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The design and rationale of a multi-center clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT)

The SPRINT Study Research Group

Abstract

Background—High blood pressure is an important public health concern because it is highly prevalent and a risk factor for adverse health outcomes, including coronary heart disease, stroke, decompensated heart failure, chronic kidney disease, and decline in cognitive function. Observational studies show a progressive increase in risk associated with blood pressure above 115/75 mm Hg. Prior research has shown that reducing elevated systolic blood pressure lowers the risk of subsequent clinical complications from cardiovascular disease. However, the optimal systolic blood pressure to reduce blood pressure-related adverse outcomes is unclear, and the benefit of treating to a level of systolic blood pressure well below 140 mm Hg has not been proven in a large, definitive clinical trial.

Purpose—To describe the design considerations of the Systolic Blood Pressure Intervention Trial (SPRINT) and the baseline characteristics of trial participants.

Methods—SPRINT is a multi-center, randomized, controlled trial that compares two strategies for treating systolic blood pressure: one targets the standard target of <140 mm Hg, and the other targets a more intensive target of <120 mm Hg. Enrollment focused on volunteers of age ≥50 years (no upper limit) with an average baseline systolic blood pressure ≥130 mm Hg and evidence of cardiovascular disease, chronic kidney disease, 10-year Framingham cardiovascular disease risk score ≥15%, or age ≥75 years. SPRINT recruitment also targeted three pre-specified subgroups: participants with chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2), participants with a history of cardiovascular disease, and participants 75 years of age or older. The primary outcome is first occurrence of a myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular disease death. Secondary outcomes include all-cause mortality, decline in kidney function or development of end-stage renal disease, incident dementia, decline in cognitive function, and small-vessel cerebral ischemic disease.

Results—Between November 11, 2010 and March 15, 2013 SPRINT recruited and randomized 9361 people at 102 clinics, including 3333 women, 2648 with chronic kidney disease, 1877 with a history of cardiovascular disease, 3962 minorities, and 2636 ≥75 years of age.

Limitations—Although the overall recruitment target was met, the numbers recruited in the high-risk subgroups were lower than planned.

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Conclusions—SPRINT will provide important information on the risks and benefits of intensive blood pressure treatment targets in a diverse sample of high-risk participants, including those with prior cardiovascular disease, chronic kidney disease, and those aged ≥75 years.

Keywords

Randomized clinical trial; major adverse cardiovascular outcomes; blood pressure targets; hypertension; stroke; cardiovascular; kidney; cognition; brain structure and function; geriatrics

Introduction, Background, and Rationale

Hypertension is highly prevalent in the adult population of the US, especially among those aged >60 years, and is estimated to affect approximately one billion adults worldwide [1]. By age 50 years, isolated systolic hypertension is the most common form of hypertension[2], and the importance of blood pressure, especially systolic blood pressure, as an independent risk factor for coronary events, stroke, heart failure, and progressive chronic kidney disease including end-stage renal disease is well documented [3–13]. There is also substantial epidemiologic and some clinical trial evidence supporting a role for hypertension therapy in reducing risk for adverse changes in brain structure and function, including dementia, cognitive decline, and cerebrovascular disease [14–20]. The Global Burden of Disease Study identified elevated blood pressure as the leading risk factor, among 67 factors studied, for worldwide mortality and disability-adjusted life years during 2010 [21]. Clinical trial experience has demonstrated that treatment of hypertension reduces cardiovascular disease outcomes, including incident stroke (35% to 40%), myocardial infarction (15% to 25%), and heart failure (up to 50%) [3,22,23]. The optimal target for systolic blood pressure lowering is uncertain. Clinical trials with systolic blood pressure targets <150 mm Hg (Systolic Hypertension in the Elderly Program (SHEP) and Hypertension in the Very Elderly Trial (HYVET)) have demonstrated reduction in cardiovascular disease outcomes, including incident stroke [24,25]. Observational studies document a progressive increase in risk of cardiovascular disease events as blood pressure rises above 115/75 mm Hg [10]. However, lowering to <120 mm Hg may be harmful or fail to produce benefits, and could be unnecessarily costly and burdensome [26–33]. Clarification of the most desirable systolic blood pressure goal during hypertension treatment is important for the health of the general population.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure trial, which was restricted to participants with diabetes mellitus who had normal or near normal kidney function, tested the hypothesis that more intensive reduction in systolic blood pressure to <120 mm Hg is beneficial compared to the frequently recommended target systolic blood pressure of <140 mm Hg. ACCORD did not demonstrate a benefit for treatment to the lower target for a composite cardiovascular disease outcome (hazard ratio 0.88, 95% CI: 0.73 to 1.06, P =0.20). However the confidence limit did not exclude a benefit as large as a 27% improvement in the composite cardiovascular disease outcome [32]. A definitive clinical trial in non-diabetic hypertensive participants to determine whether lowering systolic blood pressure <120 mm Hg reduces clinical events more than lowering systolic blood pressure to <140 mm Hg was designated by an NHLBI Expert Panel in

2007 [34] as the most important hypothesis to test regarding the prevention of hypertension-related complications. This paper describes the design of the Systolic Blood Pressure Intervention Trial (SPRINT), which aims to address this question. This paper is a summary of our protocol which is publically available [35].

Study Organization

The SPRINT organizational structures and responsibilities are similar to many previous multicenter clinical trials. Four institutes of the National Institutes of Health (NIH) co-sponsor SPRINT. The National Heart, Lung, and Blood Institute (NHLBI) initiated the study, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is a co-sponsor of the main SPRINT trial. The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA) are jointly sponsoring the cognitive sub-study, known as SPRINT MIND. Five Clinical Center Networks, the Coordinating Center, and NIH representatives formed the Steering Committee to design and conduct the trial; voting members include the Clinical Center Network Principal Investigators, the Coordinating Center Principal Investigator, the NHLBI Project Officer (representing the 4 NIH Institutes), and the Steering Committee Chair (or Co-Chair) in the case of a tie vote. In addition, there are four central units: a Central Laboratory, an Electrocardiography (ECG) Reading Center, a Magnetic Resonance Imaging (MRI) Reading Center, and a Drug Distribution Center.

