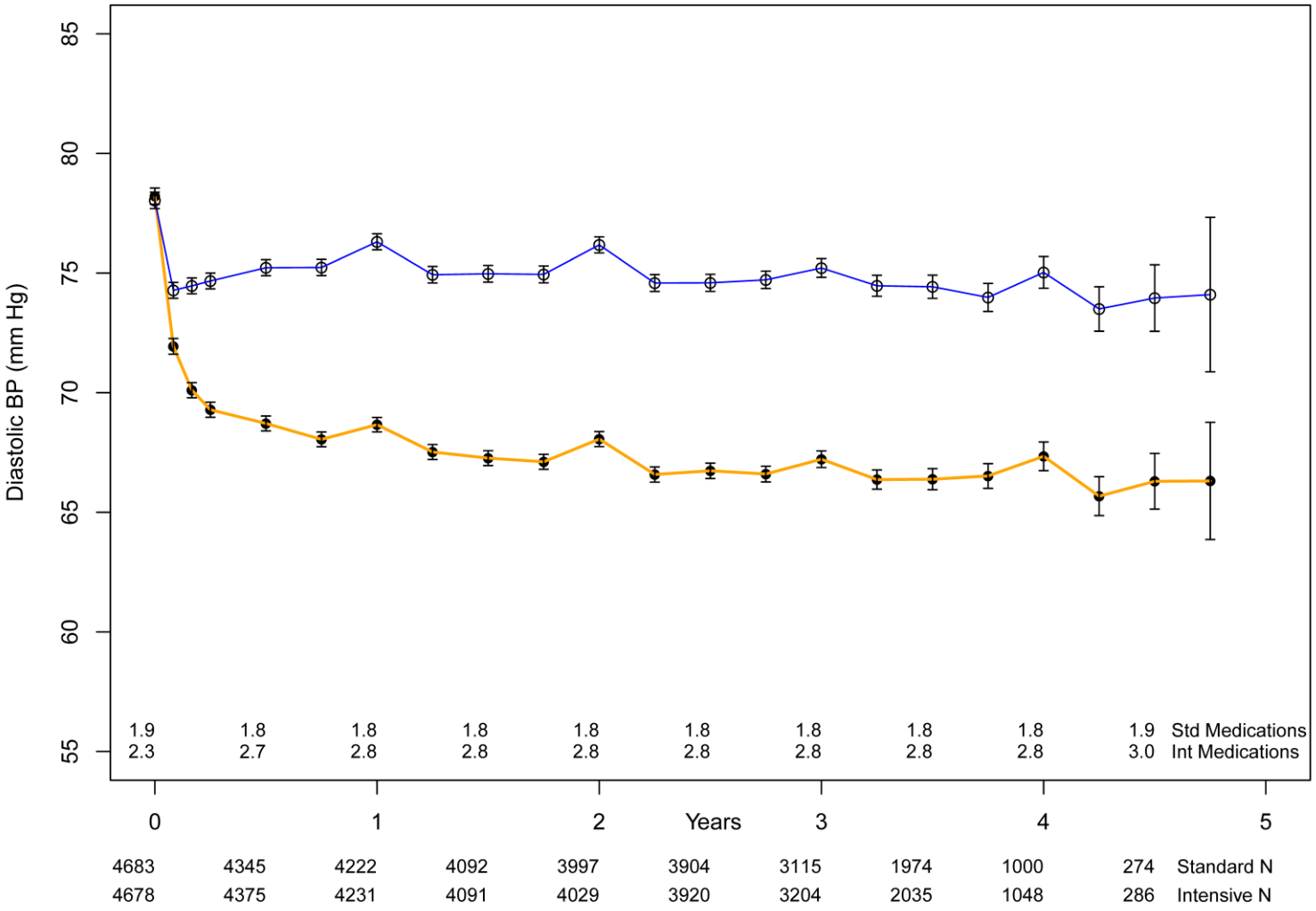


Figure S5. Forest Plot of Total Mortality by Subgroups. Overall event rates and percentages are reported for each subgroup by treatment. Estimated hazard ratios and 95% confidence intervals were estimated separately within subgroups. Unadjusted p-values for the tests of the interactions between treatment and the subgroups are reported in the right-most column. The solid line for a hazard ratio equal to 1 represents no effect and the dashed line indicates the overall 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 * P=0.34 after Hommel adjustment for multiple comparisons.

