Potential Deaths Averted and Serious Adverse Events Incurred from Adoption of the SPRINT Intensive Blood Pressure Regimen in the U.S.: Projections from NHANES

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Abstract

Background—The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated a 27% reduction in all-cause mortality with a systolic blood-pressure (SBP) goal of <120 mmHg versus <140 mmHg among U.S. adults at high cardiovascular disease (CVD) risk but without diabetes,

stroke, or heart failure. To quantify the potential benefits and risks of SPRINT intensive goal implementation, we estimated the deaths prevented and excess serious adverse events (SAEs) incurred if the SPRINT intensive SBP treatment goal was implemented in all eligible U.S. adults.

Methods—SPRINT eligibility criteria were applied to the 1999–2006 National Health and Nutrition Examination Survey and linked with the National Death Index through December 2011. SPRINT eligibility included age 50 years, SBP of 130–180 mmHg (depending on the number of antihypertensive medications being taken), and high CVD risk. Exclusion criteria were diabetes, history of stroke, >1 gram of proteinuria, heart failure, estimated glomerular filtration rate < 20 ml/min/1.73m^2, or dialysis. Annual mortality rates were calculated by dividing the Kaplan-Meier 5-year mortality by 5. Hazard ratios for all-cause mortality and heart failure and absolute risks for SAEs in SPRINT were used to estimate the number of potential deaths and heart failure cases prevented and SAEs incurred with intensive SBP treatment.

Results—The mean age was 68.6 years and 83.2% and 7.4% were non-Hispanic white and non-Hispanic black, respectively. The annual mortality rate was 2.20% (95%CI 1.91%–2.48%) and intensive SBP treatment was projected to prevent about 107,500 deaths per year (95%CI 93,300–121,200) and give rise to 56,100 (95%CI 50,800–61,400) episodes of hypotension, 34,400 (95%CI 31,200–37,600) episodes of syncope, 43,400 (95%CI 39,400–47,500) serious electrolyte disorders, and 88,700 (95%CI 80,400–97,000) cases of acute kidney injury per year. The analysis of extremes approach indicated that the range of estimated lower and upper bound number of deaths prevented per year with intensive SBP control was 34,600 to 179,600. Intensive SBP control was projected to prevent 46,100 (95%CI 41,800–50,400) cases of heart failure annually.

Conclusions—If fully implemented in eligible U.S. adults, intensive SBP treatment could prevent about 107,500 deaths per year. A consequence of this treatment strategy, however, could be an increase in SAEs.

Introduction

High blood pressure (BP) is the leading modifiable cardiovascular disease (CVD) risk factor world-wide.[1] Observational studies show a monotonic increase in risk of CVD beginning at a systolic blood pressure (SBP) of 115 mmHg.[2] However, the optimal SBP threshold for antihypertensive medication initiation and goal attainment is unclear. Current U.S. recommendations are a SBP threshold of 140 or 150 mmHg for initiation of antihypertensive medication, depending on age and other co-existing conditions.[3] Until recently, randomized trials did not provide definitive evidence supporting lower SBP goals in high-risk sub-populations.[3–5]

The Systolic Blood Pressure Intervention Trial (SPRINT) was designed to determine whether lowering SBP to an intensive goal of < 120 mmHg versus the standard goal of <140 mmHg resulted in reduced CVD risk in high-risk patients without a history of diabetes, stroke, or heart failure.[6] SPRINT achieved a mean SBP of 121 mmHg in the intensive treatment arm and 136 mmHg in the standard treatment arm, resulting in a 27% reduction (hazard ratio[HR] 0.73 95%CI 0.60–0.90) in all-cause mortality.[7] Given the mortality rate observed in SPRINT, only 90 SPRINT-eligible patients need to be treated to an intensive SBP goal to prevent one death from any cause after 3.26 years.[7] However, participants in the intensive SBP treatment group experienced a higher incidence of treatment-related serious adverse events (SAEs) and the number-needed-to-harm (NNH) for any SAE definitely or probability related to intensive treatment was 45.

Implementation of SPRINT-based intensive SBP goals has the potential to greatly reduce mortality in high CVD risk patients living in the U.S. and worldwide. In order to quantify the potential benefits and risks of SPRINT intensive goal implementation, we estimated the deaths prevented and excess SAEs incurred if the SPRINT intensive SBP goal was implemented in all eligible U.S. adults.

Methods

Study Population

Data were drawn from the National Health and Nutrition Examination Survey (NHANES), a multistage stratified probability sample of non-institutionalized U.S. adults conducted by the National Center for Health Statistics (NCHS).[4] To provide sufficient sample size, data were pooled from the 1999–2000, 2001–2002, 2003–2004, and 2005–2006 NHANES cycles.[8] Participants who completed a medical evaluation at the NHANES mobile examination center, were 20 years of age or older and had complete information on SBP measurements and use of antihypertensive medication (n = 17,746) were included. From the 8,327 NHANES participants who were   50 years old, 4,249 met SPRINT SBP criteria (Figure 1). Next, participants who did not meet the high CVD risk criteria (n=895) or who had diabetes (n=868), history of stroke (n=263), proteinuria > 1 g/day (n=53), heart failure (n=228), estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73 m^2 or end-stage renal disease on dialysis (n=30) were excluded. After these exclusions, a total of 2,185 SPRINT-eligible participants were included in the current analyses. All participants provided written informed consent and the NCHS institutional review board approved each NHANES cycle.

Baseline Data Collection

In each NHANES cycle, data were collected via a medical evaluation and participant interviews. The participant interview collected self-reported data on age, race/ethnicity, sex, smoking status, history of a diagnosis of diabetes mellitus, heart failure, hypertension, myocardial infarction, angina, coronary heart disease (CHD), or stroke as well as receipt of dialysis in the past 12 months or the use of antihypertensive or anti-diabetes medication.