Each Clinical Center Network consists of multiple collaborating clinical centers, which are primarily responsible for the recruitment, blood pressure management, safety, and follow-up of participants. The Clinical Center Networks were responsible for recruiting and providing oversight of these clinical centers. The Coordinating Center is responsible for overall trial coordination, data collection and analysis, and for oversight of the central units. The NIH Project Office is responsible for the scientific conduct and administration of SPRINT. External oversight is provided by Institutional Review Boards at the Coordinating Center, Clinical Center Networks, and clinical centers and a Data and Safety Monitoring Board appointed by NIH.

Study Design Decisions

Overall Design

The objective of SPRINT is to test whether reducing systolic blood pressure to <120 mm Hg will reduce cardiovascular disease events defined as the composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular disease. Research teams submitted proposals to NIH in May 2008 in response to a request for proposals issued by NIH in February 2008. After the contracts were awarded in September 2009, the SPRINT Steering Committee refined the overall study design. This process led to a review by an NIH-appointed Protocol Review Committee in June 2010 and final approval by NIH. Below we discuss the design considerations for SPRINT.

Eligibility, Recruitment, Retention, and Adherence

The SPRINT inclusion criteria are presented in Table 1; exclusion criteria are detailed in the protocol [35], two major exclusion criteria include diabetes mellitus and stroke. A major goal was to recruit a sample that would provide maximum generalizability and safety, adequate event rates to achieve the planned level of statistical power, and feasibility to meet the trial's enrollment objectives. Other goals included assessing whether persons with and without chronic kidney disease and older and younger participants in diverse population subgroups differ in their response to hypertension treatment and whether the treatment might slow down age-related decline in cognition and reduce dementia rates. Hence, SPRINT was to include a diverse population with hypertension and existing cardiovascular disease, existing chronic kidney disease, or an elevated estimated risk for cardiovascular disease based on age and other risk factors [36]. The overall target was to randomize 9,250 participants.

Within the 9,250 target, targets were set for three subgroups: 4,300 (46%) with chronic kidney disease (estimated glomerular filtration rate 20–59 ml/min/1.73m^2), 3,700 (40%) with clinical or subclinical cardiovascular disease, and 3,250 (35%) seniors (≥75 years old). Additional targets included enrolling 50% women and 40% minorities. The recruitment targets were closely monitored. Participant recruitment began on November 11, 2010 but proceeded more slowly than planned, and achieving the original chronic kidney disease, cardiovascular disease, and senior targets was more challenging than expected (Figure 1). From November 4, 2012, through March 15, 2013, recruitment was focused on enrolling seniors or participants with existing chronic kidney disease or cardiovascular disease. The overall enrollment experience is shown in the CONSORT diagram (Figure 2).

The SPRINT study also recruited participants into two important nested sub-studies, SPRINT MIND and SPRINT MIND MRI, both of which were pre-specified in the NIH RFP. While all SPRINT participants are assessed for incident dementia (see below), our target was a subset of 2800 SPRINT participants to undergo more extensive cognitive assessment than that performed in the total sample, with the goal of evaluating the impact of the intervention on decline in cognitive function. A smaller number of 640 SPRINT MIND participants attending clinics located near a SPRINT MIND MRI center was targeted to be recruited into the SPRINT MIND MRI sub-study.

Attention to adherence and retention began before enrollment, during the screening process, and continues throughout the trial. During screening, individuals who demonstrated a significant risk for non-adherence to study medication or for completing study visits were excluded from trial participation. Once participants were enrolled, a baseline assessment of adherence using standardized, valid adherence measures in conjunction with assessment of behavioral "red flags" by clinic staff allowed for early identification of potential problems so that study resources could be devoted to improving adherence and retention for these individuals. Throughout the trial, ongoing monitoring of adherence is critical for identifying low adherence and enabling clinic staff to intervene and address problems as they develop.

Study procedures, including obtaining written informed consent from all participants, were approved in advance by relevant Institutional Review Boards.

Intervention

Participants were randomized to one of two systolic blood pressure targets: <120 and <140 mm Hg. The intervention is a treatment algorithm similar to that used in the ACCORD Trial, which produced average systolic blood pressures of 119 mm Hg and 134 mm Hg in the Intensive and Standard Treatment groups, respectively (Figures 3 and 4) [32].

Representative medications from all major classes of antihypertensive agents are provided by the trial at no cost to the participants. Other antihypertensive medications can be used by SPRINT investigators but are not provided by the trial. The protocol recommended that antihypertensive regimens should include one or more drug classes with the strongest evidence for capacity to prevent cardiovascular disease outcomes: thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), with priority for prescription of thiazide-type diuretics [3,37]. However, clinical center investigators are given discretion regarding which drugs to use at initiation and during intensification of therapy. Loop diuretics are recommended for participants with advanced chronic kidney disease. Use of beta-adrenergic blockers is encouraged in participants with coronary artery disease. Chlorthalidone is encouraged as the primary thiazide-type diuretic, and amlodipine as the preferred CCB, since they have the most robust evidence for prevention of cardiovascular disease outcomes and blood pressure reduction within their respective classes [38,39]. Antihypertensive drug classes with guideline recommendations for specific nonhypertensive indications can be used in place of other agents in order to achieve and maintain systolic blood pressure targets (e.g., use of ACE-inhibitors and ARBs in participants with chronic kidney disease). The SPRINT formulary is presented in Table 2.

In both groups participants are evaluated monthly for the first three months, and thereafter every three months. Monthly visits continue in the Intensive Group until a systolic blood pressure <120 mm Hg is achieved or no more titration is planned and in the Standard Group whenever a systolic blood pressure ≥160 mm Hg is noted. Additional visits can be scheduled as needed for monitoring medications and safety.

For most participants in the Intensive Group, a two- or three-drug regimen was initiated at randomization (occasionally only one drug for participants ≥75 years). Drug doses are increased and/or additional antihypertensive medications are added at monthly visits until the target of <120 mm Hg is reached or the investigator decides no further antihypertensive medications should be added. “Milepost Visits” are scheduled every 6 months. If the systolic blood pressure is not <120 mm Hg at a Milepost Visit, an antihypertensive drug from an additional class is added, absent contraindications.

