4-25-2017

Potential Deaths Averted and Serious Adverse Events Incurred From Adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) Intensive Blood Pressure Regimen in the United States: Projections From NHANES (National Health and Nutrition Examination Survey)

Adam P. Bress

Holly Kramer

Rasha Khatib

Srinivasan Beddhu

Alfred K. Cheung

See next page for additional authors

Recommended Citation
Bress AP, Kramer H, Khatib R, Beddhu S, Cheung AK, Hess R, Bansal VK, Cao G, Yee J, Moran AE, Durazo-Arvizu RA, Muntner P, and Cooper RS. Potential deaths averted and serious adverse events incurred from adoption of the sprint intensive blood pressure regimen in the u.S.: Projections from nhanes. Circulation 2017; 135(17):1617-1628.

Authors

Adam P. Bress, Holly Kramer, Rasha Khatib, Srinivasan Beddhu, Alfred K. Cheung, Rachel Hess, Vinod K. Bansal, Guichan Cao, Jerry Yee, Andrew E. Moran, Ramon Durazo-Arvizu, Paul Muntner, and Richard S. Cooper

Potential Deaths Averted and Serious Adverse Events Incurred From Adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) Intensive Blood Pressure Regimen in the United States

Projections From NHANES (National Health and Nutrition Examination Survey)

Editorial, see p 1629

BACKGROUND: SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated a 27% reduction in all-cause mortality with a systolic blood pressure (SBP) goal of <120 versus <140 mm Hg among US adults at high cardiovascular disease risk but without diabetes mellitus, 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 incurred if the SPRINT intensive SBP treatment goal were implemented in all eligible US adults.

METHODS: SPRINT eligibility criteria were applied to the 1999 to 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 to 180 mm Hg (depending on the number of antihypertensive medications being taken), and high cardiovascular disease risk. Exclusion criteria were diabetes mellitus, history of stroke, >1 g proteinuria, heart failure, estimated glomerular filtration rate <20 mL·min^{-1}·1.73 m^{-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 serious adverse events in SPRINT were used to estimate the number of potential deaths and heart failure cases prevented and serious adverse events 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% confidence interval [CI], 1.91–2.48), and intensive SBP treatment was projected to prevent ≈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 US adults, intensive SBP treatment could prevent ≈107 500 deaths per year. A consequence of this treatment strategy, however, could be an increase in serious adverse events.

Adam P. Bress, PharmD, MS
Holly Kramer, MD, MPH
Rasha Khatib, PhD
Srinivasan Beddhu, MD
Alfred K. Cheung, MD
Rachel Hess, MD, MS
Vinod K. Bansal, MD
Guichan Cao, MS
Jerry Yee, MD
Andrew E. Moran, MD, MPH
Ramon Durazo-Arvizu, PhD
Paul Muntner, PhD
Richard S. Cooper, MD

Correspondence to: Adam Bress, PharmD, MS, Division of Health System Innovation and Research Department of Population Health Sciences, University of Utah School of Medicine, 295 Chipeta Way, Room 1S116, Salt Lake City, UT 84158. E-mail adam.bress@hsc.utah.edu

Sources of Funding, see page 1626

Key Words: blood pressure ■ hypertension ■ treatment outcome

Clinical Perspective

What Is New?

- In this population-based study, if fully implemented in eligible US adults, intensive blood pressure treatment was projected to prevent ≈107 500 deaths per year and give rise to ≈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 with standard blood pressure treatment.

What Are the Clinical Implications?

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

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

SPRINT (Systolic Blood Pressure Intervention Trial) was designed to determine whether lowering SBP to an intensive goal of <120 mm Hg compared with the standard goal of <140 mm Hg resulted in reduced CVD risk in high-risk patients without a history of diabetes mellitus, stroke, or heart failure.[6] SPRINT achieved a mean SBP of 121 mm Hg in the intensive treatment arm and 136 mm Hg in the standard treatment arm, resulting in a 27% reduction (hazard ratio [HR], 0.73; 95% confidence interval [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 1 death resulting 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 for any SAE possibly or definitely related to the intervention was 45.

Implementation of SPRINT-based intensive SBP goals has the potential to greatly reduce mortality in patients at high CVD risk living in the United States and worldwide. 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 were implemented in all eligible US adults.