Subgroup	Intensive	Standard	HR	Int P
Overall	155/4678 (3.31)	210/4683 (4.48)	0.73 (0.60,0.90)	
No Prior CKD	85/3348 (2.54)	115/3367 (3.42)	0.75 (0.57,1.00)	0.76
Prior CKD	70/1330 (5.26)	95/1316 (7.22)	0.73 (0.53,1.00)	
Age < 75	82/3361 (2.44)	104/3364 (3.09)	0.77 (0.58,1.03)	0.58
Age ≥ 75	73/1317 (5.54)	106/1319 (8.04)	0.68 (0.50,0.92)	
Female	46/1684 (2.73)	54/1648 (3.28)	0.85 (0.57,1.26)	0.49
Male	109/2994 (3.64)	156/3035 (5.14)	0.71 (0.55,0.91)	
African−American	53/1454 (3.65)	55/1493 (3.68)	0.96 (0.65,1.40)	0.06*
Non African−American	102/3224 (3.16)	155/3190 (4.86)	0.64 (0.50,0.82)	
No Prior CVD	106/3738 (2.84)	140/3746 (3.74)	0.75 (0.58,0.96)	0.78
Prior CVD	49/940 (5.21)	70/937 (7.47)	0.70 (0.48,1.02)	
SBP ≤ 132	46/1583 (2.91)	64/1553 (4.12)	0.73 (0.49,1.07)	0.70
132 < SBP < 145	41/1489 (2.75)	63/1549 (4.07)	0.69 (0.46,1.03)	
SBP ≥ 145	68/1606 (4.23)	83/1581 (5.25)	0.81 (0.59,1.13)	

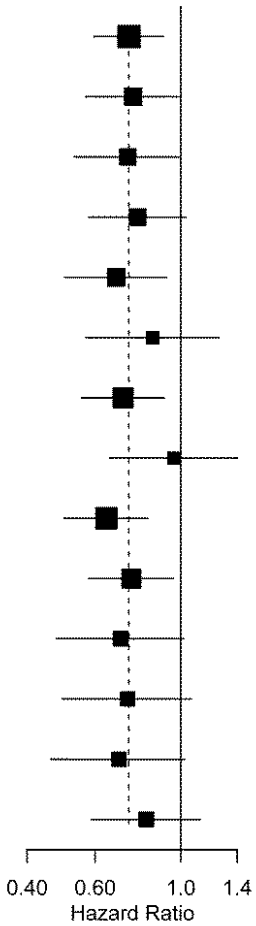


Table S1. SPRINT Formulary

Class	Drug	Available Strengths	Usual Dose Range / day	Usual Daily Frequency
Diuretic	Chlorthalidone	25mg	12.5-25 mg	1
	Furosemide	20mg, 40mg, 80mg	20-80 mg	2
	Spironolactone	25mg	25-50 mg	1
	Triamterene/HCTZ	75/50mg	37.5/25 mg – 75/50 mg	1
	Amiloride	5mg	5-10 mg	1-2
Ace Inhibitor	Lisinopril	5mg, 10mg 20mg, 40mg	5-40 mg	1
Angiotensin Receptor Blocker	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 Agonist	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 but 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 Inhibitor	Lisinopril/HCTZ	20/12.5 mg, 20/25mg	10-40 / 12.5-50	1
Adrenergic inhibitor	Reserpine	0.1mg, 0.25mg	0.1-0.25	1
Alpha 2 Agonist	Clonidine patch	0.1mg, 0.2mg, 0.3mg	0.1-0.3	1 wkly
Beta blocker	Metoprolol ER	25mg, 50mg, 100 mg, 200 mg	50-200	1
Diuretic	Amiloride/HCTZ	5/50mg	5/50	1
Thiazide diuretic	HCTZ	12.5, 25 mg	12.5 – 50	1
Angiotensin Receptor Blocker	Valsartan	80mg, 160mg, 320mg	80-320	1-2

Table S2. Utilization of Antihypertensive Medication Classes at Most Recent Visit

	Intensive (N=4678)	***Standard (N=4683)***
Number of agents		
Average	**2.7 (1.2)**	**1.8 (1.1)**
0	**125 (2.7)**	**530 (11.3)**
1	**493 (10.5)**	**1455 (31.1)**
2	**1429 (30.5)**	**1559 (33.3)**
3	**1486 (31.8)**	**807 (17.2)**
4+	**1137 (24.3)**	**323 (6.9)**
ACE-I or angiotensin II antagonist	**3580 (76.7)**	**2582 (55.2)**
ACE inhibitors	**1729 (37.0)**	**1320 (28.2)**
Angiotensin II antagonists	**1854 (39.7)**	**1264 (27.0)**
Renin inhibitors	**1 (0.0)**	**1 (0.0)**
Diuretics	**3127 (67.0)**	**2006 (42.9)**
Thiazide-type diuretics	**2562 (54.9)**	**1557 (33.3)**
Aldosterone receptor blockers	**405 (8.7)**	**185 (4.0)**
Other potassium-sparing diuretics	**144 (3.1)**	**119 (2.5)**
Alpha-1 blockers	**482 (10.3)**	**258 (5.5)**
Beta blockers	**1919 (41.1)**	**1440 (30.8)**
With intrinsic sympathomimetic activity	**0 (0.0)**	**0 (0.0)**
Without intrinsic sympathomimetic activity	**1919 (41.1)**	**1440 (30.8)**
Central alpha-2 agonists or other centrally acting drugs	**107 (2.3)**	**44 (0.9)**
Calcium channel blockers	**2667 (57.1)**	**1654 (35.4)**
Dihydropyridines	**2465 (52.8)**	**1463 (31.3)**
Non-dihydropyridines	**218 (4.7)**	**199 (4.3)**
Direct vasodilators	**340 (7.3)**	**110 (2.4)**

