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Impact of cumulative SBP and serious adverse events on efficacy of intensive blood pressure treatment: a randomized clinical trial

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Background: Intensive blood pressure lowering is increasingly gaining attention. In addition to higher baseline blood pressure, cumulative SBP, visit-to-visit variability, and treatment-induced serious adverse events (SAEs) could impact treatment efficacy over time. Our aim was to assess the impact of cumulative SBP and SAEs on intensive hypertension treatment efficacy in the Systolic Blood Pressure Intervention Trial (SPRINT) population during follow-up.

Methods: Secondary analysis of the SPRINT study: a randomized, controlled, open-label trial including 102 clinical sites in the United States. We included 9068 SPRINT participants with 128 139 repeated SBP measurements. Participants were randomly assigned to intensive (target SBP < 120 mmHg) versus standard treatment (target SBP between 135 and 139 mmHg). We used cumulative joint models for longitudinal and survival data analysis. Primary outcome was a composite outcome of myocardial infarction, other acute coronary syndromes, acute decompensated heart failure, stroke, and cardiovascular mortality.

Results: Although intensive treatment decreased the risk for the primary SPRINT outcome at the start of follow-up, its effect lost significance after 3.4 years of follow-up in the total SPRINT population and after 1.3, 1.3, 1.1, 1.8, 2.1, 1.8, and 3.4 years among participants with prevalent chronic kidney disease, prevalent cardiovascular disease, women, black individuals, participants less than 75 years, those with baseline SBP more than 132 mmHg, and individuals who suffered SAEs during follow-up, respectively.

Conclusion: The initial beneficial impact of intensive hypertension treatment might be offset by cumulative SBP and development of SAEs during follow-up.

Keywords: adverse effects, cumulative joint model, intensive treatment, randomized controlled trial, SBP, treatment efficacy

Abbreviations: cJM, cumulative joint model; CKD, chronic kidney disease; CVD, cardiovascular disease; LMM, linear mixed effect model; SAEs, serious adverse events; SPRINT, Systolic Blood Pressure Intervention Trial

INTRODUCTION

High blood pressure (BP) is a major modifiable risk factor for cardiovascular disease (CVD) [1,2]. In addition to higher baseline BP, visit-to-visit variability and cumulative exposure to BP have been linked to higher risk for CVD and kidney dysfunction [3–5]. Intraindividual BP fluctuations are not random and tend to persist within individuals [6,7]. Therefore, the conventional approach of correlating baseline BP with outcomes of interest in clinical trials might lead to biased estimates regarding treatment efficacy.

Treatment of hypertension and lowering BP has been consistently associated with beneficial clinical outcomes in observational studies and randomized clinical trials [8]. As the epidemiological associations of BP with cardiovascular risk do not indicate a clear lower bound threshold [9], lowering the BP to the lowest tolerable levels is deemed to yield the greatest clinical benefit [10,11]. However, intensive BP lowering has adverse effects that could impact the efficacy of this intervention [12]. Recent evidence from the Systolic Blood Pressure Intervention Trial (SPRINT) showed that intensive lowering of BP significantly reduced major vascular events [13]. Although the frequency of serious adverse events (SAEs) was equal in both conventional and intensive treatment arms

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of the SPRINT, it remains unclear whether benefits from intensive lowering of BP outweigh the risk for adverse events during the course of treatment, in particular among those who developed SAEs, over time.

Taking into account the cumulative effect of the SBP, its intraindividual variability and the adverse effects produced during the follow-up, we asked the question: Do the beneficial effects of intensive SBP reduction remain in the long term in SPRINT total population and in each subgroups under analysis? Using the SPRINT database, we aimed to assess the impact of cumulative exposure to BP on the beneficial effects of intensive hypertension treatment. We further sought to evaluate the impact of SAEs on the efficacy of intensive treatment during follow-up.

METHODS

Original Systolic Blood Pressure Intervention Trial

The SPRINT included 9361 hypertensive participants with SBP between 130 and 180 mmHg, older than 50 years, with increased cardiovascular risk. Exclusion criteria were diabetes mellitus, stroke, advanced chronic kidney disease (CKD), proteinuria more than 1 g/day, polycystic kidney disease, congestive heart failure, dementia, or residence in a nursing home. Participants were randomly assigned to intensive (target SBP < 120 mmHg) versus standard treatment (target SBP between 135 and 139 mmHg) and were evaluated monthly during the first trimester of follow-up and every 3 months afterwards. The trial stopped at 3.26 years median follow-up (range 0–4.5 years) based on recommendation from the data safety monitoring board. Primary outcome was a composite of myocardial infarction, other acute coronary syndromes, acute decompensated congestive heart failure, stroke, and cardiovascular mortality. SAEs were the events meeting any of the following criteria: fatal or life-threatening event resulting in significant or persistent disability, required or prolonged hospitalization, representing significant hazards or harm to research participants potentially requiring medical or surgical intervention [13].

Hypotension, bradycardia, falls, syncope, acute kidney injury, and electrolytes abnormalities were SAEs included in original SPRINT. Participants were coded having experienced SAEs with the first episode, whatever it was.