The NHANES medical evaluation included measurements of height and weight that were used to calculate body mass index (BMI). A blood sample was collected for measurement of

serum creatinine and glucose, and glycosylated hemoglobin (hemoglobin A1c). Urine albumin and creatinine concentrations were analyzed from spot, random urine samples. Diabetes was defined by a prior diagnosis, excluding during pregnancy, with concurrent use of insulin or oral hypoglycemic medication, or a hemoglobin A1c 6.5%, non-fasting glucose 200 mg/dL, or fasting glucose 126 mg/dL. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR.[9] NHANES participants were asked to bring all prescription medications taken in the past two weeks to their NHANES medical evaluation. Trained study personnel reviewed the pill bottles and medication names were recoded into medication classes according to their generic equivalents. Use of antihypertensive medication was defined by self-report and report of taking one or more classes of antihypertensive medication identified through the pill bottle review.

Baseline BP measurement

Using an appropriately sized cuff, BP was measured with participants seated after five minutes of rest using a mercury sphygmomanometer by a trained study physician. SBP and diastolic BP (DBP) were defined as the mean of three BP measurements taken one-minute apart.

Death Ascertainment

Mortality follow-up for the NHANES participants was available through December 31, 2011. To identify vital status, probabilistic matching was used to link NHANES participants with the National Death Index. Matching was based on 12 identifiers for each participant, including data of birth, sex, and Social Security Number. The follow-up period for each participant was calculated as the interval between their NHANES evaluation and the data of death or December 31, 2011, for participants who did not die.

Statistical Analysis

Annual mortality rates in the SPRINT-eligible population overall and within subgroups defined by sex, age (< 75, and 75 years), race/ethnicity, history of CHD, SBP groups (132, 133–144, and 145 mmHg; pre-specified SBP strata defined in SPRINT), and by eGFR 20–59 ml/min/1.73 m^2 were calculated. The Kaplan-Meier method was used to calculate the 5-year survival probability, S(5), which was then used to calculate the 5-year mortality, F(5), which is equal to 1-S(5), which amounts to the 5-year cumulative incidence (under the exponential model approximation). The annual mortality rate was then approximated by dividing this probability by 5. Population estimates for annual deaths in the overall population meeting the SPRINT eligibility criteria and in subgroups was determined by multiplying the population size for that group or subgroup by their respective annual all-cause mortality rate. The projected annual number of deaths that would occur if SPRINT intensive SBP goals were fully implemented was determined by multiplying the observed annual mortality rate and its 95% confidence intervals in the overall SPRINT-eligible NHANES population by 0.73, the observed HR for all-cause mortality with intensive SBP treatment in SPRINT compared to standard SBP treatment (i.e., usual care).[7] This was done for the overall population and within subgroups defined by sex, age (< 75, and 75 years), race/ethnicity, history of CHD, SBP groups (132, 133–144, and 145 mmHg) and

moderate stage chronic kidney disease (defined by SPRINT as eGFR 20–59 ml/min/1.73 m^2). Deaths postponed were then calculated as the difference between total and expected deaths with full implementation of intensive SBP treatment. Because the oscillometric blood pressure measurement methods used in SPRINT by research personnel may result in a lower mean SBP than observed using manual auscultatory method by physicians in NHANES, we performed a sensitivity analysis including the NHANES population with a 10 and 20 mm Hg higher SBP than the SPRINT entry criteria (e.g., 140–190 mmHg and 150–200 versus 130–180 mm Hg for those on 0–1 antihypertensive medications, respectively.[10] Since heart failure was the component of the primary composite outcome in SPRINT that was statistically significantly different between treatment groups, we also estimated the number of new cases of heart failure prevented by multiplying the HR for incident heart failure observed in SPRINT (0.62) by the number of heart failure cases expected with standard SBP treatment. The number of heart failure cases expected with standard SBP treatment was calculated by taking the annual rate of rate incident heart failure observed in SPRINT (0.67%/year) by the SPRINT-eligible NHANES population size and it's 95% confidence interval overall and within subgroups.

SAEs were defined in SPRINT as an event that was fatal or life-threatening that resulted in clinically significant or persistent disability, required or prolonged a hospitalization, or judged by the investigator to represent a clinically significant hazard or harm to the participant that might require intervention to prevent another SAE. To project the number of SAEs expected with intensive SBP treatment, we multiplied the absolute risk difference for each SAE of interest reported in the main SPRINT manuscript that were statistically significantly different between intensive and standard SBP treatment arms (i.e., hypotension, syncope, bradycardia, electrolyte abnormality, and acute kidney injury) by the number of U.S. adults meeting the SPRINT eligibility criteria.[7] This was done for these SAEs overall and for these SAEs classified as possibly or definitely related to the intervention. This number was then divided by 3.26 (the median follow-up in SPRINT) to yield the projected SAEs incurred per year. To account for the uncertainty in treatment effects from SPRINT, sensitivity analyses were conducted using the analysis-of-extremes methodology, where the upper and lower confidence bounds of the treatment effects for all-cause mortality, heart failure, and SAEs were used.[11, 12] Since confidence bounds were not available for SAEs in SPRINT main results publication, we calculated 95% confidence intervals for SAEs from the p value (Supplemental Table 1). The number-needed-to-treat (NNT) was calculated for all-cause mortality and heart failure and the NNH was calculated for each individual SAE by taking the reciprocal of the absolute reduction in risk overall and within subgroups. SUDAAN 10.1 (Research Triangle Institute, Research Triangle Park, NC) was used for all analyses to account for the complex sampling design of NHANES.