METHODS

Study Population

Data were drawn from the NHANES (National Health and Nutrition Examination Survey), a multistage, stratified probability sample of noninstitutionalized US adults conducted by the National Center for Health Statistics.[4] To provide sufficient sample size, data were pooled from the 1999 to 2000, 2001 to 2002, 2003 to 2004, and 2005 to 2006 NHANES cycles.[8] Participants who completed a medical evaluation at the NHANES mobile examination center, were ≥20 years of age, and had complete information on SBP measurements and use of antihypertensive medication (n=17 746) were included. Of the 8327 NHANES participants who were ≥50 years old, 4249 met SPRINT SBP criteria (Figure 1). Next, participants who did not meet the high CVD risk criteria (n=895) or who had diabetes mellitus (n=868), history of stroke (n=263), proteinuria >1 g/d (n=53), heart failure (n=228), estimated glomerular filtration rate (eGFR) <20 mL·min^{-1}·1.73 m^{-2}, or end-stage renal disease on dialysis (n=30) were excluded. After these exclusions, a total of 2185 SPRINT-eligible participants were included in the current analyses. All participants provided written informed consent, and the National Center for Health Statistics 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, or stroke, as well as receipt of dialysis in the past 12 months or the use of antihypertensive or antidiabetes medication.

The NHANES medical evaluation included measurements of height and weight that were used to calculate body mass index. A blood sample was collected for measurement of serum creatinine, glucose, and glycosylated hemoglobin (hemoglobin A_{1c}). Urine albumin and creatinine concentrations were analyzed from spot random urine samples. Diabetes mellitus was defined by a prior diagnosis, excluding during pregnancy, with concurrent use of insulin or oral hypoglycemic medication or a hemoglobin A_{1c} ≥6.5%, nonfasting glucose ≥200 mg/dL, or fasting glucose ≥126 mg/dL. The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to calculate eGFR.[9] NHANES participants were asked to bring all prescription medications taken in the past 2 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.

Circulation. 2017;135:1617–1628. DOI: 10.1161/CIRCULATIONAHA.116.025322

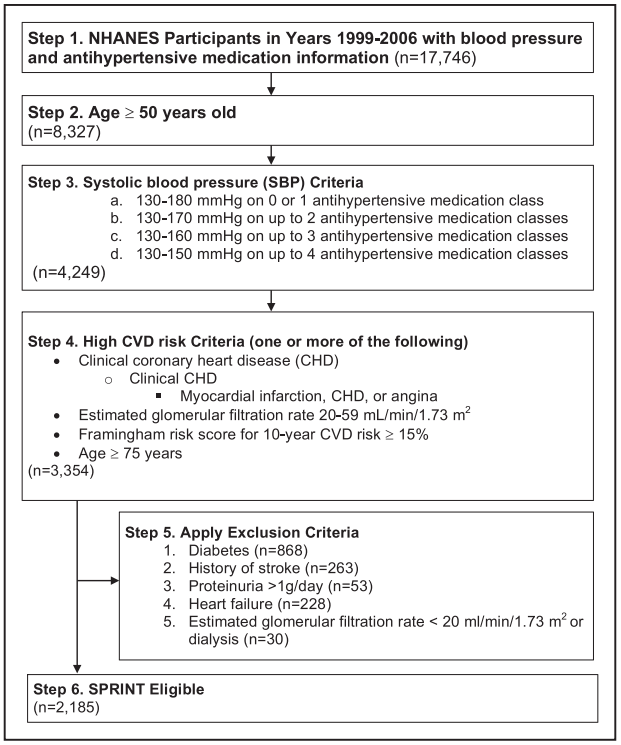

Figure 1. Flowchart showing the SPRINT (Systolic Blood Pressure Intervention Trial) eligibility criteria applied to the NHANES (National Health and Nutrition Examination Survey), 1999 to 2006.
CHD indicates coronary heart disease; and CVD, cardiovascular disease.

Use of antihypertensive medication was defined by self-report and report of taking ≥1 classes of antihypertensive medication identified through the pill bottle review.