Our secondary analysis of Systolic Blood Pressure Intervention Trial

For this secondary analysis, we used the original SPRINT database available by data request #4536 to Biologic Specimen and Data Repository Information Coordinating Center repository (National Heart, Lung and Blood Institute) under the SPRINT data analysis challenge initiative, organized by The New England Journal of Medicine. Our research protocol was approved by the Ethical Committee of Universidad Industrial de Santander, Bucaramanga, Colombia. Participants with missing data on covariates or without repeated SBP measurements and observations occurring after the primary event were removed. After exclusion of 293 participants (26 primary outcomes), the current analyses included 9068 participants (97% of the original SPRINT participants) with 128 139 SBP measurements and 536 primary outcomes (95.4% of the original SPRINT outcomes) (Fig. 1).

Statistical analysis

Two researchers independently built the long format database for the analyses to ensure no data management inconsistences. First, we focused on analyzing the SBP longitudinal evolutions. To account for the correlations among the repeated measurements of each patient, we used linear mixed effects models (LMM). Initial descriptive analysis showed that patients experienced an immediate SBP drop after initiation of treatment (Fig. 2). To account for this feature in both the fixed and random effects parts of the LMM, we used natural cubic splines with internal knots placed at 0.25, 0.5, and 1.4 years, and boundary knots (in this case the upper knot) not to the maximum (i.e. the default) but to the 95th percentile of the time variable (0, 3.5 year) to capture the time evolutions. We used a diagonal covariance matrix for the random effects. The treatments effect was included in the fixed effects part both as main effects and interacting with the nonlinear time effect. Second, for the primary SPRINT outcome a Cox model was used in which again treatment was included as an explanatory variable. Finally, to explicitly capture the association between the serial SBP measurements of each patient and the hazard of the primary outcome, we utilized the framework of joint models for longitudinal and survival outcomes [14–17]. This framework combines the two aforementioned mixed effects and Cox models. In the specific joint model we used (cumulative joint model – cJM), we accounted for the cumulative exposure of SBP (that is the whole history of SBP values of each patient) to the hazard of the primary endpoint. Regarding treatment differences, the major advance of joint models versus the traditional Cox model is that they allow to disentangle the total treatment effect into two parts (Fig. 3); namely a direct effect of treatment to the hazard of the endpoint and an indirect effect of treatment via SBP. We also derived the total treatment effect from the cJM that accounts for differences in SBP values over time, and associated 95% confidence intervals (CIs) using bootstrapping (refer to Supplemental Appendix for additional information about cJM, http://links.lww.com/HJH/B41).

In addition, we examined the distribution of different types of SAEs in the total population and in each subgroup. We further evaluated the risk of developing SAEs related to the intervention type (intensive versus standard treatment) using Cox proportional hazards analyses. We then introduced an interaction term in the cJM for occurrence of SAEs during follow-up and stratified the analyses accordingly. Similar to the original SPRINT report, we performed subgroup analyses among CKD/non-CKD, female/male, black/nonblack race, age less than 75/at least 75, CVD/non-CVD, and baseline SBP categories ($\leq$132, 133–144, and $\geq$145 mmHg). All analyses were performed using JM package [15] of R software (R 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table 1 presents characteristics of the 9068 included participants. Similar to the original SPRINT report, the intensive and standard treatment groups are balanced in all variables.

Figure 2 shows the average SBP changes during follow-up in the intensive and standard treatment groups (these