Table S3. Causes of Death

Cause of death	Overall	Intensive	Standard
CVD Death	102	37	65
__CHD Death	50	18	32
__Stroke	17	8	9
__Sudden cardiac death	13	2	11
__CHF	17	8	9
__Not cardiac but other cardiovascular	5	1	4
Non-CVD Death	192	90	102
__Death from kidney disease	2	1	1
__Death related to dialysis procedure	1	0	1
__Other cardiac/non-ischemic	2	0	2
__Cancer	101	49	52
__Accident/Injury/Suicide/Homocide	14	4	10
__Other noncardiac, nonstroke death	72	36	36
Undetermined	71	28	43
__Unclassifiable	35	13	22
__Not yet adjudicated	36	15	21
Total	365	155	210

Table S4. MedDRA Coding of Preferred Terms Occurring in at least 1% of Serious Adverse Events*

	Intensive (N=4678)			Standard (N=4683)			Ratio
Preferred Name	Number of Events	Participants With Events (N)	Participants With Events (%)	Number of Events	Participants With Events (N)	Participants With Events (%)	Int/Std
Chest pain	237	198	4.2	229	191	4.1	1.04
Tachyarrhythmia	191	141	3	230	176	3.8	0.80
Other ischaemic heart disease	210	170	3.6	206	182	3.9	0.94
Death	155	155	3.3	210	210	4.5	0.74
Knee arthroplasty	152	138	2.9	134	119	2.5	1.16
Ischaemic cerebrovascular conditions	128	109	2.3	144	121	2.6	0.90
Pneumonia	120	100	2.1	132	114	2.4	0.88
Cardiac failure	82	58	1.2	146	98	2.1	0.59
Myocardial infarction	71	70	1.5	117	106	2.3	0.66
Chronic obstructive pulmonary disease	74	42	0.9	112	64	1.4	0.66
Hip arthroplasty	75	67	1.4	87	81	1.7	0.83
Hypertension	60	58	1.2	82	69	1.5	0.84
Urinary tract infection	50	48	1	61	47	1	1.02
Dyspnoea	55	48	1	46	45	1	1.07
Dehydration	54	51	1.1	43	41	0.9	1.25
Cellulitis	59	40	0.9	34	30	0.6	1.33
Sepsis	37	36	0.8	42	40	0.9	0.90
Spinal fusion surgery	49	46	1	30	30	0.6	1.53
Cardiac pacemaker insertion	35	33	0.7	39	39	0.8	0.85
Spinal laminectomy	36	36	0.8	38	32	0.7	1.13
Pulmonary embolism	36	34	0.7	33	32	0.7	1.06
Dizziness	37	34	0.7	30	25	0.5	1.36
Pulmonary embolism	34	32	0.7	32	31	0.7	1.03

* MedDRA denotes Medical Dictionary for Regulatory Activities. Conditions of Interest are not included.

Table S5. Serious Adverse Events and Conditions of Interest Classified as Possibly or Definitely Related to the Intervention.

	Intensive (N=4678)	Standard (N=4683)	
	no. of patients (%)	no. of patients (%)	Hazard Ratio (P Value)
Serious Adverse Events[1]	220 (4.7)	118 (2.5)	1.88 (<0.001)
Conditions of Interest			
SAE Only			
Hypotension	83 (1.8)	37 (0.8)	2.52 (<0.001)
Syncope	64 (1.4)	28 (0.6)	2.15 (0.006)
Bradycardia	34 (0.7)	24 (0.5)	1.28 (0.44)
Electrolyte abnormality	69 (1.5)	48 (1.0)	1.58 (0.05)
Injurious fall[2]	19 (0.4)	13 (0.3)	1.99 (0.21)
Acute Kidney Injury or Acute Renal Failure[3]	88 (1.9)	34 (0.7)	3.14 (<0.001)
ER Visit or SAE			
Hypotension	125 (2.7)	58 (1.2)	2.24 (<0.001)
Syncope	94 (2.0)	44 (0.9)	2.13 (0.005)
Bradycardia	51 (1.1)	29 (0.6)	1.68 (0.05)
Electrolyte abnormality	93 (2.0)	62 (1.3)	1.61 (0.02)
Injurious fall[2]	36 (0.8)	23 (0.5)	2.22 (0.05)
Acute Kidney Injury or Acute Renal Failure[3]	96 (2.1)	36 (0.8)	3.13 (<0.001)

1. 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.