Baseline BP Measurement

BP was measured with participants seated after 5 minutes of rest by a trained study physician using a mercury sphygmomanometer with an appropriately sized cuff. SBP and diastolic BP were defined as the mean of 3 BP measurements taken 1 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 coronary heart disease, SBP groups (≤132, 133–144, and ≥145 mm Hg; prespecified SBP strata defined in SPRINT), and eGFR of 20 to 59 mL·min^{-1}·1.73 m^{-2} were calculated. The Kaplan-Meier method was used to calculate the 5-year survival probability, which was then used to calculate the 5-year mortality, which is equal to 1 minus the 5-year survival probability, 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 were 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% CIs in the overall SPRINT-eligible NHANES population by 0.73, the observed HR for all-cause mortality with intensive SBP treatment in SPRINT compared with standard SBP treatment (ie, 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 coronary heart disease, SBP groups (≤132, 133–144, and ≥145 mm Hg), and moderate stage chronic kidney disease (defined by SPRINT as eGFR of 20–59 mL·min^{-1}·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 BP 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 (eg, 140 to 190 and 150 to 200 versus 130 to 180 mm Hg for those on 0 or 1 antihypertensive medication, respectively.[10] Because 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 dividing the annual rate of rate incident heart failure observed in SPRINT (0.67%/y) 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 was 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 report that was statistically significantly different between intensive and standard SBP treatment arms (ie, hypotension, syncope, bradycardia, electrolyte abnormality, and acute kidney injury) by the number of US 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 years of 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 with the analysis-of-extremes methodology in which the upper and lower confidence bounds of the treatment effects for all-cause mortality, heart failure, and SAEs were used.[11,12] Because confidence bounds were not available for SAEs in the SPRINT main results publication, we calculated 95% CIs for SAEs from the *P* value (Table I in the online-only Data Supplement). The number needed to treat was calculated for all-cause mortality and heart failure, and the number needed to harm 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) US 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% being ≥75 years of age (Table 1). More than half (53.8%) were men; 83.2% were non-Hispanic white; 7.4% were non-Hispanic black, and 3.0% were 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 (ie, usual care; Table 2). On the basis of 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). We estimate that 107 500 deaths (95% CI, 93 300–121 200) could be prevented annually with full implementation of intensive SBP treatment in this group of SPRINT-eligible US 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 (Table II in the online-only Data Supplement). 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 and 20 mm Hg higher than the SPRINT entry criteria, respectively (Figures I and II and Tables III–VI in the online-only Data Supplement).

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%/y (95% CI, 1.15–1.82), resulting in a projected decrease of 40 600 deaths per year (95% CI, 31 600–49 800). Among those who were 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 US adults ≥75 years of age, among whom intensive SBP treatment could prevent 67 300 (95% CI, 58 600–77 200) deaths per year. SPRINT-eligible US adults with an eGFR of 20 to 59 mL·min^{-1}·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 US adults with an eGFR of 20 to 59 mL·min^{-1}·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 (Table VII in the online-only Data Supplement). 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 US adults overall, standard SBP treatment (ie, 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 Table VIII in the online-only Data Supplement.

DISCUSSION

In the present analysis, we project that ≈107 500 deaths could be averted annually if an intensive SBP target goal of <120 mm Hg were to be adopted among all US 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 present study indicate that the number of deaths that could be prevented with intensive SBP treatment in eligible US adults is similar to that of

Circulation. 2017;135:1617–1628. DOI: 10.1161/CIRCULATIONAHA.116.025322

Table 1. Characteristics of US Adults Eligible for SPRINT Overall and by Antihypertensive Medication Status Using NHANES, 1999 to 2006

Group	Overall (n=18.1 million)	Taking Antihypertensive Medication (n=7.4 million)	Not Taking Antihypertensive Medication (n=10.7 million)	SPRINT* (n=9361)
Age, mean (SE), y	68.6 (0.26)	68.8 (0.32)	68.5 (0.37)	67.9 (9.4)
Age group, %				
<75 y	68.0	68.1	67.7	71.8
≥75 y	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), kg/m^2	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}·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	75.9
History of CHD, %	12.1	16.9	8.7	16.7
Systolic blood pressure, %				
≤132 mm Hg	9.9	7.3	11.7	33.5
133–144 mm Hg	40.7	43.6	38.8	32.5
≥145 mm Hg	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

Values are expressed as mean (SE) when appropriate. Percentages are based on weighted data. CHD indicates coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; and SPRINT, Systolic Blood Pressure Intervention Trial.

Obesity is defined as body mass index ≥30.0 kg/m^2. Framingham Risk Score was calculated with the equation for general clinical practice. [13] Use of antihypertensive medication was defined by self-report and report of taking ≥1 classes of antihypertensive medication identified through the pill bottle review.