Results

For the years between 1999 and 2006, an estimated 18.1 million (95%CI 16.4–19.8 million) U.S. adults met the SPRINT eligibility criteria, including 7.4 million (95%CI 6.5–8.3 million) and 10.7 million (95%CI 9.9–11.5 million) who were taking and not taking antihypertensive medication, respectively. The mean age in the sample was 68.6 years with

32.0% age 75 years or older (Table 1). Over half were men (53.8%) while 83.2% were non-Hispanic white and 7.4% non-Hispanic black and 3.0% Mexican American.

The overall observed annual mortality of the study population was 2.20% (95%CI 1.91%–2.48%), resulting in 398,200 projected deaths per year (95%CI 345,700–448,900) with standard SBP treatment (i.e., usual care) (Table 2). Based on the HR for all-cause mortality observed in SPRINT, intensive SBP treatment was projected to decrease annual mortality to 1.61% (95%CI 1.39%–1.81%), resulting in 290,700 deaths per year (95%CI 252,400–327,700 deaths). We estimate that 107,500 deaths (95%CI 93,300–121,200 deaths) could be prevented annually with full implementation of intensive SBP treatment in this group of SPRINT-eligible U.S. adults. After accounting for the uncertainty of the HR for all-cause mortality in SPRINT in the analysis of extremes sensitivity analysis, the range of estimated lower and upper bound number of deaths prevented per year with intensive SBP treatment was 34,600 to 179,600 (Supplemental Table 2). In sensitivity analyses, 84,000 (95%CI 73,600–95,700) and 62,700 (95% CI 55,400–71,300) deaths could be averted with intensive SBP treatment when we required SBP to be 10 mm Hg and 20 mm Hg higher than the SPRINT entry criteria, respectively (Supplemental Figures 1 and 2 and Supplemental Tables 3–6).

The observed annual mortality among the SPRINT-eligible population taking antihypertensive medication was 2.03% (95%CI 1.58–2.49) (Table 3). Within this group, intensive SBP treatment could reduce annual mortality to 1.48% per year (95%CI 1.15%–1.82%) resulting in a projected decrement of 40,600 deaths per year (95%CI 31,600–49,800). Among those SPRINT-eligible and not currently taking antihypertensive medication, the observed annual mortality was 2.31% (95%CI 1.89%–2.73%). Intensive SBP treatment was projected to prevent 66,700 deaths per year among this group (95%CI 54,600–78,900).

The highest annual mortality rate was noted for SPRINT-eligible U.S. adults age 75 years, among whom intensive SBP treatment could prevent 67,300 (95%CI 58,600–77,200) deaths per year. SPRINT-eligible U.S. adults with eGFR 20–59 ml/min/1.73 m^2 had annual mortality rates of 3.02% (95%CI 2.18%–4.16%) if taking antihypertensive medication and 2.88% (95%CI 2.15–3.84) if not taking antihypertensive medication, yielding total annual deaths of 121,000 (95%CI 97,200–149,700). Intensive SBP treatment among SPRINT-eligible U.S. adults with eGFR 20–59 ml/min/1.73 m^2 was projected to prevent 32,700 (95%CI 26,200–40,400) deaths per year.

Intensive SBP treatment was projected to prevent 46,100 (95%CI 41,800–50,400) new cases of heart failure annually (Supplemental Table 7). After accounting for uncertainty in both the estimates for the population size and treatment effect on incident heart failure, intensive SBP treatment is projected to prevent between 17,600 and 73,000 new cases of heart failure per year.

Among SPRINT-eligible U.S. adults overall, standard SBP treatment (i.e., usual care) could lead to 77,800 (95%CI 70,500–85,100) episodes of hypotension, 94,100 (95%CI 85,300–103,000) episodes of syncope, 128,500 (95%CI 116,400–140,600) electrolyte abnormalities,

and 139,400 (95%CI 126,300–152,500) cases of acute kidney injury per year (Table 4 and Figure 2). In this same group, intensive SBP treatment is projected to result in 56,100 (95%CI 50,800–61,400) additional episodes of hypotension, 34,400 (95%CI 31,200–37,600) additional episodes of syncope, 43,400 (95%CI 39,400–47,500) additional electrolyte abnormalities, and 88,700 (95%CI 80,400–97,000) additional cases of acute kidney injury per year. The analysis-of-extremes sensitivity analyses for SAEs are shown in Supplemental Table 8.

Discussion

In the current analysis, we project that about 107,500 deaths could be averted annually if an intensive SBP target goal of < 120 mmHg were to be adopted among all U.S. adults meeting the SPRINT eligibility criteria. To provide context, this number represents nearly 20% of the 614,348 Americans who died of heart disease in 2014.[13] Moreover, projections from the current study indicate a similar number of deaths could be prevented with intensive SBP treatment in eligible US adults as another public health strategy of dietary salt reduction in the entire US adult population.[14] Benefits of intensive SBP treatment were more pronounced in high risk subgroups such as those age   75 years. Intensive SBP treatment was also projected to prevent about 46,100 new cases of heart failure per year. These benefits are tempered by a projected increase in SAEs, including about 56,100 additional episodes of hypotension, 88,700 cases of acute kidney injury, 34,400 episodes of syncope, and 43,400 episodes of electrolyte abnormalities.