For Standard Group participants, the protocol is designed to achieve a systolic blood pressure of 135–139 mm Hg, starting with the randomization visit. Dose titration or addition of another drug occurs if systolic blood pressure is ≥160 mm Hg at a single visit or ≥140 mm Hg at two successive visits. Medication may be reduced if the systolic blood pressure is <130 mm Hg at a single visit or <135 mm Hg at two consecutive visits.

Titration of medications to target is based on a mean of three office blood pressure measurements obtained in the seated position using an automated measurement device (Omron Healthcare, Lake Forest, IL). Blood pressure is also measured one minute after standing at screening, baseline, 1 month, 6 months, 12 months, and annually thereafter. While standing, participants are asked about symptoms of hypotension (see Safety section).

All participants are advised to follow lifestyle recommendations and background therapy consistent with current practice guidelines to minimize differences in the effects of non-study strategies that could influence systolic blood pressure or cardiovascular disease outcomes in the two treatment arms. Specific lifestyle recommendations include weight loss for overweight participants, a heart-healthy diet (e.g., the DASH diet) with appropriate modifications for participants with chronic kidney disease, reducing sodium intake and alcohol consumption below maximum recommended levels, regular aerobic exercise, and smoking cessation [3].

Hypotheses and choice of outcomes

The primary hypothesis for SPRINT is that treating to a systolic blood pressure target of <120 mm Hg (the intensive intervention) compared to a systolic blood pressure target of <140 mm Hg (the standard intervention) will reduce the composite outcome of nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular disease. Three subgroups are of particular interest since the intervention effect may be modified by the baseline values defining them: participants with (estimated glomerular filtration rate <60 ml/min/1.73m^2) and without chronic kidney disease, race (Black or non-Black), and participants < or ≥75 years.

We selected a composite primary outcome for three reasons. First, there is previous evidence that each component of the primary outcome may be modifiable with intensive blood pressure reduction [12,24,25,40,41]. Second, use of a primary outcome based on a single clinical event would have resulted in a sample size that is unfeasible. Third, the integrated effect of the intervention on overall cardiovascular disease outcomes (or mortality) is the most important clinical question upon which a significantly lower blood pressure goal would be widely recommended.

SPRINT prespecifies three types of secondary outcomes: (1) secondary outcomes to support the primary analysis, including components of the primary composite outcome, total mortality, and a composite of the primary composite with total mortality (i.e., cardiovascular disease-free survival), (2) kidney outcomes, and (3) brain outcomes. Additional secondary cardiovascular disease outcomes include peripheral arterial disease, coronary revascularization, transient ischemic attack, left ventricular hypertrophy on ECG, and atrial fibrillation or flutter. Peripheral arterial disease includes carotid and peripheral revascularization, abdominal aortic aneurysm repair, and other objectively defined peripheral arterial disease events.

The main secondary kidney outcome, restricted to the chronic kidney disease subgroup, is a composite of a 50% decrease in estimated glomerular filtration rate from baseline or incident

end-stage renal disease. Among the nonchronic kidney disease subgroup, the kidney outcomes are (1) a decrease in estimated glomerular filtration rate by >30% to <60 ml/min/1.73m^2 and (2) incident albuminuria, defined as a doubling of urinary albumin-to-creatinine ratio from a value of <10 mg/g to a value of >10 mg/g. The second of these also applies to the chronic kidney disease subgroup. These kidney outcomes are ascertained by laboratory tests obtained during regularly scheduled study visits, except for end-stage renal disease, which is ascertained by history and review of clinical records.

The main secondary brain hypothesis is that incidence of all-cause dementia will be lower in the Intensive compared to the Standard Group. We also hypothesize that compared to the Standard Group, the Intensive Group will have slower decline in a composite measure of general cognitive function across all domains of cognition (measured in the SPRINT MIND participants) and a lower load of small vessel ischemic disease and higher total brain volume (measured in the SPRINT MIND MRI participants).

Consistency of effects of the intervention on the cardiovascular primary outcome will be examined in subgroups defined by six baseline variables (chronic kidney disease vs non-chronic kidney disease, Black vs. non-Black, age (≥ vs. <75 years), gender, presence vs. absence of cardiovascular disease (see Table 1), and tertiles of baseline systolic blood pressure). Subgroup analyses will also be performed for the kidney outcomes. These subgroups are defined by race, age, gender, baseline urinary albumin-to-creatinine ratio (>300 mg/g vs. ≤300 mg/g) and baseline estimated glomerular filtration rate (< vs. ≥ the median). For dementia and the cognitive outcomes, we will examine the subgroups for the primary outcome, mild cognitive impairment at baseline (presence vs. absence), and baseline orthostatic hypotension (presence vs. absence; defined as an orthostatic systolic blood pressure decrease of ≥20 mm Hg or a diastolic blood pressure decrease of ≥10 mm Hg).

Health-related quality of life is assessed in the total SPRINT sample using the Veterans Rand Short-Form 12 (VR-12) [42,43], the EuroQol-5D-3L [44], and the Patient Health Questionnaire-9 (PHQ-9) [45,46]. In addition, two items developed by the SPRINT Health-related Quality of Life Subcommittee are used to assess participant satisfaction with antihypertensive medications and treatment for hypertension. In a health-related quality of life subsample, the Falls Self-Efficacy Scale International [47] is assessed. Among women, the Female Sexual Function Index (FSFI) [48,49] is assessed, and among men, the International Index of Erectile Function 5-item version (IIEF-5) [50] is assessed.

Measurement, Ascertainment, and Follow-up

The algorithm for classifying myocardial infarction is presented in Table 3. The definition includes myocardial infarction that occurred during surgery or a procedure and myocardial infarction aborted by thrombolytic therapy or procedure. Silent myocardial infarction, determined using 12-lead ECG at years 2 and 4 and the close-out visit compared to baseline, is determined centrally in the absence of clinically detected myocardial infarction using the Minnesota ECG classification [52]. The diagnosis of non-myocardial infarction acute coronary syndrome requires hospitalization for evaluation, with documented new or changing cardiac ischemic symptoms. Further, confirmatory evidence of coronary artery disease is required.