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

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 ≥75 years of age. Intensive SBP treatment was also projected to prevent ≈46 100 new cases of heart failure per year. These benefits are tempered

Table 2. Observed and Predicted Annual Mortality if SPRINT Is Fully Implemented Among NHANES Participants Who Meet the SPRINT Eligibility Criteria

	SPRINT-Eligible US Adults, ×10⁶ (95% CI)	Observed Annual Mortality Among SPRINT-Eligible NHANES Participants		Predicted Annual Mortality if SPRINT Fully Applied		Deaths Prevented if SPRINT Fully Applied, ×10³ (95% CI)	No. Needed to Treat (for 3.26 y)
		% (95% CI)	×10³ per year (95% CI)	% (95% CI)	×10³ per year (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, y							
<75	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	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, mm Hg							
≤132	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
133–144	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
≥145	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}·1.73 m^{-2}	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 indicates coronary heart disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; and SPRINT, Systolic Blood Pressure Intervention Trial. eGFR was estimated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation using 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.

by a projected increase in SAEs, including ≈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 number needed to treat from SPRINT to prevent 2 death resulting from any cause was 90 over 3.26 years.[7] Although varying assumptions could change our overall estimate, the combination of a low number needed to treat (ie, 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

Circulation. 2017;135:1617–1628. DOI: 10.1161/CIRCULATIONAHA.116.025322

Table 3. Observed and Predicted Annual Mortality if SPRINT-Based Systolic Blood Pressure Goals Are Fully Implemented Among NHANES Participants Who Meet the SPRINT Eligibility Criteria by Antihypertensive Medication Use

	SPRINT-Eligible US Adults, ×10⁶ (95% CI)	Observed Annual Mortality		Predicted Annual Mortality if SPRINT Fully Applied*		Deaths Prevented if SPRINT Fully Applied, ×10³ (95% CI)	No. Needed to Treat (for 3.26 y)
		% (95% CI)	No. per Year, ×10³ (95% CI)	% (95% CI)	No. per Year, ×10³ (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, y							
<75	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	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, mm Hg							
≤132	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
133–144	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
≥ 145	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}·1.73 m^{-2}	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
Age group, y							
<75	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	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

(*Continued*)

Table 3. Continued

	SPRINT-Eligible US Adults, ×10⁶ (95% CI)	Observed Annual Mortality		Predicted Annual Mortality if SPRINT Fully Applied*		Deaths Prevented if SPRINT Fully Applied, ×10³ (95% CI)	No. Needed to Treat (for 3.26 y)
		% (95% CI)	No. per Year, ×10³ (95% CI)	% (95% CI)	No. per Year, ×10³ (95% CI)		
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, mm Hg							
≤132	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
133–144	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
≥145	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}·1.73 m^{-2}	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 indicates coronary heart disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; and SPRINT, Systolic Blood Pressure Intervention Trial. eGFR was estimated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation using serum creatinine. Other race/ethnicity groups are not shown because of unstable estimates of mortality in stratified analyses.

Use of antihypertensive medication was defined by self-report and report of taking ≥1 classes of antihypertensive medication identified through the pill bottle review.

*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.

interventions are currently available that could have such a large and immediate public health impact on broad sectors of the US 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 and 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 the risk of CVD events and stroke compared with 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, regardless of frailty status at baseline.[16] The HR among participants >75 years of age at entry was 0.67 for all-cause mortality, and on the basis of 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, whereas 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 ≥75 years of age, 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 HYVET (Hypertension in the Very Elderly Trial) and SHEP (Systolic Hypertension in the Elderly Program), 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 has accounted for the majority of the 80% decline in CVD deaths in the United States and many other countries over the last several decades.[19,20] Recently, however, it appears that the decline in CVD in the United States has slowed.[21] More aggressive use of the available safe, effective, and inexpensive antihypertensive medications to reduce SBP to <120 mm Hg among eligible US adults may restore the downward trend in CVD mortality that has transformed adult health in the United States over the last 50 years.

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

Table 4. Projected Number of SAEs Incurred per Year With Intensive SBP Control

Serious Adverse Events	Annual Risk Observed in SPRINT, %		Risk Difference, %	Expected No. of SAEs per Year, ×10³*		SAEs Incurred per Year, n (95% CI)†	No. Needed to Harm (Over 3.26 y 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 or 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

CI indicates confidence interval; SAE, serious adverse event; SBP systolic blood pressure; and SPRINT, Systolic Blood Pressure Intervention Trial.