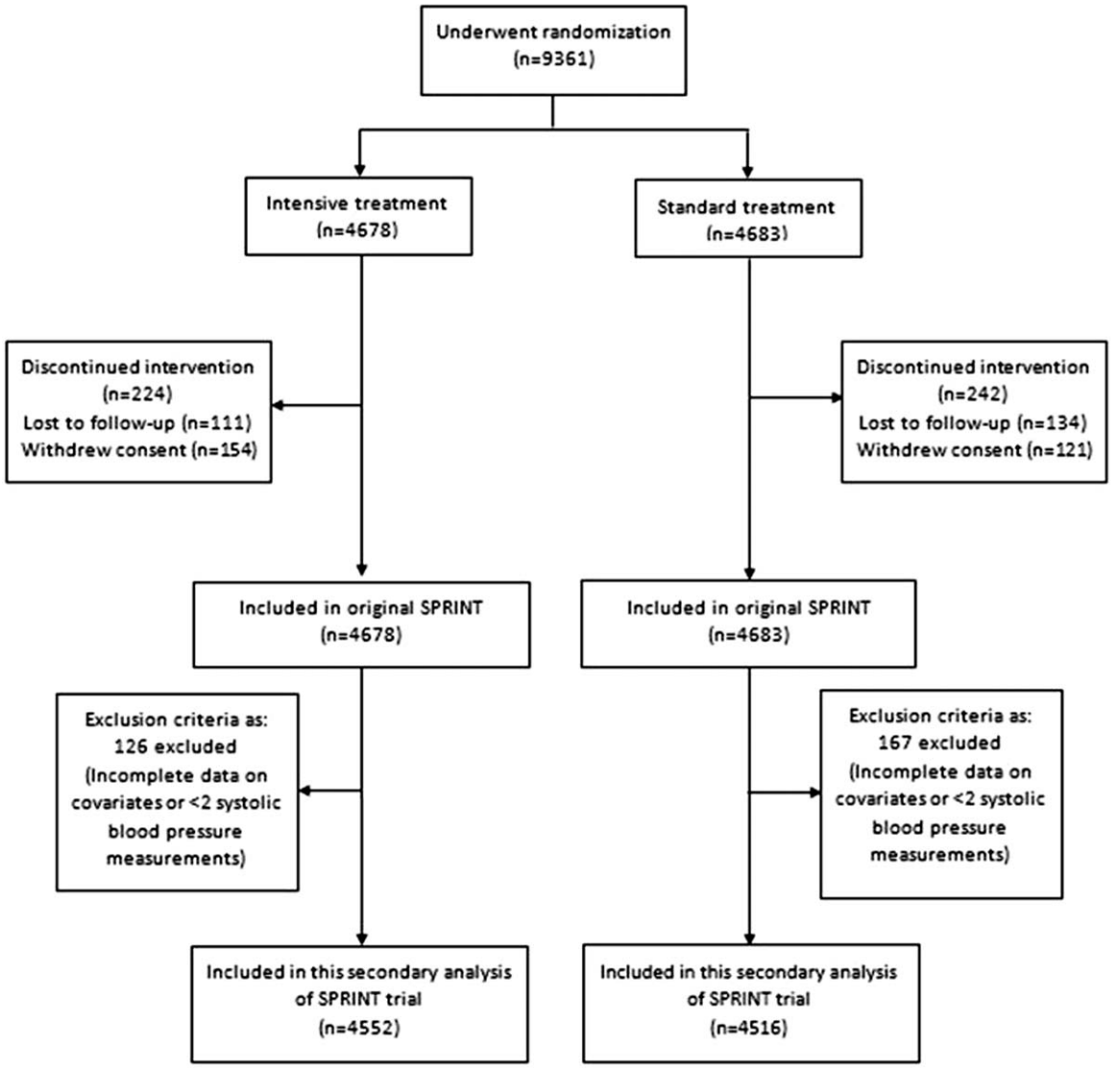

FIGURE 1 Flow chart of the original SPRINT trial participants and participants in our secondary analysis of SPRINT trial.

averages were estimated through the fixed-effects part of the LMM). Figure 4 shows the SBP variability within each individual for several randomly selected participants (this variability was estimated in all participants through the random effects part of the LMM). The plot indicates a large variability of SBP within individuals. Most of the decline in SBP occurred during the first 3 months of follow-up. In the LMM, mean SBP at baseline was 139.7 mmHg in both groups. Intensive treatment significantly reduced SBP by an average 12.73 mmHg during follow-up. This corresponds to the overall difference in average SBP during follow-up between the intensive and standard treatment groups depicted in Fig. 2. Hazard ratio for intensive treatment in the overall population, using traditional Cox model, was similar to the original SPRINT report (hazard ratio; 95% CI: 0.75; 0.63, 0.89). The cJM approach hazard ratio (95% CI) was 0.60 (0.50, 0.72) at the start of follow-up. However, the effect significance was lost after 3.36 years (Fig. 5).

In all subgroups, hazard ratios for intensive treatment using traditional Cox model were similar to the original SPRINT report. Using the cJM approach, intensive treatment decreased the risk for the primary outcome among all subgroups at the start of follow-up. However, the effect lost its significance after 1.3 and 3.4 years among participants with and without baseline CKD, after 1.1 and 3.5 years among women and men, after 1.8 and 3.1 years among black and nonblack individuals, after 2.1 and 3.4 years among individuals less than 75 years and at least 75 years, after 1.3 and 3.4 years among participants with and without prevalent CVD, after 2.5, 2.0, and 1.8 years for individuals with baseline SBP of 132 mmHg or less, between 133 and 144 mmHg, and at least 145 mmHg, respectively (Fig. 6a–l). Appendix Table S1, http://links.lww.com/HJH/B41 presents the hazard ratios (95% CIs) at the start and end of follow-up for all subgroups.

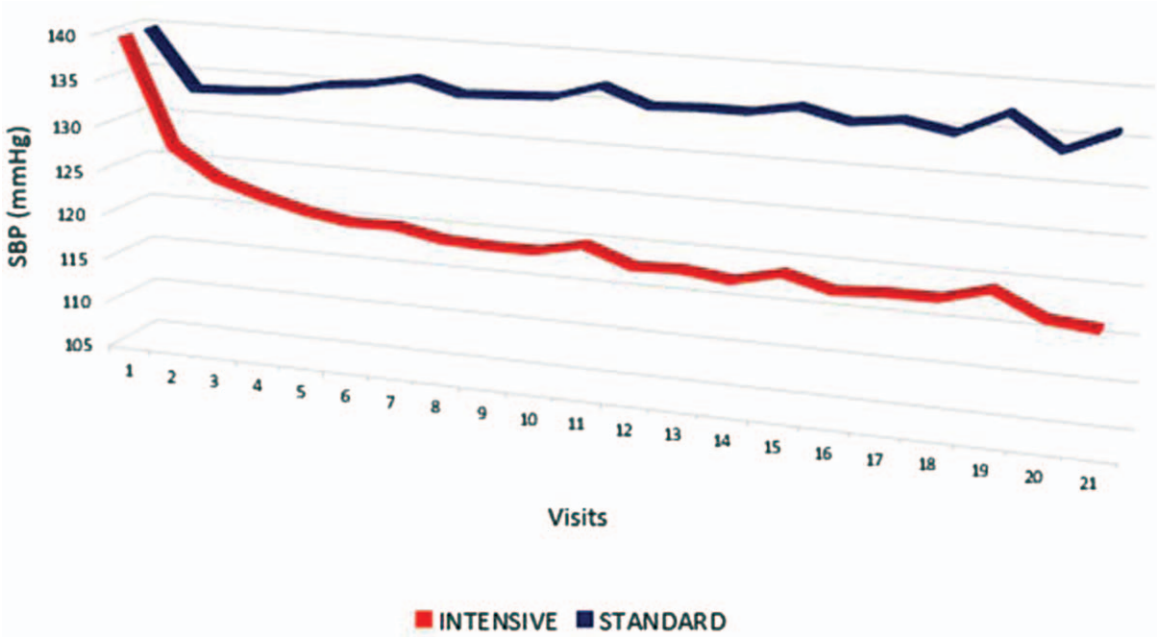

FIGURE 2 Mean SBP trajectories for the intensive treatment and standard treatment groups in Systolic Blood Pressure Intervention Trial.