The magnitude of the potential benefit estimated can be conceptualized in practical terms by recognizing that the NNT from SPRINT to prevent one death from any cause was 90 over 3.26 years.[7] While varying assumptions could change our overall estimate, the combination of a low NNT (i.e., 90 over 3.26 years) and the large number of US adults meeting the SPRINT eligibility criteria supports the contention that an impact in the range of 100,000 deaths averted per year is realistic. Few other medical interventions are currently available that could have such a large and immediate public health impact on broad sectors of the U.S. adult population. Adding to the evidence supporting intensive SBP target goals in the general population, a recent meta-analysis of 34 BP lowering trials comparing intensive versus standard BP lowering including SPRINT found that the direction of effect was consistent across the component trials, and that overall more intensive SBP lowering significantly reduced risk of CVD events and stroke compared to standard SBP lowering.[15]

Intensive BP treatment involves the potential risk of SAEs, especially in the elderly. Both the relative and absolute CVD and all-cause mortality risk reductions were greater in SPRINT participants 75 years of age or older, regardless of frailty status at baseline.[16] The HR among participants over age 75 at entry was 0.67 for all-cause mortality, and, based on the 3-year interval of the trial, only 27 patients would need to be treated with the intensive SBP control to prevent the primary SPRINT outcome of CVD, while treatment of 41 people would prevent a death.[16]

SPRINT provided detailed estimates of SAEs, virtually all of which were either without lasting consequence or reversible with dose de-escalation. Even in participants age 75 and

older, SAEs related to hypotension were only slightly increased in the intensive group - an excess that did not reach statistical significance.[16] Together with past results from the Hypertension in the Very Elderly Trial (HYVET) and the Systolic Hypertension in the Elderly Program (SHEP), the SPRINT results in elderly participants support a recommendation of the same BP treatment goals in young adults and most elderly patients.[17, 18] At the same time, neither SPRINT nor NHANES studied institutionalized elderly patients; intensive goals may not be appropriate in such patients until more evidence emerges.

Reduction in CVD risk factor levels through primary and secondary prevention have accounted for the majority of the 80% decline in CVD deaths in the U.S. and many other countries over the last several decades.[19, 20] Recently, however, it appears that the decline in CVD in the U.S. has slowed.[21] More aggressive use of the available safe, effective, and inexpensive antihypertensive medications to reduce SBP to < 120 mmHg among eligible U.S. adults may restore the downward trend in CVD mortality that has transformed adult health in the U.S. over the last 50 years.

Intensive SBP treatment in patients with diabetes yielded more equivocal evidence in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial. Therefore, there is uncertainty as to whether the benefits observed in SPRINT extend to patients with diabetes.[4] However, a recent meta-analysis including ACCORD and other BP lowering trials in diabetes patients estimated a significant CVD and all-cause mortality reductions with lower SBP target goals in patients with diabetes, with no evidence of diminished risk reductions below 130 mmHg.[22] On the contrary, another meta-analysis of BP trials found an attenuation of the treatment effect in people with diabetes when SBP was lowered to < 130 mmHg.[23] More definitive evidence on the role of intensive BP treatment in patients with diabetes, with outcome definitions more similar to SPRINT, is urgently needed.

Implementation of the SPRINT intensive regimen will require overcoming a number of obstacles. Because SPRINT was a practice-based trial and recruited patients from clinics, it is unclear how likely intensive SBP goals will be achieved among population-based free-dwelling adults. It is likely that an additional investment will be required from providers and patients (e.g., more frequent clinic visits, lab testing and additional medications) to produce the mean SBP change achieved in SPRINT (14.8 mmHg after one year of treatment). Integrated health systems such as Kaiser Permanente of Northern California are already achieving control rates of > 90% for SBP and DBP targets goals of <140/90 mmHg.[24, 25] However, consistent with the history of implementing evidence from virtually any new trial that substantially challenges established practice, reluctance to implement an SBP goal of < 120 mmHg could be encountered among some health care providers for months and possibly years, due to worry about SAEs and simple clinical inertia. Cognitive bias that weights negative consequences of a preventive therapy more heavily than long-term benefit is common in providers. Patients treated to intensive goals will require careful monitoring in order to avoid hypotension, syncope, electrolyte abnormalities, or acute kidney injury. Active involvement of patients who desire a CVD-free life despite a small risk of an SAE may be a positive force to overcome providers' resistance to change and clinical inertia.

This report draws on several major strengths. NHANES provides accurate estimates of the target U.S. adult population and has enrolled a large sample size allowing us to conduct analyses in several subgroups. Inclusions and exclusions did not exactly match, since NHANES did not have information on some of the SPRINT eligibility criteria (i.e., the presence of reduced left ventricular ejection fraction, coronary calcium score, ankle brachial index, or left ventricular hypertrophy) or a history of medication non-adherence. SPRINT excluded individuals whose SBP was <110 mm Hg after one minute of standing. As standing BP was not obtained in NHANES, these individuals could not be excluded from the current analysis. There also was a higher percentage of black participants in SPRINT than were in the SPRINT-eligible NHANES sample in the current analysis. As there were no statistically significant interactions in pre-specified subgroups in SPRINT, we assumed no heterogeneity of treatment effect across these subgroups. The observed mortality was substantially higher in the U.S. population meeting SPRINT criteria compared to SPRINT. This is likely because volunteers for clinical trials, including SPRINT, tend to be healthier than the general population. As a result, the smaller absolute mortality reduction observed in this trial may lead to an underestimate of preventable deaths in the population. Likewise, it could have led to under-estimation of SAE rates. Both SPRINT and NHANES used the mean of three BP measurements after five minutes of seated rest, however, SPRINT used an automated device (Model 907, Omron Healthcare), whereas NHANES used a mercury sphygmomanometer. Unless an automated office BP without an observer being present is taken, usual clinic SBP could be expected to be approximately 10 mm Hg higher than usual, observed clinic BP.[10, 26, 27] The results of sensitivity analysis requiring SBP levels to be 10 and 20 mm Hg higher than the SPRINT entry criteria indicated that a somewhat smaller number of deaths would be averted with intensive SBP treatment (about 63 to 84) thousand deaths averted per year). However, the projected number of deaths averted due to intensive treatment would remain high.