Stroke is defined as the rapid onset of focal neurologic symptoms, headache, or meningismus not due to other conditions (e.g., central nervous system infection), plus a lesion on brain imaging consistent with symptoms except when death occurs within 24 hours without resolution of symptoms [53,54]. Clinical strokes are subtyped using the Causative Classification of Stroke (CCS) system [55,56]. Diagnosis of heart failure requires a 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 or inadequate cardiac pump function [57]. This outcome includes heart failure with preserved or reduced left ventricular ejection fraction. Cardiovascular disease death includes fatal coronary heart disease [51], sudden cardiac death, heart failure, stroke, and other non-cardiac cardiovascular events adjudicated centrally as the underlying cause of death. Fatal cardiovascular disease events are defined based on temporal relationship to a documented event (e.g., hospitalization for myocardial infarction), or postmortem findings of an acute cardiovascular disease event.

Cardiovascular disease outcomes are ascertained primarily through surveillance for self-reported events, review of pertinent medical records, and ECG collection. Clinical events are ascertained in both arms only every 3 months during follow-up using a structured interview to minimize ascertainment bias. Deaths are investigated at any time the clinical site staff becomes aware of a potential death.

Blood samples are collected at randomization and at months 1, 3, 6, 12, then every 6 months until the close-out visit. Urine samples are collected at randomization and at months 1, 6, 12, then yearly through month 60. DNA is extracted from whole blood samples collected at randomization. The analytes measured and methods used to measure them are shown in Table 4.

SPRINT MIND—The primary outcome of the MIND component of SPRINT is all-cause dementia. This outcome is assessed using a screening battery and an extended cognitive assessment battery. Dementia incidence is assessed in SPRINT using a three-step process. All SPRINT participants undergo a cognitive function screening battery at baseline, 2 and 4 years of follow-up. In participants who score below screening thresholds, the Functional Assessment Questionnaire (FAQ) [58] is administered to a participant contact to identify functional impairment associated with low cognitive scores. An extended cognitive battery is then administered to all participants scoring >0 on the FAQ or a score of 0–1 on the delayed recall component of the Montreal Cognitive Assessment (MoCA) [59]. All participants who receive the extended cognitive battery are presented to an expert panel (composed of neurologists, neuropsychologists, and geriatricians with clinical expertise in the diagnosis of dementia) for adjudication of cognitive status. For participants who cannot be assessed in person at follow-up, we attempt to administer a telephone battery [60,61]. In instances where participants are unable to communicate by telephone, a pre-specified proxy contact is administered the Dementia Questionnaire [62]. Structural brain imaging in a subset of at least 640 participants is performed using MRI.

Quality Control

Steps to standardize measures include the use of the Central Lab and ECG Reading Center; use of standard forms, equipment, and procedures; training; and standard event definitions and event validation procedures. A central training session was held prior to the start of recruitment to train clinic investigators and staff in study procedures. A second central training session was held in March 2014. Clinical Center Network staff provide training sessions to newly hired staff in their respective clinical sites as turnover occurs. The Clinical Center Networks and Coordinating Center organize refresher training sessions using conference calls, webinars, and on-site training. The Measurement, Procedures, and Quality Control Subcommittee is responsible for ongoing quality control monitoring and quality assurance activities. On a quarterly basis, the Measurement, Procedures, and Quality Control subcommittee monitors quality control reports from the ECG Reading Center and Central Lab; it also monitors clinical site performance, and communicates issues regarding specific sites to the respective Clinical Center Networks for follow-up. The Clinical Center Networks track performance of clinical sites within their networks and conduct standardized site visits. Site visit reports are submitted to the Coordinating Center and evaluated by the Measurement, Procedures, and Quality Control subcommittee. Completeness of data collection, with a special focus on events ascertainment, was monitored by both the study and the Data Safety and Monitoring Board. Site-specific feedback was provided and improvement plans were required when necessary.

Statistical analysis, sample size, and power considerations

The primary analysis will use Cox proportional hazards regression to compare time to first occurrence of the primary cardiovascular disease composite endpoint between the randomized groups using all participants under the intention-to- treat principle and two-sided tests at the 5% level. The model will include an indicator for intervention arm as its sole predictor variable with clinical site at randomization as a stratifying factor. Follow-up time will be censored on the date of the last event ascertainment or at death. For the subgroup comparisons described above, we will add terms to the Cox model for the subgroup and the subgroup by treatment interactions and use a likelihood ratio test for the interaction at the 5% level with Hommel adjusted p-values. Other time-to-event data (e.g., incident chronic kidney disease) will be analyzed similarly. Mixed models will be used for continuous outcomes. Interim analyses will be performed on a periodic basis using O'Brien-Fleming boundaries [63].

Several sensitivity analyses are planned. These include inclusion of baseline variables that may modify treatment (e.g., the factors defining the pre-specified subgroups (possibly as continuous predictors), diastolic blood pressure, metabolic syndrome), exploration of missing data on our conclusions, and exploration of competing risks. The missing data analysis will include multiple imputation, an exploration of which variables predict missingness and their inclusion in analytic models, and exploration of several "worst-case" scenarios. Additional details are available in our protocol [35].

We assumed a 2-year recruitment period, a maximum follow-up of 6 years, and a loss to follow-up of 2%/yr. With the targeted 9250 participants, we calculated 88.7% power to

detect a 20% effect for our primary outcome, assuming a 2.2%/yr event rate in the Standard Group. We calculated 81.9% power for a 20% effect for the primary outcome in people with chronic kidney disease at baseline assuming a 4%/yr event rate, 84.5% power to detect a 25% effect for the primary outcome among those ≥ 75 yr. old at baseline assuming a 3.5%/yr event rate. We have 96.3% power to detect a 20% effect rate for incident dementia assuming an event rate of 3.1%/yr.