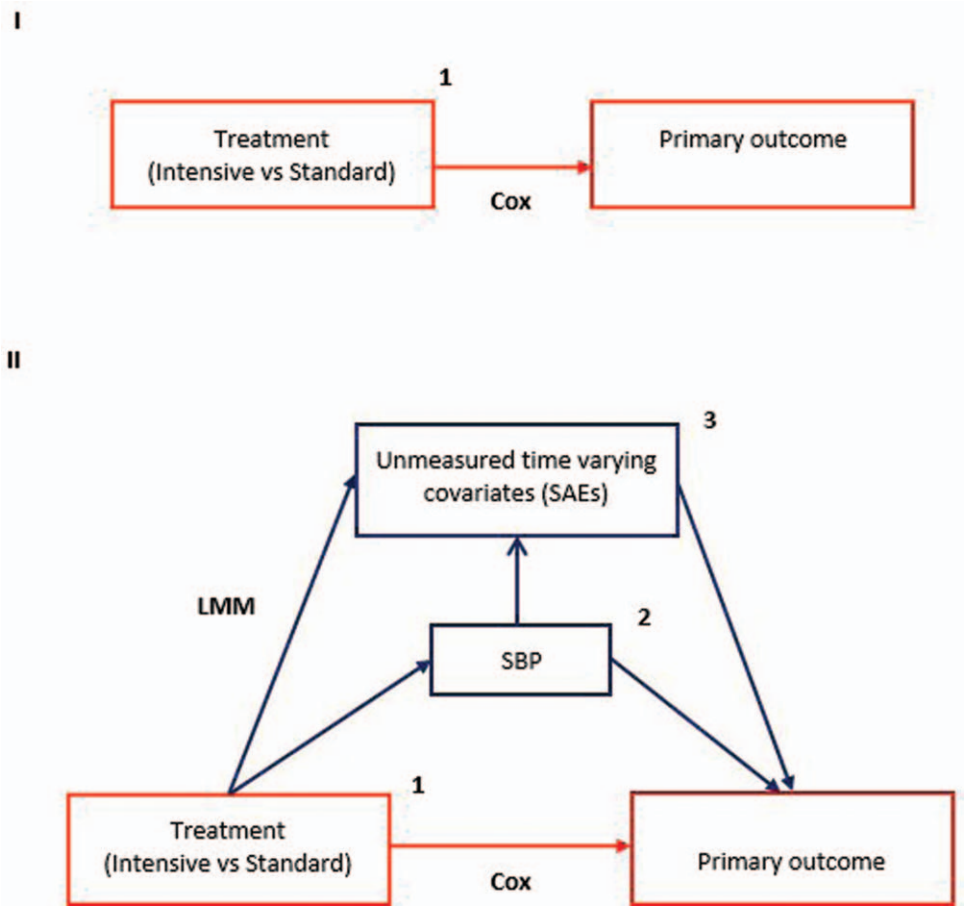

FIGURE 3 Comparison between traditional Cox proportional hazards and cumulative joint model approaches in the total Systolic Blood Pressure Intervention Trial. Cox denotes Cox proportional hazard model, LMM linear mixed effects model, SAEs serious adverse events, I. Traditional Cox model analysis. II. Joint model for longitudinal and time-to-event-data. 1. Baseline characteristics between intervention groups are balanced by randomization. 2. Changes in SBP over time between individuals by groups (fixed part of LMM) and changes in SBP over time within individuals by groups (random part of LMM). 3. All (including unmeasured) time varying covariates (such as SAEs) (random part of LMM).