2. An Injurious fall was defined as a fall that resulted in evaluation in an emergency department or resulted in hospitalization.

3. 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. A few cases of AKI were noted in an emergency department if the participant presented for one of the other conditions of interest.

Table S6. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Measures in Participants Over 75.

	Intensive (N=1317)	Standard (N=1319)	
	no. of patients (%)	no. of patients (%)	Hazard Ratio (P Value)
Serious Adverse Events[1]	640 (48.6)	638 (48.4)	1.00 (0.93)
Conditions of Interest			
SAE Only			
Hypotension	36 (2.7)	24 (1.8)	1.49 (0.13)
Syncope	46 (3.5)	37 (2.8)	1.24 (0.33)
Bradycardia	41 (3.1)	43 (3.3)	0.94 (0.79)
Electrolyte abnormality	58 (4.4)	41 (3.1)	1.40 (0.10)
Injurious fall[2]	70 (5.3)	79 (6.0)	0.88 (0.42)
Acute Kidney Injury or Acute Renal Failure[3]	75 (5.7)	54 (4.1)	1.38 (0.07)
ER Visit or SAE			
Hypotension	49 (3.7)	35 (2.7)	1.40 (0.13)
Syncope	64 (4.9)	50 (3.8)	1.28 (0.19)
Bradycardia	49 (3.7)	50 (3.8)	0.97 (0.87)
Electrolyte abnormality	66 (5.0)	48 (3.6)	1.37 (0.01)
Injurious fall[2]	158 (12.0)	193 (14.6)	0.79 (0.03)
Acute Kidney Injury or Acute Renal Failure[3]	78 (5.9)	55 (4.2)	1.42 (0.05)
Monitored Clinical Events			
Laboratory Measures[4]			
Sodium <130 mmol/L	66 (5.0)	44 (3.3)	1.50 (0.04)
Sodium >150 mmol/L	1 (0.1)	0 (0.0)	-- (0.50)
Potassium <3.0 mmol/L	17 (1.3)	11 (0.8)	1.53 (0.27)
Potassium >5.5 mmol/L	68 (5.2)	65 (4.9)	1.04 (0.81)
Signs and Symptoms			
Orthostatic hypotension[5]	277 (21.0)	288 (21.8)	0.95 (0.53)
Orthostatic hypotension with dizziness	25 (1.9)	17 (1.3)	1.26 (0.26)

1. 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.

2. An Injurious fall was defined as a fall that resulted in evaluation in an emergency department or resulted in hospitalization.

3. 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. A few cases of AKI were noted in an emergency department if the participant presented for one of the other conditions of interest.

4. Detected on routine or PRN SPRINT labs; routine labs drawn quarterly for first year, then q 6 months; numbers represent the number (%) of participants having 1 or more alert value.

5. Defined as drop in systolic BP ≥20 mmHg or drop in diastolic ≥10 mmHg 1 minute after standing. Standing blood pressures were measured at screening, baseline, 1, 6, and 12 months and yearly thereafter. Participants were asked if they felt dizzy at the time the orthostatic measure was taken.

REFERENCES

1. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, et al., Case Definitions for Acute Coronary Heart Disease in Epidemiology and Clinical Research Studies: A Statement From the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute: Circulation. 2003;108(20):2543-9.

2. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012 Oct;33(20):2551-67.

3. Apple F, Wu A, Jaffe A. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: How to use existing assays clinically and for clinical trials. American Heart Journal. 2002 Dec; 144(6): 981-986.

4. Thygesen K, Alpert J, White H. Universal Definition of Myocardial Infarction. Circulation. 2007; 116 (22):2634-2653.

5. World Health Organization. Cerebrovascular disorders: a clinical and research classification. Geneva: WHO Offset Publications, 1978. Available at: http://apps.who.int/iris/handle/10665/37194

6. Mohr JP, Thompson JLP, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444-51

7. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke 2007;38: 2979–2984.

8. Gordon D, Bendixen B, Adams HJ, et al. Interphysician agreement in the diagnosis of subtypes of acute ischemic stroke: implications for clinical trials. The TOAST Investigators. Neurology 1993; 43:1021–7.

9. Easton JD, Saver JL, Albers GW, et al. Definition and Evaluation of Transient Ischemic Attack: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease: The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276-2293.

10. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064-2089.

11. Rosamond WD, Chang PP, Baggett C, et al. Classification of Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study. A Comparison of Diagnostic Criteria. Circ Heart Fail. 2012;5:152-159.