Safety Monitoring

All sites monitor and report serious adverse events to the Coordinating Center. An serious adverse event is an event that is fatal or life threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalization, or is an important medical event that the investigator judges to be a significant hazard or harm to the participant and may have required medical or surgical intervention to prevent one of the other events listed above [64,65]. Because SPRINT is using FDA-approved anti-hypertensive medications with well documented side effect profiles, adverse events that do not meet the severity threshold of an serious adverse event are not generally collected. However, a specific list of expected events that could be related to the study intervention is being monitored to assess safety. These include emergency department visits for injurious falls, syncope, bradycardia, hypotension, and electrolyte disturbances. Sites are notified of alert values for electrolytes (sodium ≤132 or >150 mEq/L; potassium <3.0 or >5.5 mEq/L) and serum creatinine (increase by at least 50% from the last study value to a level ≥1.5 mg/dL). Sites are also notified of participants with moderate or higher depressive symptoms on the PHQ-9 and participants who are adjudicated as probable dementia. Electrocardiograms are flagged for clinician review if the heart rate is <40 or >120 beats per minute or the ECG suggests acute ischemia, ventricular arrhythmias, or new onset atrial fibrillation. Clinically important findings on brain MRI are reported directly to the site physician investigator and study coordinator. Blinded reports of serious adverse events and safety events are monitored by the Safety Committee monthly and unblinded reports are reviewed by the Data Safety and Monitoring Board semiannually.

Web-based trial management

Participant and visit-specific form sets are created dynamically, and data are entered directly into web-based forms and saved to the database. The web-based system allows real-time data entry checks as the data are entered, including verification of eligibility prior to randomization, and range and logic checks on individual data items. The data are immediately available for dynamic reports for study management. The website is also used to manage the outcome adjudication process [66].

Results

Description of the SPRINT sample

Descriptive statistics can be seen in Table 5. 9361 participants volunteered to participate and met the inclusion criteria, enrolled at 102 clinics within the 5 Clinical Center Networks over a 2.3-year period, and will be followed for 4–6 years. Among our sample, 3333 (35.5%) were women, 2636 (28.2%) were at least 75 years old, 2648 (28.3%) had chronic kidney

disease, and 1877 (20.1%) had prior cardiovascular disease. Our sample is racially and ethnically diverse with 2802 (29.9%) Black, 984 (10.5%) Hispanic, 5399 (57.7%) white, and 176 (1.9%) participants of other races/ethnicities. The baseline mean systolic and diastolic blood pressures were 139.7 (15.6 (SD)) and 78.1 (11.9) mm Hg. We recruited 2914 for SPRINT MIND and 667 for SPRINT MIND MRI.

Ancillary Studies

Ancillary Studies utilizing the SPRINT population, biospecimens, and rich data base are strongly encouraged, provided these studies do not place undue burden on answering the main study question. As of March 2014, seven ancillary studies have begun. Topics include ambulatory blood pressure, arterial stiffness, cardiac structure and function, atherosclerosis progression in chronic kidney disease, cognitive function and brain structure in chronic kidney disease, kidney tubule damage and dysfunction, as well as genetic influences on nephropathy. Additional ancillary studies are in various stages of development.

Discussion

SPRINT was jointly developed by scientific staff at the National Institutes of Health (NIH) and the SPRINT investigators whose efforts are supported by contracts from the NIH awarded via the peer-reviewed competitive process. As SPRINT was developed, key decisions were made in an attempt to balance the trial's scientific goals with the resources available to conduct the study. First, we decided to use the ACCORD Blood Pressure trial as a model for our intervention as it had already been proven to be safe and successful in achieving our systolic blood pressure targets for the Intensive and Standard Groups. It also facilitates comparison of the effect of this intervention on complementary populations. Our specific target for recruitment of persons ≥75 years old was established to explore the results of HYVET [24] which while testing a higher target (systolic blood pressure <150 mm Hg) than the Standard Group in SPRINT suggest that benefit of treatment might be larger in persons ≥80 years than our hypothesized 20% reduction in cardiovascular disease events. HYVET also had an intriguing but non-significant impact on cognition as the study was stopped early [67]. In addition, recent guidelines [68,69] have questioned the ideal systolic blood pressure target for older individuals. ACCORD excluded individuals with serum creatinine levels above 1.5 mg/dl and individuals over the age of 80 years. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial, which compared a systolic blood pressure treatment target of <130 mm Hg to a target of 130–149 mm Hg in participants with a recent lacunar stroke, showed a non-significant reduction in recurrent stroke in the group randomized to the lower target [70]. Our specific goal for participants with chronic kidney disease was to obtain additional information on whether more intensive blood pressure goals would reduce cardiovascular events in these older patients with chronic kidney disease. Two additional trials in the chronic kidney disease population (African American Study of Kidney Disease and Hypertension (AASK) and Modification of Diet in Renal Disease (MDRD)) tested the effects of blood pressure targets that are higher than that being used for the SPRINT intensive treatment group and excluded older participants [33,71]. In addition, AASK and MDRD specifically targeted kidney outcomes but not cardiovascular disease outcomes. The trial evidence is equivocal about whether hypertension therapy reduces the

risk of age-related cognitive decline and dementia [67], both are recognized as very important public health problems. SPRINT offers an efficient vehicle to address important questions related to cardiovascular, kidney, and dementia prevention.

To further enhance the value of SPRINT, we address possible adverse effects of blood pressure lowering using measures of sexual functioning, falls, and fear of falls. In addition, orthostatic blood pressure values and emergency department visits are tracked, as well as hospitalizations and major clinical events. Finally, our events ascertainment process begins with scheduled participant (or surrogate) interviews every three months in order to minimize differential ascertainment. We exceeded our overall recruitment target (9361 actual vs. 9250 planned) and our target for minority recruitment (42.3% actual vs. 40% planned). However, we did not meet our recruitment targets for enrolling women (35.6% actual vs. 50% planned), participants above 75 years old (28.2% actual vs. 35% planned), participants with chronic kidney disease (28.3% actual vs. 46% planned), and participants with cardiovascular disease (20.1% actual vs. 40% planned). Although subgroup enrollment was monitored carefully during the recruitment phase, it proved difficult to enroll the number of participants initially proposed for each of the subgroups while maintaining overall recruitment goal rates. Unless event rates are higher than expected or follow-up is extended, the lower than expected enrollment for these subgroups may result in diminished power to explore the primary hypothesis among women, persons above 75 years, and persons with chronic kidney disease.