TABLE 1. Baseline characteristic of the study participants

Characteristic[a]	Intensive treatment, $N = 4552$	Standard treatment, $N = 4516$	*P* value
Criterion for increased cardiovascular risk, *n* (%)[b]			
Age ≥75 years	1276 (28.03)	1258 (27.86)	0.853
Chronic kidney disease[c]	1296 (28.47)	1262 (27.95)	0.578
Cardiovascular disease	921 (20.23)	905 (20.04)	0.818
Clinical	762 (16.74)	757 (16.76)	0.977
Subclinical	245 (5.38)	237 (5.25)	0.776
Framingham 10-year CVD risk score ≥15%	2800 (61.51)	2782 (61.6)	0.928
Female sex, *n* (%)	1625 (35.70)	1582 (35.03)	0.506
Age (years)			
Overall	67.9 ± 9.4	67.8 ± 9.4	0.756
Among those ≥75 years of age	79.8 ± 3.8	79.8 ± 3.9	0.846
Race or ethnic group, *n* (%)[d]			
Non-Hispanic black	1338 (29.39)	1371 (30.36)	0.228
Hispanic	492 (10.81)	470 (10.41)	
Non-Hispanic white	2626 (57.69)	2603 (57.64)	
Other	96 (2.11)	72 (1.59)	
Black race[e]	1413 (31.04)	1438 (31.84)	0.411
Baseline blood pressure (mmHg)			
SBP	139.67 ± 15.8	139.67 ± 15.4	0.993
DBP	78.2 ± 11.9	78.1 ± 12.0	0.519
Distribution of SBP, *n* (%)			
≤132 mmHg	1543 (33.90)	1490 (33.00)	0.345
133–144 mmHg	1451 (31.88)	1504 (33.30)	
≥145 mmHg	1558 (34.23)	1522 (33.70)	
Serum creatinine (mg/dl)	1.07 ± 0.34	1.07 ± 0.33	0.869
Estimated GFR (ml/min per 1.73 m^2)			
Among all participants	71.81 ± 20.6	71.83 ± 20.5	0.973
Among those with estimated GFR ≥ 60	81.4 ± 15.5	81.1 ± 15.5	0.522
Among those with estimated GFR < 60	47.9 ± 9.4	47.9 ± 9.5	0.907
Ratio of urinary albumin (mg) to creatinine (g)	43.0 ± 174.5	41.2 ± 154.4	0.612
Fasting total cholesterol (mg/dl)	190.1 ± 41.5	190.2 ± 41.1	0.971
Fasting HDL cholesterol (mg/dl)	52.92 ± 14.4	52.76 ± 14.5	0.593
Fasting total triglycerides (mg/dl)	125.1 ± 86.4	127.2 ± 94.2	0.262
Fasting plasma glucose (mg/dl)	98.9 ± 13.8	98.8 ± 13.3	0.797
Statin use, *n* (%)	1947 (42.77)	2019 (44.71)	0.063
Aspirin use, *n* (%)	2348 (51.66)	2278 (50.52)	0.278
Smoking status, *n* (%)			
Never smoked	1994 (43.80)	1990 (44.07)	0.670
Former smoker	1934 (42.49)	1936 (42.87)	
Current smoker	622 (13.66)	586 (12.98)	
Missing data	2 (0.04)	4 (0.09)	
Framingham 10-year CVD risk score (%)	20.06 ± 10.9	20.1 ± 10.8	0.789
BMI[f]	29.92 ± 5.8	29.81 ± 5.7	0.373
Antihypertensive agents	1.85 ± 1.04	1.83 ± 1.04	0.379
Not using antihypertensive agents, *n* (%)	419 (9.20)	437 (9.68)	0.442

[a]Plus–minus values are means ± SD. There were no significant differences ($P < 0.05$) between the two groups. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. CVD, cardiovascular disease; GFR, glomerular filtration rate; *n* or *N*, numbers.
[b]Increased cardiovascular risk was one of the inclusion criteria.
[c]Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2 of BSA.
[d]Race and ethnic group were self-reported.
[e]Black race includes Hispanic black and black as part of a multiracial identification.
[f]The BMI is the weight in kilograms divided by the square of the height in meters.

SAEs occurred in 96.3% ($n = 516$) of participants who suffered the primary outcome. Appendix Table S2, http://links.lww.com/HJH/B41, shows distribution of SAEs by subgroup. Using Cox proportional hazards analyses (hazard ratio; 95% CI), hypotension (1.71; 1.26, 2.33), electrolyte abnormalities (1.38; 1.07, 1.79), and acute renal failure (1.68; 1.33, 2.12) were significantly associated with intensive treatment (Table 2). In the cJM, the interaction term for having experienced SAEs during follow-up in the overall population was significant (*P* for interaction SAEs × treatment <0.0001). Therefore, we stratified the cJM analyses based on occurrence of SAEs during follow-up. Cox analyses hazard ratios (95% CI) for intensive treatment in groups with and without SAEs were 0.74 (0.62, 0.88) and 0.25 (0.084, 0.75), respectively. Using the cJM approach, the hazard ratios (95% CI) at the start of follow-up were 0.60 (0.50, 0.72) and 0.19 (0.06, 0.63) for the groups with and without SAEs, respectively (Table S1, http://links.lww.com/HJH/B41). The effect lost significance after 3.4 years for participants with SAEs but remained significant until 4.2 years of follow-up for the non-SAEs group. The wider 95% CI for the non-SAEs group reflects the small number of primary outcomes in this group ($n = 20$; 4% of all primary outcomes) (Fig. 6m and n). Finally, we evaluated the