In conclusion, the current analysis projects that if the intensive SBP treatment studied in SPRINT were widely adopted in eligible, high CVD risk US adults, about 107,500 deaths could be prevented annually. This benefit must be balanced against increased risk of SAEs including a projected 56,100 and 88,700 additional cases per year of hypotension and acute kidney injury incurred with intensive SBP treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Perspective

What is new?

- In this population based study, if fully implemented in eligible U.S. adults, intensive blood pressure treatment was projected to prevent about 107,500 deaths per year and give rise to about 56,100 episodes of hypotension, 34,400 episodes of syncope, 43,400 serious electrolyte disorders, and 88,700 cases of acute kidney injury per year compared to standard blood pressure treatment.

What are the clinical implications?

- If fully implemented in eligible U.S. adults with raised blood pressure and at high risk for cardiovascular disease, intensive blood pressure treatment has the potential to prevent about 107,500 deaths per year compared to standard blood pressure treatment.

- Careful patient selection and implementation are important because intensive treatment is associated with increased risk of hypotension, syncope, electrolyte abnormalities, and acute kidney injury.

Step 1. NHANES Participants in Years 1999-2006 with blood pressure and antihypertensive medication information (n=17,746)

Step 2. Age ≥ 50 years old
(n=8,327)

Step 3. Systolic blood pressure (SBP) Criteria
     a. 130-180 mmHg on 0 or 1 antihypertensive medication class
     b. 130-170 mmHg on up to 2 antihypertensive medication classes
     c. 130-160 mmHg on up to 3 antihypertensive medication classes
     d. 130-150 mmHg on up to 4 antihypertensive medication classes
(n=4,249)

Step 4. High CVD risk Criteria (one or more of the following)
- Clinical coronary heart disease (CHD)
  - Clinical CHD
    - Myocardial infarction, CHD, or angina
- Estimated glomerular filtration rate 20-59 mL/min/1.73 m^2
- Framingham risk score for 10-year CVD risk ≥ 15%
- Age ≥ 75 years

(n=3,354)

Step 5. Apply Exclusion Criteria
1. Diabetes (n=868)
2. History of stroke (n=263)
3. Proteinuria >1g/day (n=53)
4. Heart failure (n=228)
5. Estimated glomerular filtration rate < 20 ml/min/1.73 m^2 or dialysis (n=30)

Step 6. SPRINT Eligible
(n=2,185)

Figure 1.
Flowchart showing the SPRINT eligibility criteria applied to the National Health and Nutrition Examination Survey 1999–2006
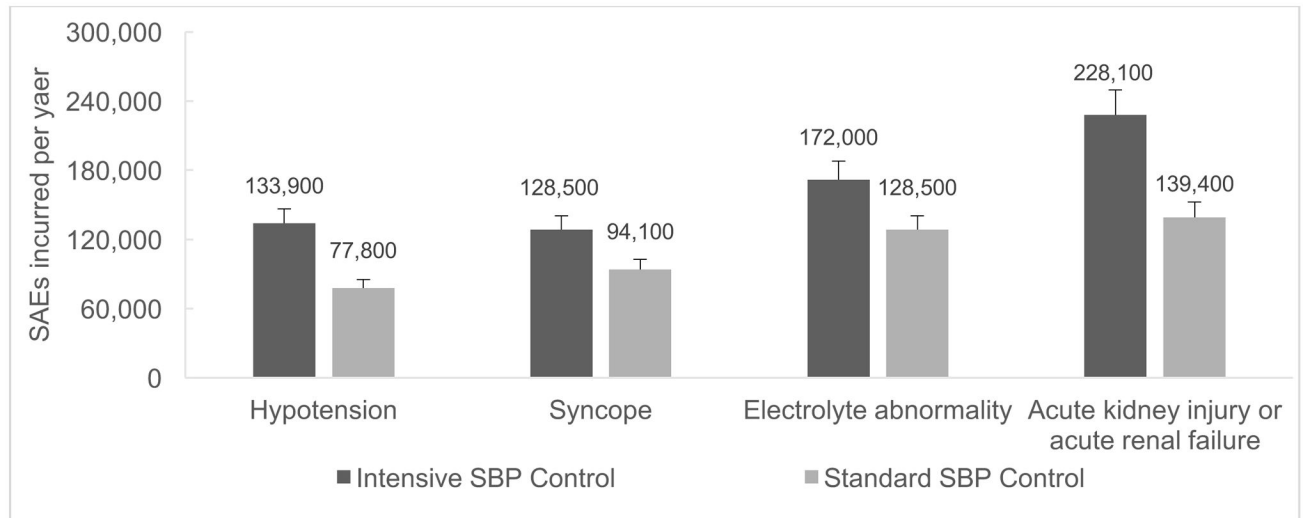
Figure 2. Potential number of serious adverse events per year with standard and intensive SBP control among NHANES participants who meet the SPRINT eligibility criteria

Projected number of SAEs from standard and intensive SBP control were calculated by taking the observed SAE rate in SPRINT and dividing it by 3.26 (the median follow-up in SPRINT) and then multiplying it by 18,100,000 which is the number of U.S. Adults meeting the sprint eligibility criteria from 1999–2006 SAEs= Serious adverse events, SBP=systolic blood pressure, SPRINT - Systolic Blood Pressure Intervention Trial.

Vertical lines denote the upper limit of the 95% confidence interval.

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Table 1

Characteristics of U.S. adults eligible for SPRINT overall and by antihypertensive medication status using NHANES 1999–2006.