With the successful completion of enrollment and preliminary safety of the intervention well-established, the SPRINT team is focused on participant retention, ensuring adherence to study medications and the assigned systolic blood pressure targets, ensuring high quality data collection, monitoring safety, and collecting and adjudicating trial endpoints. Follow-up is scheduled to end in the Fall of 2016. We look forward to sharing the results of this trial with the scientific community in the Fall of 2017 via papers and presentations. We expect that SPRINT will inform the clinical management of hypertension in a diverse population and potentially our ability to prevent outcomes of major public health interest.

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For a full list of contributors to SPRINT, plase see the supplementary acknowledgement list.

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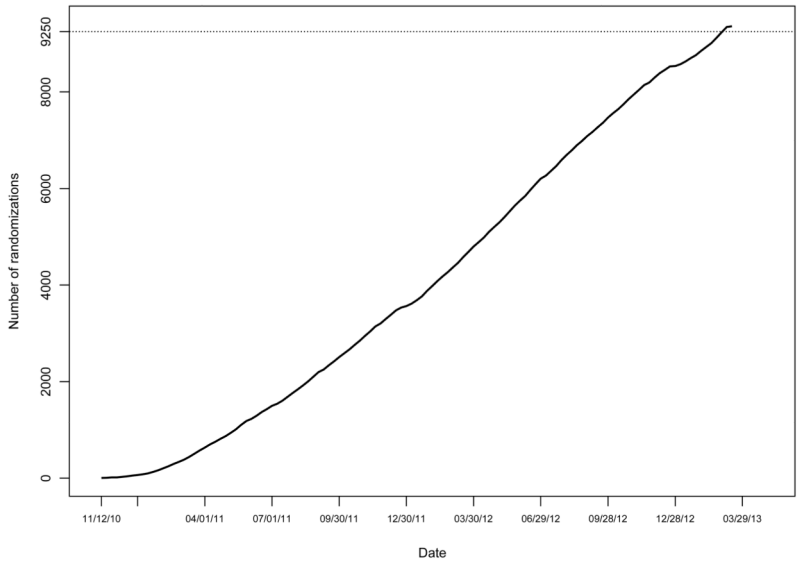

Figure 1.
Overall cumulative recruitment in SPRINT to total of 9361.

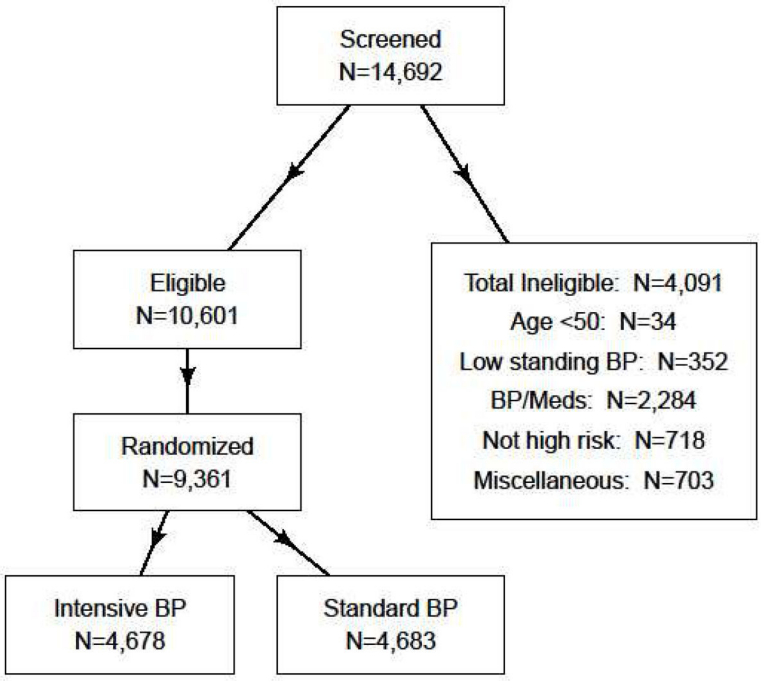

Figure 2.

CONSORT Diagram. Inclusion/exclusion criteria were applied in the order asked and are described in greater detail in Table 1 and Supplementary Table 1. BP/Meds refers to the allowable systolic blood pressure depending on the number of anti-hypertensive medications taken. High-risk factors included ≥75 years of age, history of clinical or subclinical cardiovascular disease other than stroke, chronic kidney disease, or having a ≥ 15% 10-year Framingham risk score for cardiovascular disease. Participants without at least one were excluded. Miscellaneous reasons for exclusion include a known secondary cause of hypertension that causes safety concern (N=17), significant proteinuria within the past 6 months (N=67), history of diabetes (N=116) or stroke (N=49), end-stage renal disease or polycystic kidney disease (N=7), glomerulonephritis treated with immunosuppressive therapy (N=1), symptomatic heart failure within last 6 months or left ventricular ejection fraction <35% (N=15), expected survival less than three years (N=5), cancer diagnosed within the last two years (N=33), living in the same household as another SPRINT participant (N=11), organ transplant (N=2), indication for a specific blood pressure medication that is not currently being taken without documented intolerance (N=16), cardiovascular event, procedure, or hospitalization for unstable angina within the last 3 months (N=6), factors likely to limit adherence (N=319), participation in another trial (N=30), unintentional weight loss > 10% in last 6 months (N=8), and pregnancy, trying to become pregnant, or of child-bearing potential and not practicing birth control (N=1).