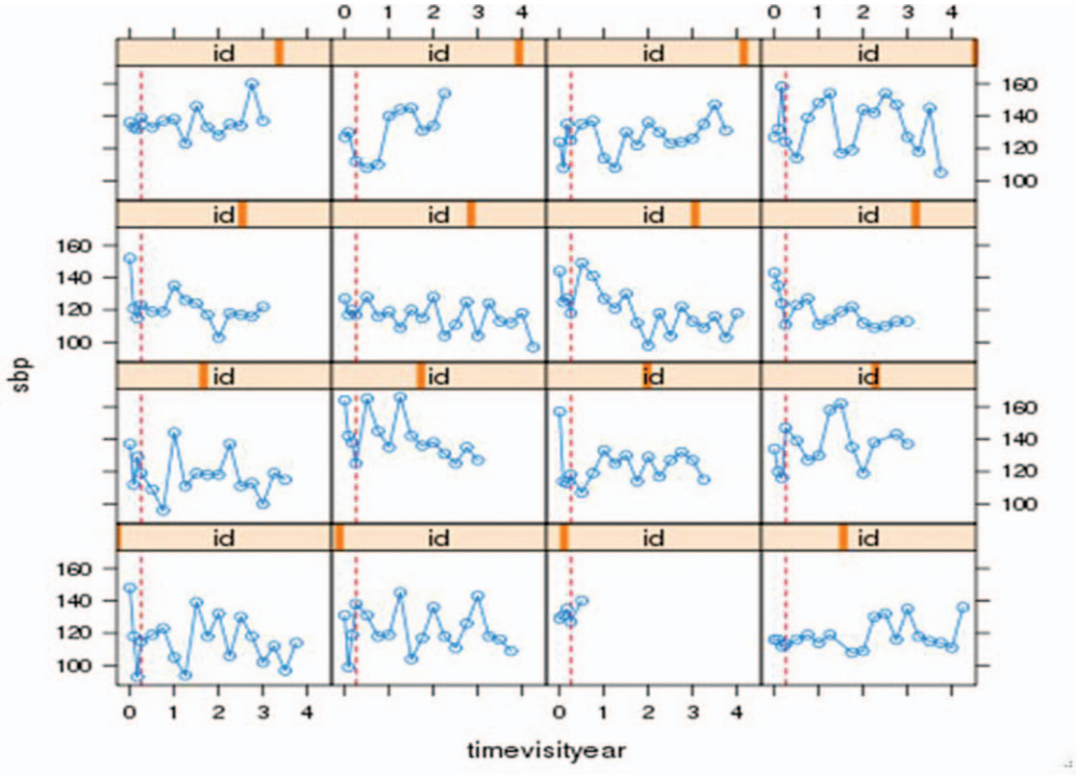

FIGURE 4 Intraindividual SBP variability during follow-up for several randomly selected Systolic Blood Pressure Intervention Trial participants.

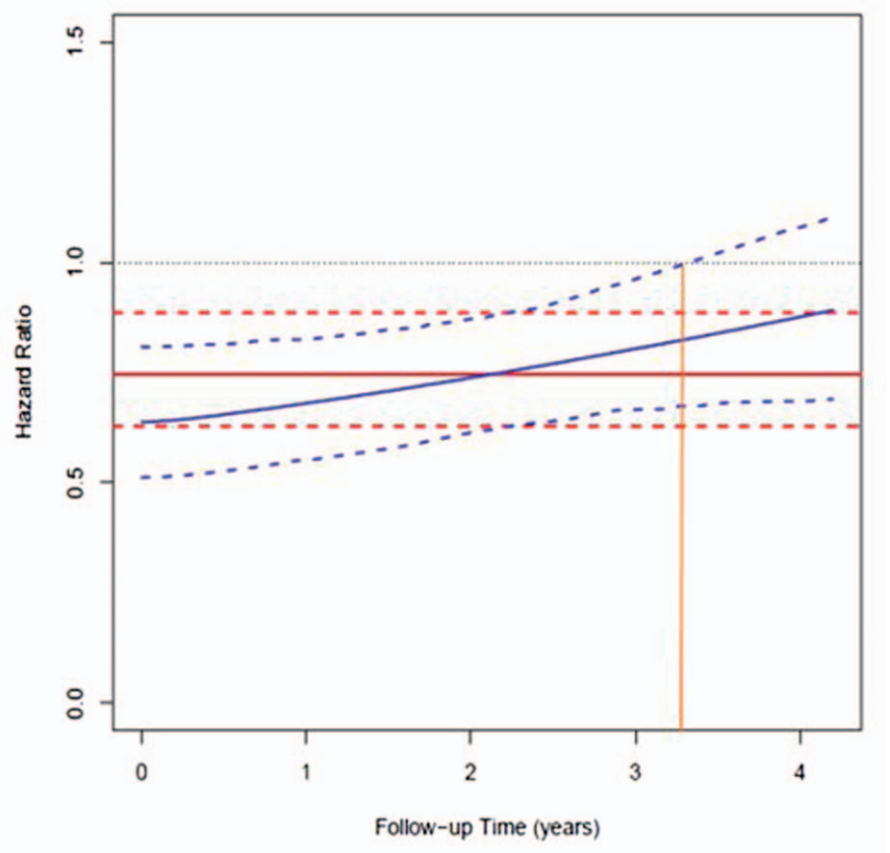

FIGURE 5 Dynamic changes in hazard ratio for primary Systolic Blood Pressure Intervention Trial outcome over time in total population. Hazard ratio and 95% confidence interval for intensive SBP treatment based on traditional Cox proportional hazard approach (red lines) and cumulative joint model approach (blue lines). Orange vertical line denotes the time point at which the statistical significance of the effect estimate is lost.