Group	Overall (n=18.1 million)	Taking Antihypertensive Medication (n=7.4 million)	Not Taking Antihypertensive Medication (n=10.7 million)	SPRINT[*] (n=9,361)
Age, mean (SE), years	68.6 (0.26)	68.8 (0.32)	68.5 (0.37)	67.9 (9.4)
Age group, %				
< 75 years	68.0	68.1	67.7	71.8
75 years	32.0	31.9	32.3	28.2
Male sex, %	53.8	46.1	53.8	64.4
Race/ethnicity, %				
Non-Hispanic White	83.2	82.9	83.4	57.7
Non-Hispanic Black	7.4	9.3	6.0	29.9
Mexican American	3.0	2.2	3.5	NA
Other	6.5	5.6	7.1	1.88
Current smoker, %	17.6	10.3	17.6	13.2
Body mass index, mean (SE)	28.1 (0.13)	29.1 (0.21)	27.5 (0.17)	29.9 (5.7)
Obese, %	31.0	37.2	26.7	NA
eGFR 20 to 59 ml/min/1.73 m^2, %	23.0	26.1	20.2	28.3
Framingham risk score groups, %				
< 5%	0.2	0.0	0.39	NA
5.0–7.4%	0.8	0.8	0.7	NA
7.5–9.9%	1.6	1.5	1.6	NA
10 – 14.9%	6.3	5.9	6.6	NA
15%	91.1	91.9	90.6	61.3
History of CHD, %	12.1	16.9	8.7	16.7
Systolic blood pressure, mmHg, %				
132	9.9	7.3	11.7	33.5
133 – 144	40.7	43.6	38.8	32.5
145	49.4	49.1	49.5	34.0
Education, %				
Less than high school	26.0	23.1	28.0	NA
High school only	29.5	27.8	30.7	NA
More than high school	25.2	27.7	23.4	NA
Completed college	19.3	21.3	17.9	NA
No insurance, %	11.0	7.4	13.5	NA

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Numbers in table are expressed as mean (Standard error [SE]) or percentages. Percentages are based on weighted data. CVD - cardiovascular disease, eGFR - estimated glomerular filtration rate, SPRINT - Systolic Blood Pressure Intervention Trial, CHD=coronary heart disease, NHANES= National Health and Nutrition Examination Survey, NA=not applicable.

Obesity defined as body mass index ≥ 30.0 kg/m2. Framingham risk score was calculate using the using the equation for general clinical practice. 13 Use of antihypertensive medication was defined by self-report and report of taking one or more classes of antihypertensive medication identified through the pill bottle review.

*
Baseline characteristics from SPRINT are shown for comparisons (mean and standard deviation are shown for age and body mass index).

Table 2

Observed and predicted annual mortality if SPRINT is fully implemented among NHANES participants who meet the SPRINT eligibility criteria.

	SPRINT-eligible U.S. adults in millions (95%CI)	Observed annual mortality among SPRINT-eligible NHANES participants		Predicted annual mortality if SPRINT fully applied		Deaths Prevented if SPRINT fully applied, thousands (95%CI)	Number needed to treat (for 3.26 years)
		% (95%CI)	No. per year, thousands (95%CI)	% (95%CI)	No. per year, thousands (95%CI) *		
Overall	18.1 (16.4–19.8)	2.20 (1.91–2.48)	398.2 (345.7–448.9)	1.61 (1.39–1.81)	290.7 (252.4–327.7)	107.5 (93.3–121.2)	52
Sex							
Men	9.7 (8.7–10.8)	2.53 (2.13–2.99)	245.4 (206.6–290)	1.85 (1.55–2.18)	179.1 (150.8–211.7)	66.3 (55.8–78.3)	45
Women	8.4 (7.4–9.3)	1.81 (1.49–2.20)	152.0 (125.2–184.8)	1.32 (1.09–1.61)	111.0 (91.4–134.9)	41.1 (33.8–49.9)	63
Age Group							
<75 years	12.3 (11.2–13.5)	1.21 (0.95–1.54)	148.8 (116.9–189.4)	0.88 (0.69–1.12)	108.6 (85.3–138.3)	40.2 (31.5–51.1)	94
75 years	5.8 (5.1–6.5)	4.30 (3.74–4.93)	249.4 (216.9–285.9)	3.14 (2.73–3.6)	182.1 (158.4–208.7)	67.3 (58.6–77.2)	26
Race/ethnicity							
Non-Hispanic White	15.1 (13.2–16.9)	2.18 (1.90–2.51)	329.2 (286.9–379)	1.59 (1.39–1.83)	240.3 (209.4–276.7)	88.9 (77.5–102.3)	52
Non-Hispanic Black	1.3 (1.1–1.6)	2.52 (1.87–3.36)	32.8 (24.3–43.7)	1.84 (1.37–2.45)	23.9 (17.7–31.9)	8.8 (6.6–11.8)	45
Mexican American	0.05 (0.04–0.07)	1.46 (0.95–2.24)	0.7 (0.5–1.1)	1.07 (0.69–1.64)	0.5 (0.3–0.8)	0.2 (0.1–0.3)	78
Other	1.2 (0.8–1.5)	2.35 (1.17–4.56)	28.2 (14–54.7)	1.72 (0.85–3.33)	20.6 (10.2–39.9)	7.6 (3.8–14.8)	48
History of CHD	2.2 (1.7–2.6)	3.31 (2.33–4.65)	72.8 (51.3–102.3)	2.42 (1.7–3.39)	53.2 (37.4–74.7)	19.7 (13.8–27.6)	34
Baseline SBP							
SBP 132 mmHg	1.8 (1.5–2.1)	2.02 (1.25–3.21)	36.4 (22.5–57.8)	1.47 (0.91–2.34)	26.5 (16.4–42.2)	9.8 (6.1–15.6)	56
SBP 133–144 mmHg	7.4 (6.7–8.1)	1.85 (1.48–2.29)	136.9 (109.5–169.5)	1.35 (1.08–1.67)	99.9 (79.9–123.7)	37.0 (29.6–45.8)	61
SBP 145 mmHg	8.9 (7.9–9.9)	2.52 (2.15–2.96)	224.3 (191.4–263.4)	1.84 (1.57–2.16)	163.7 (139.7–192.3)	60.6 (51.7–71.1)	45
eGFR 20–59 ml/min/1.73m²	4.1 (3.5–4.7)	2.95 (2.37–3.65)	121.0 (97.2–149.7)	2.15 (1.73–2.66)	88.3 (70.9–109.2)	32.7 (26.2–40.4)	39