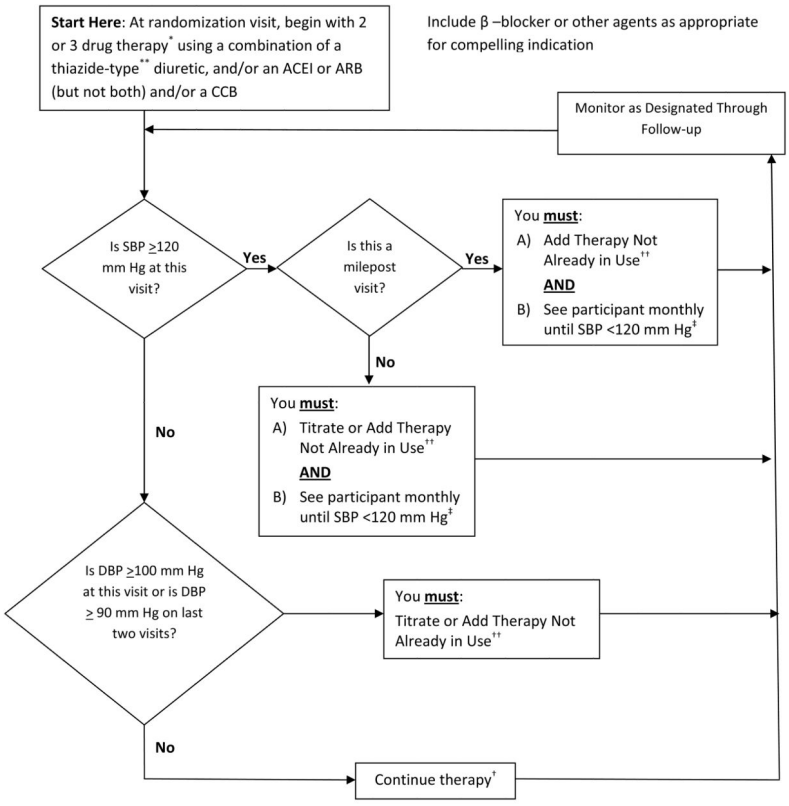

Figure 3.

Treatment algorithm for intensive group (target systolic blood pressure (SBP) < 120 mm Hg)

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

** May use loop diuretic for participants with advanced chronic kidney disease

† 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

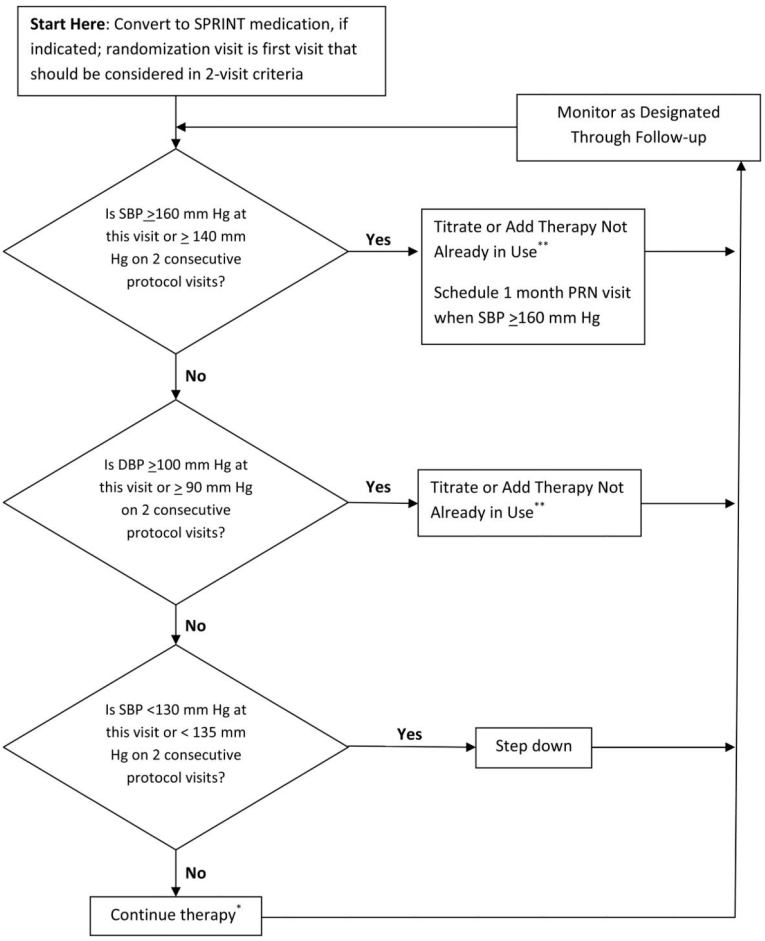

Figure 4.

Treatment algorithm for standard group (Target systolic blood pressure (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

Table 1

SPRINT inclusion criteria. To be eligible, a participant must meet 1, 2, and 3.

General Inclusion Criteria

1. ≥50 years old
2. Systolic blood pressure (SBP)
   - 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. At Risk (one or more of the following):
   - **a.** Presence of clinical or subclinical cardiovascular disease (CVD) other than stroke
     - **i.** 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
     - **ii.** 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.** Chronic kidney disease, defined as estimated glomerular filtration rate 20 – 59 ml/min/1.73m^2
   - **c.** Framingham Risk Score for 10-year CVD risk ≥ 15% based on clinical features and laboratory results within the past 12 months for lipids
   - **d.** Age ≥75 years.

Targeted High-Risk Subgroup Inclusion Criteria

Chronic kidney disease: Qualifying chronic kidney disease was defined by estimated glomerular filtration rate, determined at baseline between 20 and 59 ml/min/1.73m^2, inclusive, based on the 4-variable MDRD equation.
Senior: Participants who were at least 75 years old at the baseline visit.
Cardiovascular disease: Participants who met any of the inclusion criteria listed in 4 or 5 above at baseline.

Table 2

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	1–2
	Amiloride/HCTZ*	5/50mg	5/50	1
	HCTZ*	12.5, 25 mg	12.5 – 50	1
Ace Inhibitor (ACEI)	Lisinopril	5mg, 10mg 20mg, 40mg	5–40 mg	1
ACEI / Diuretic	Lisinopril/HCTZ*	20/12.5 mg, 20/25mg	10–40 / 12.5–50	1
Angiotensin Receptor Blocker (ARB) ARB / Diuretic	Valsartan*	80mg, 160mg, 320mg	80–320 mg	1–2
	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
	Metoprolol ER*	25mg, 50mg, 100 mg, 200 mg	50–200	1
	Atenolol	25mg, 50mg, 100mg	25–100 mg	1
Beta Blocker / Diuretic	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
	Clonidine patch*	0.1mg, 0.2mg, 0.3mg	0.1–0.3	1 wkly
Alpha Blockers	Doxazosin	1mg, 2mg, 4mg, 8mg	1–16 mg	1
Potassium Supplements	KCL tablets	20mEq	20–80 mEq	1–2

Class	Drug	Available Strengths	Usual Dose Range / day	Usual Daily Frequency
	KCL oral solution (10%)	20mEq/15ml	20–80 mEq	1–2

* Medications provided by the study for restricted use after consultation with and approval from a designated representative for each Clinical Center Network.