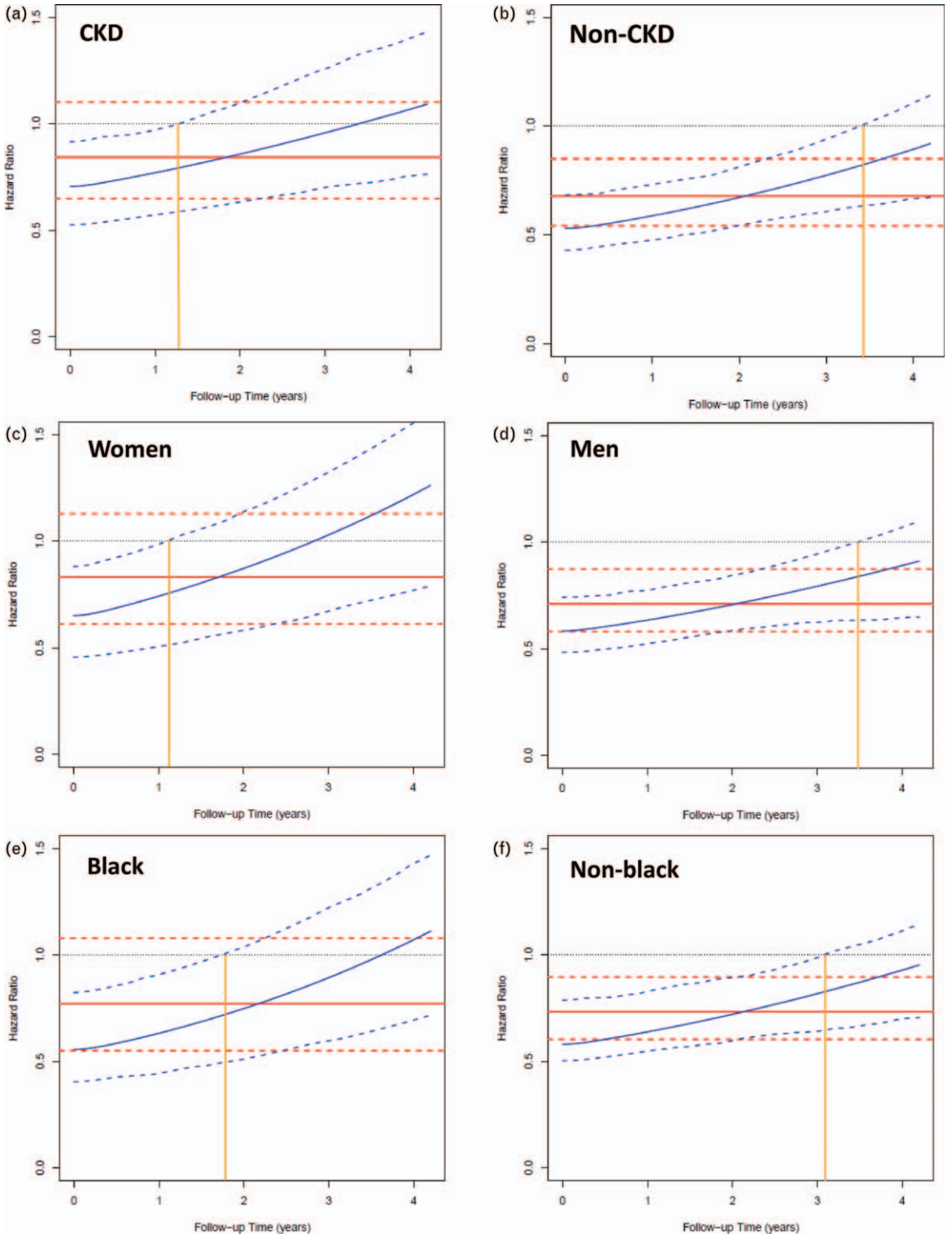

FIGURE 6 Proportional hazards and cumulative joint model approaches among Systolic Blood Pressure Intervention Trial subgroups. Hazard ratio and 95% confidence interval for intensive SBP treatment based on traditional Cox proportional hazard approach (red lines) and cumulative joint model approach (blue lines) for different subgroups: individuals with and without chronic kidney disease at baseline (a and b); women and men (c and d); black and nonblack ethnicities (e and f); individuals less than 75 and at least 75 years of age (g and h); individuals with and without prevalent cardiovascular disease at baseline (i and j); baseline SBP categories of 133–144 and 132 mmHg or less (k and l); subgroups with serious adverse events (m) and without serious adverse events (n) during follow-up. Orange vertical line denotes the time-point at which the statistical significance of the effect estimate is lost in each subgroup.