CHD = coronary heart disease, SBP=systolic blood pressure, SPRINT - Systolic Blood Pressure Intervention Trial, NHANES= National Health and Nutrition Examination Survey. Estimated glomerular filtration rate (eGFR) in ml/min/1.73 m2 was estimated using the CKD-EPI equation using the serum creatinine;

*
Calculated by multiplying the hazard ratio for all-cause mortality from SPRINT (0.73) by the number of deaths among the NHANES population meeting the SPRINT eligibility criteria

Table 3

Observed and predicted annual mortality if SPRINT-based SBP goals are fully implemented among NHANES participants who meet the SPRINT eligibility criteria by antihypertensive medication use.

	SPRINT-eligible U.S. adults in millions (95%CI)	Observed annual mortality		Predicted annual mortality if SPRINT fully applied*		Deaths Prevented if SPRINT fully applied, thousands (95%CI)	Number needed to treat (for 3.26 years)
		% (95%CI)	No. per year, thousands (95%CI)	% (95%CI)	No. per year, thousands (95%CI)		
Taking Antihypertensive Medication							
Overall	7.4 (6.5–8.3)	2.03 (1.58–2.49)	150.2 (116.9–184.3)	1.48 (1.15–1.82)	109.7 (85.4–134.5)	40.6 (31.6–49.8)	56
Sex							
Men	3.4 (2.9–3.9)	2.59 (2.01–3.33)	88.1 (68.3–113.2)	1.89 (1.47–2.43)	64.3 (49.9–82.7)	23.8 (18.5–30.6)	44
Women	4.0 (3.4–4.6)	1.56 (1.07–2.25)	62.4 (42.8–90)	1.14 (0.78–1.64)	45.6 (31.2–65.7)	16.8 (11.6–24.3)	73
Age Group							
<75 years	5.1 (4.4–5.7)	1.20 (0.85–1.69)	61.2 (43.4–86.2)	0.88 (0.62–1.23)	44.7 (31.6–62.9)	16.5 (11.7–23.3)	95
75 years	2.3 (1.9–2.7)	3.85 (3.04–4.83)	88.6 (69.9–111.1)	2.81 (2.22–3.53)	64.6 (51–81.1)	23.9 (18.9–30)	30
Race/ethnicity							
Non-Hispanic White	6.1 (5.2–7.0)	2.09 (1.62–2.68)	127.5 (98.8–163.5)	1.53 (1.18–1.96)	93.1 (72.1–119.3)	34.4 (26.7–44.1)	54
Non-Hispanic Black	0.70 (0.52–0.86)	2.63 (1.84–3.72)	18.4 (12.9–26.0)	1.92 (1.34–2.72)	13.4 (9.4–19)	5.0 (3.5–7)	43
Mexican American	0.02 (0.01–0.02)	2.20 (1.01–4.64)	0.4 (0.2–0.9)	1.61 (0.74–3.39)	0.3 (0.1–0.7)	0.1 (0.1–0.3)	52
History of CHD	1.3 (0.92–1.6)	2.69 (1.82–4.72)	35.0 (23.7–61.4)	1.96 (1.33–3.45)	25.5 (17.3–44.8)	9.4 (6.4–16.6)	42
Baseline SBP							
SBP 132 mmHg	0.054 (0.037–0.071)	1.82 (0.66–4.80)	1.0 (0.4–2.6)	1.33 (0.48–3.50)	0.7 (0.3–1.9)	0.3 (0.1–0.7)	62
SBP 133–144 mmHg	3.2 (2.6–3.7)	2.14 (1.51–3.00)	68.5 (48.3–96)	1.56 (1.10–2.19)	50.0 (35.3–70.1)	18.5 (13–25.9)	53
SBP 145 mmHg	3.8 (3.1–4.2)	1.98 (1.49–2.62)	75.2 (56.6–99.6)	1.45 (1.09–1.91)	54.9 (41.3–72.7)	20.3 (15.3–26.9)	57
eGFR 20–59 ml/min/1.73 m²	2.0 (1.6–2.3)	3.02 (2.18–4.16)	60.4 (43.6–83.2)	2.20 (1.59–3.04)	44.1 (31.8–60.7)	16.3 (11.8–22.5)	38
Not Taking Antihypertensive Medication							
Overall	10.7 (9.9–11.5)	2.31 (1.89–2.73)	247.2 (202.2–292.1)	1.69 (1.38–1.99)	180.4 (147.6–213.2)	66.7 (54.6–78.9)	49
Sex							
Men	6.3 (5.8–6.9)	2.49 (2.03–3.05)	156.9 (127.9–192.2)	1.82 (1.48–2.23)	114.5 (93.4–140.3)	42.4 (34.5–51.9)	46
Women	4.4 (2.9–4.7)	2.04 (1.49–2.80)	89.8 (65.6–123.2)	1.49 (1.09–2.04)	65.5 (47.9–89.9)	24.2 (17.7–33.3)	56