*Calculated by multiplying the annual SAE rate by 18 100 000 and its 95% CI (16 400 000–19 800 000), which is the number of US adults meeting the sprint eligibility criteria from 1999 to 2006. †Calculated by multiplying the risk difference for each SAE by 18 100 000, which is the number of US adults meeting the sprint eligibility criteria from 1999 to 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.

treatment in patients with diabetes mellitus, with outcome definitions more similar to those in 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 it is that 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 (eg, more frequent clinic visits,

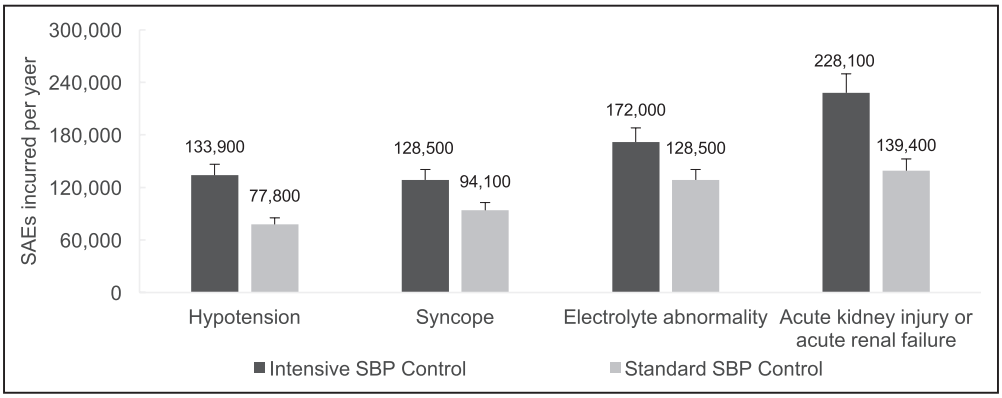

Figure 2. Potential number of serious adverse events (SAEs) per year with standard and intensive systolic blood pressure (SBP) control among NHANES (National Health and Nutrition Examination Survey) participants who meet the SPRINT (Systolic Blood Pressure Intervention Trial) eligibility criteria.

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 US adults meeting the SPRINT eligibility criteria from 1999 to 2006. Vertical lines denote the upper limit of the 95% confidence interval.

laboratory testing, and additional medications) to produce the mean SBP change achieved in SPRINT (14.8 mm Hg after 1 year of treatment). Integrated health systems such as Kaiser Permanente of Northern California are already achieving control rates of >90% for SBP and diastolic BP targets goals of <140/90 mm Hg.[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 mm Hg could be encountered among some healthcare providers for months and possibly years because of 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 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 US adult population and has enrolled a large sample size, allowing us to conduct analyses in several subgroups. Inclusions and exclusions did not exactly match because NHANES did not have information on some of the SPRINT eligibility criteria (ie, the presence of reduced left ventricular ejection fraction, coronary calcium score, ankle-brachial index, or left ventricular hypertrophy) or a history of medication nonadherence. SPRINT excluded individuals whose SBP was <110 mm Hg after 1 minute of standing. Because 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 in the SPRINT-eligible NHANES sample in the present analysis. Because there were no statistically significant interactions in prespecified subgroups in SPRINT, we assumed no heterogeneity of treatment effect across these subgroups. The observed mortality was substantially higher in the US population meeting SPRINT criteria compared with SPRINT. The likely reason is that 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 underestimation of SAE rates. Both SPRINT and NHANES used the mean of 3 BP measurements after 5 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 ≈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 (≈63–84 thousand deaths averted per year). However, the projected number of deaths averted as a result of intensive treatment would remain high.

CONCLUSIONS

The present analysis projects that if the intensive SBP treatment studied in SPRINT were widely adopted in eligible, high-CVD-risk US adults, ≈107 500 deaths could be prevented annually. This benefit must be balanced against an 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.

SOURCES OF FUNDING

Dr Bress was supported by 1K01HL133468-01 from the National Heart, Lung, and Blood Institute, Bethesda, MD. Dr Moran was supported by R01 HL130500-01A1 from the National Heart, Lung, and Blood Institute. Dr Muntner was supported by grant 15SFRN2390002 from the American Heart Association.

DISCLOSURES

Dr Bress receives research support from Novartis not related to the current project. Drs Bress, Kramer, Khatib, and Cooper had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The other authors report no conflicts.