Table 3

Classification of myocardial infarction in SPRINT [51]. Definite indicates definite myocardial infarction; Probable, probable myocardial infarction; Possible, possible myocardial infarction; and No, no myocardial infarction. Classification of case is at highest level allowed by combinations of 3 characteristics (cardiac signs and symptoms, ECG findings, biomarkers).

	Biomarker findings							
	Cardiac symptoms or signs present				Cardiac symptoms or signs absent			
ECG Findings*	Diagnostic†	Equivocal†	Missing†	Normal†	Diagnostic	Equivocal	Missing	Normal
Evolving diagnostic	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite
Positive	Definite	Probable	Probable	No	Definite	Probable	Possible	No
Nonspecific	Definite	Possible	No	No	Definite‡	Possible	No	No
Negative for evolving ischemia	Definite	Possible	No	No	Definite‡	No	No	No

*See Tables 2–4 of Leupker et al[51].

†Biomarkers include CK, CK-MB, CK-MBm, and troponin (cTn) with diagnostic value increasing from CK to CK-MB to CK-MBm to troponin. Diagnostic is at least one positive biomarker (≥2×ULN) in an adequate set of biomarkers showing a rising or falling pattern in the setting of clinical cardiac ischemia and the absence of non-cardiac causes of biomarker elevation. Equivocal is present but not diagnostic.

‡In absence of diagnostic troponin, downgrade to possible.

Table 4

Laboratory Method Principles by Analyte*.

Analyte	Method Principle
Na, K, Cl, CO_2	Ion-specific electrode
BUN, creatinine (plasma and urine)	Enzymatic
Glucose	Hexokinase
Cholesterol	Cholesterol oxidase
High-density lipoprotein cholesterol	Magnesium-dextran sulfate precipitation followed by cholesterol oxidase
Calculated low-density lipoprotein cholesterol	Friedewald equation
Total triglycerides	Lipase (glycerol-blanked)
Albumin (urine)	Nephelometry

*Analytes in plasma unless otherwise specified.

Table 5

Baseline characteristics of the 9361 SPRINT participants, presented as N (%) or mean (SD).

Characteristic	SPRINT N=9361	Intensive (N=4678)	Standard (N=4683)
Gender (Female)	3333 (35.6)	1684 (36.0%)	1649 (35.2%)
Age (years)	67.9 (9.4)	67.9 (9.4)	67.9 (9.5)
Race/Ethnicity			
Black	2802 (29.9)	1379 (29.5)	1423 (30.4)
Hispanic	984 (10.5)	503 (10.8)	481 (10.3)
White	5399 (57.7)	2698 (57.7)	2701 (57.7)
Other	176 (1.9)	98 (2.1)	78 (1.7)
Age ≥75 years	2636 (28.2)	1317 (28.2)	1319 (28.2)
Age among ≥75 (years)	79.8 (4.0)	79.8 (3.9)	79.9 (4.1)
Baseline blood pressure (mm Hg)			
Systolic	139.7 (15.6)	139.7 (15.8)	139.7 (15.4)
Diastolic	78.1 (11.9)	78.2 (11.9)	78.0 (12.0)
Baseline chronic kidney disease (estimated glomerular filtration rate<60)	2648 (28.3)	1331 (28.4)	1317 (28.1)
Serum creatinine (mg/dL)	1.07 (0.34)	1.07 (0.34)	1.08 (0.34)
estimated glomerular filtration rate (mL/min/1.73 m^2)	71.8 (20.6)	71.8 (20.7)	71.7 (20.5)
estimated glomerular filtration rate<45 mL/min/1.73 m^2	890 (9.5)	446 (9.5)	444 (9.5)
Urine albumin/creatinine (mg/g)	42.6 (166.3)	44.1 (178.7)	41.1 (152.9)
Prior cardiovascular disease	1877 (20.1)	940 (20.1)	937 (20.0)
Total cholesterol (mg/dL)	190.1 (41.2)	190.2 (41.4)	190.0 (40.9)
Fasting HDL-C (mg/dL)	52.9 (14.5)	52.9 (14.3)	52.8 (14.6)
Fasting LDL-C (mg/dL)	112.4 (35.1)	112.6 (35.4)	112.2 (34.8)
Fasting total triglycerides (mg/dL)	125.9 (90.5)	124.8 (85.8)	127.1 (95.0)
Fasting plasma glucose (units)	98.8 (13.5)	98.8 (13.7)	98.8 (13.4)
Statin use	4052 (43.3)	1977 (42.3)	2075 (44.3)
Aspirin use	4756 (51.0)	2405 (51.6)	2351 (50.4)
10-Year Framingham risk (%)	20.1 (10.9)	20.1 (10.9)	20.1 (10.8)
Body mass index (kg/m^2)	29.9 (5.8)	29.9 (5.8)	29.8 (5.7)
Smoking			
Never smoker	4196 (45.0)	2097 (45.0)	2098 (45.0)
Former smoker	3898 (41.8)	1929 (41.4)	1969 (42.2)
Current smoker	1239 (13.3)	639 (13.7)	600 (12.9)
Gait speed (m/s) (only for age ≥75 yrs)	0.87 (0.22)	0.87 (0.22)	0.87 (0.21)
Logical Memory I	19.1 (4.9)	19.1 (4.9)	19.2 (4.9)
Logical Memory II	8.2 (3.4)	8.1 (3.4)	8.2 (3.3)
Digit Symbol	50.8 (15.3)	50.7 (15.3)	50.8 (15.4)
Montreal Cognitive Assessment (MoCA)	22.9 (4.1)	22.9 (4.1)	22.9 (4.1)