	SPRINT-eligible U.S. adults in millions (95%CI)	Observed annual mortality		Predicted annual mortality if SPRINT fully applied*		Deaths Prevented if SPRINT fully applied, thousands (95%CI)	Number needed to treat (for 3.26 years)
		% (95%CI)	No. per year, thousands (95%CI)	% (95%CI)	No. per year, thousands (95%CI)		
Age Group							
<75 years	7.2 (6.7–7.7)	1.21 (0.86–1.71)	87.1 (61.9–123.1)	0.88 (0.63–1.25)	63.6 (45.2–89.9)	23.5 (16.7–33.2)	94
75 years	3.5 (3.1–3.8)	4.60 (3.84–5.49)	161.0 (134.4–192.2)	3.36 (2.80–4.01)	117.5 (98.1–140.3)	43.5 (36.3–51.9)	25
Race/ethnicity							
Non-Hispanic White	8.9 (8.0–9.9)	2.25 (1.89–2.68)	200.3 (168.2–238.5)	1.64 (1.38–1.96)	146.2 (122.8–174.1)	54.1 (45.4–64.4)	50
Non-Hispanic Black	0.64 (0.57–0.71)	2.40 (1.54–3.68)	15.4 (9.9–23.6)	1.75 (1.12–2.87)	11.2 (7.2–17.2)	4.1 (2.7–6.4)	47
Mexican American	0.36 (0.27–0.48)	1.14 (0.71–1.82)	4.1 (2.6–6.6)	0.83 (0.52–1.33)	3.0 (1.9–4.8)	1.1 (0.7–1.8)	100
History of CHD	0.98 (0.81–1.05)	3.78 (2.52–5.57)	37.0 (24.7–54.6)	2.76 (1.84–4.07)	27.0 (18.0–39.8)	10.0 (6.7–14.7)	30
Baseline SBP							
SBP 132 mmHg	1.3 (1.1–1.4)	2.10 (1.22–3.57)	27.3 (15.9–46.4)	1.53 (0.89–2.61)	19.9 (11.6–33.9)	7.4 (4.3–12.5)	54
SBP 133–144 mmHg	4.2 (3.9–4.4)	1.62 (1.21–2.16)	68.0 (50.8–90.7)	1.18 (0.88–1.58)	49.7 (37.1–66.2)	18.4 (13.7–24.5)	70
SBP 145 mmHg	5.3 (4.9–5.8)	2.90 (2.34–3.58)	153.7 (124.0–189.7)	2.12 (1.71–2.61)	112.2 (90.5–138.5)	41.5 (33.5–51.2)	39
eGFR 20–59 ml/min/1.73 m²	2.1 (1.9–2.4)	2.88 (2.15–3.84)	60.5 (45.2–80.6)	2.10 (1.57–2.80)	44.2 (33–58.9)	16.3 (12.2–21.8)	39

CHD = coronary heart disease, SBP=systolic blood pressure, SPRINT - Systolic Blood Pressure Intervention Trial, NHANES= National Health and Nutrition Examination Survey. Estimated glomerular filtration rate (eGFR) in ml/min/1.73 m2 was estimated using the CKD-EPI equation using the serum creatinine;

*
Calculated by multiplying the hazard ratio for all-cause mortality from SPRINT (0.73) by the annual mortality rate and the number of deaths among the NHANES population meeting the SPRINT eligibility criteria

Other race/ethnicity group not shown due to unstable estimates of mortality in stratified analyses

Use of antihypertensive medication was defined by self-report and report of taking one or more classes of antihypertensive medication identified through the pill bottle review.

Table 4

Projected number of serious adverse events incurred per year with intensive SBP control

Serious Adverse Events	Annual Risk Observed in SPRINT		Risk Difference	Expected Number of SAEs per year, thousands*		SAEs incurred per year (95%CI)†	Number Needed to Harm (over 3.26 years of treatment)
	Intensive	Standard		Intensive	Standard		
Hypotension	0.74%	0.43%	0.31%	133.9 (121.4–146.5)	77.8 (70.5–85.1)	56.1 (50.8–61.4)	99
Syncope	0.71%	0.52%	0.19%	128.5 (116.4–140.6)	94.1 (85.3–103.0)	34.4 (31.2–37.6)	161
Electrolyte abnormality	0.95%	0.71%	0.24%	172.0 (155.8–188.1)	128.5 (116.4–140.6)	43.4 (39.4–47.5)	128
Acute kidney injury or acute renal failure	1.26%	0.77%	0.49%	228.1 (206.6–249.5)	139.4 (126.3–152.5)	88.7 (80.4–97.0)	63
SAEs Possibly of Definitely Related to the Intervention							
Hypotension	0.55%	0.25%	0.30%	99.6 (90.2–108.9)	45.3 (41.0–49.5)	54.3 (49.2–59.4)	102
Syncope	0.43%	0.18%	0.25%	77.8 (70.5–85.1)	32.6 (29.5–35.6)	45.3 (41.0–49.5)	123
Electrolyte abnormality	0.46%	0.31%	0.15%	83.3 (75.4–91.1)	56.1 (50.8–61.4)	27.2 (24.6–29.7)	204
Acute kidney injury or acute renal failure	0.58%	0.21%	0.37%	105.0 (95.1–114.8)	38.0 (34.4–41.6)	67.0 (60.7–73.3)	83

SBP= systolic blood pressure, SAE = serious adverse event, SPRINT=Systolic Blood Pressure Intervention Trial.

*
Calculated by multiply the annual SAE rate by 18,100,000 and its 95%CD (16,400,000–19,800,000) which is the number of U.S. Adults meeting the sprint eligibility criteria from 1999–2006.

†
Calculated by multiplying the risk difference for each SAE by 18,100,000 which is the number of U.S. Adults meeting the sprint eligibility criteria from 1999–2006. Acute kidney injury or acute renal failure was defined in SPRINT as an event that occurred during a hospitalization and were reported in the hospital discharge summary as a primary or main secondary diagnosis.

An SAE was defined in SPRINT as an event that was fatal or life-threatening, that resulted in clinically significant or persistent disability, that required or prolonged a hospitalization, or that was judged by the investigator to represent a clinically significant hazard or harm to the participant that might require medical or surgical intervention to prevent another SAE