AFFILIATIONS

From Division of Health System Innovation and Research, Department of Population Health Sciences, University of Utah School of Medicine, Salt Lake City (A.P.B., R.H.); Department of Public Health Sciences (H.K., R.K., G.C., R.D.-A., R.S.C.) and Division of Nephrology and Hypertension (H.K., V.K.B.), Loyola Medical Center, Maywood, IL; Division of Nephrology and Hypertension, University of Utah, Salt Lake City (S.B., A.K.C.); Division of General Internal Medicine, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City (R.H.); Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI (J.Y.); Division of General Medicine, Department of Medicine, Columbia University Medical Center, New York, NY (A.E.M.); and School of Public Health, Department of Epidemiology, University of Alabama at Birmingham (P.M.).

FOOTNOTES

Received September 2, 2016; accepted January 25, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.025322/-/DC1.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD 3rd, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA 3rd, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stöckl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2224–2260. doi: 10.1016/S0140-6736(12)61766-8.
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
3. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520. doi: 10.1001/jama.2013.284427.
4. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.
5. Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, Pergola PE, Szychowski JM. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382:507–515.
6. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, Fine LJ, Goff DC Jr, Johnson KC, Killeen AA, Lewis CE, Oparil S, Reboussin DM, Rocco MV, Snyder JK, Williamson JD, Wright JT Jr, Whelton PK; SPRINT Study Research Group. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials*. 2014;11:532–546. doi: 10.1177/1740774514537404.
7. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
8. Mirel LB, Mohadjer LK, Dohrmann SM, Clark J, Burt VL, Johnson CL, Curtin LR. National Health and Nutrition Examination Survey: estimation procedures, 2007–2010. *Vital Health Stat 2*. 2013:1–17.
9. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
10. Myers MG. A short history of automated office blood pressure: 15 years to SPRINT. *J Clin Hypertens (Greenwich)*. 2016;18:721–724. doi: 10.1111/jch.12820.
11. Chew DP, Huynh LT, Liew D, Astley C, Soman A, Brieger D. Potential survival gains in the treatment of myocardial infarction. *Heart*. 2009;95:1844–1850. doi: 10.1136/hrt.2009.174276.
12. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential mortality reduction with optimal implementation of angiotensin receptor neprilysin inhibitor therapy in heart failure. *JAMA Cardiol*. 2016;1:714–717. doi: 10.1001/jamacardio.2016.1724.
13. Health, United States, 2015: With Special Feature on Death and Dying. Hyattsville, MD: National Center for Health Statistics; 2015:107.
14. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010;362:590–599. doi: 10.1056/NEJMoa0907355.
15. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension, 7: effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels: updated overview and meta-analyses of randomized trials. *J Hypertens*. 2016;34:613–622. doi: 10.1097/HJH.0000000000000881.
16. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT Jr, Pajewski NM; SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. *JAMA*. 2016;315:2673–2682. doi: 10.1001/jama.2016.7050.
17. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP): SHEP Cooperative Research Group. *JAMA*. 1991;265:3255–3264.
18. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898. doi: 10.1056/NEJMoa0801369.
19. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388–2398. doi: 10.1056/NEJMsa053935.
20. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981

and 2000. *Circulation*. 2004;109:1101–1107. doi: 10.1161/01.CIR.0000118498.35499.B2.
21. Sidney S, Quesenberry CP Jr, Jaffe MG, Sorel M, Nguyen-Huynh MN, Kushi LH, Go AS, Rana JS. Recent trends in cardiovascular mortality in the United States and public health goals. *JAMA Cardiol*. 2016;1:594–599. doi: 10.1001/jamacardio.2016.1326.
22. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8.
23. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ*. 2016;352:i717.
24. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. *JAMA*. 2013;310:699–705. doi: 10.1001/jama.2013.108769.
25. Jaffe MG, Young JD. The Kaiser Permanente Northern California story: improving hypertension control from 44% to 90% in 13 years (2000 to 2013). *J Clin Hypertens (Greenwich)*. 2016;18:260–261. doi: 10.1111/jch.12803.
26. Sica DA, Phillips RA, White WB, Bisognano JD, Townsend RR. "Translational" medicine: transforming SPRINT findings into clinical practice. *J Am Soc Hypertens*. 2016;10:382–386. doi: 10.1016/j.jash.2016.03.192.
27. Phillips RA. Current and future treatment of hypertension in the SPRINT era. *Methodist Debakey Cardiovasc J*. 2015;11:206–213. doi: 10.14797/mdcj-11-4-206.