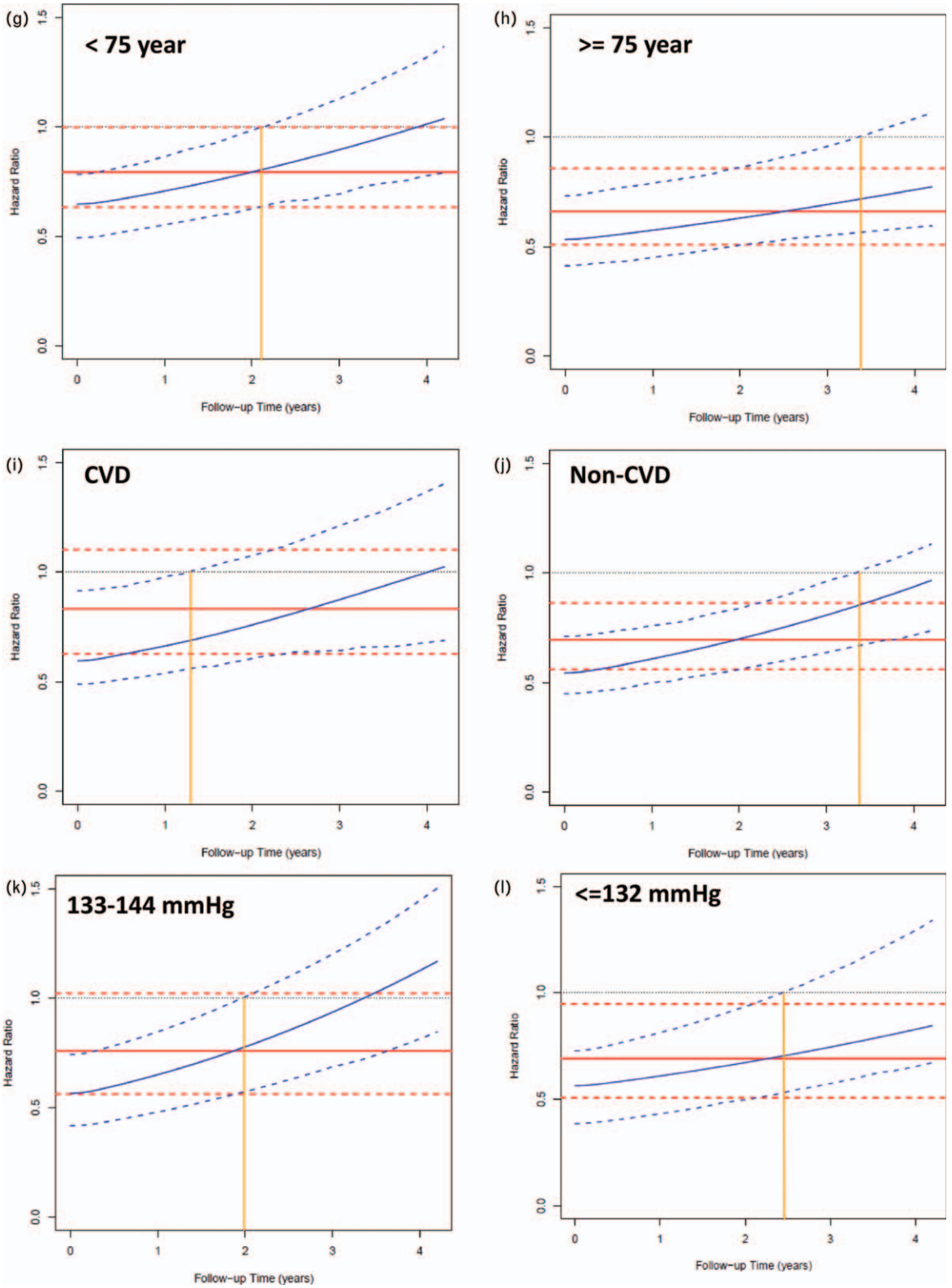

FIGURE 6 (Continued).

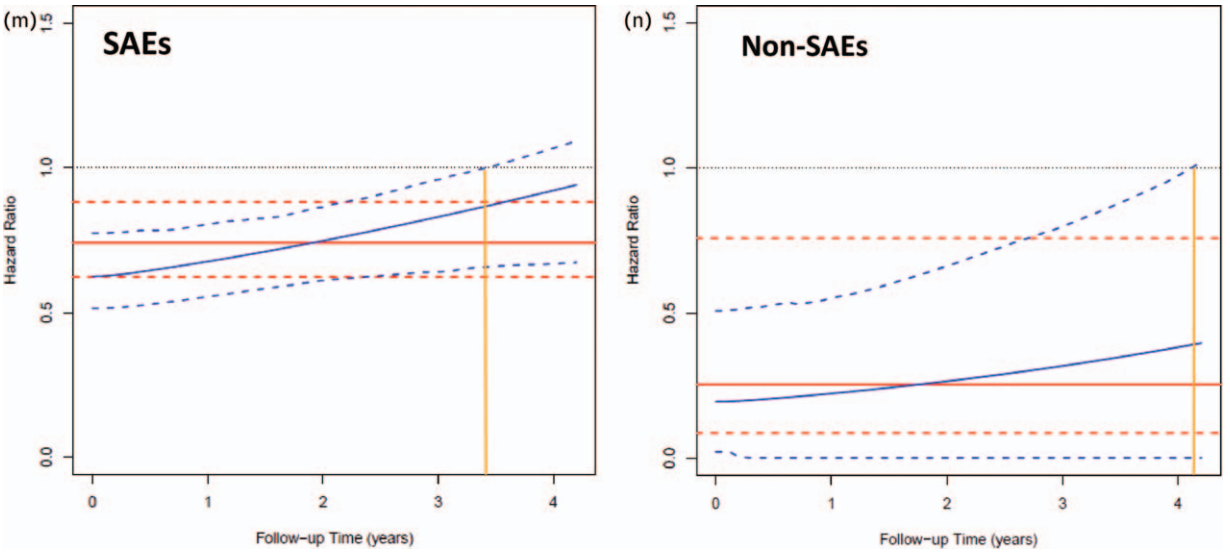

FIGURE 6 (Continued).

differential effect of SAEs in the SPRINT primary outcome among interventions groups using Cox proportional analysis. We found significantly three times larger effects of SAEs on the hazard ratio for primary outcome, in the intensive treatment group (hazard ratio: 96.95; $P < 0.000$) compared with standard treatment (hazard ratio: 33.42; $P < 0.000$) in the overall SPRINT population.

DISCUSSION

Our secondary analysis of SPRINT confirmed that intensive hypertension treatment lowered the risk for the primary outcome at start of follow-up. However, the initial beneficial effect was lost during follow-up in the overall population and particularly among participants with prevalent CKD or CVD, women, black individuals, younger participants, and those with SBP above 132 mmHg at baseline. The beneficial effect of intensive treatment was also lost earlier among patients who suffered SAEs during follow-up.

Conventionally, trials correlate the baseline BP values with outcomes of interest. The original SPRINT analysis showed a 25% reduction in the primary outcome for intensive treatment, using the traditional Cox approach assuming that the benefits remain constant over time. However, besides higher BP at baseline, cumulative exposure to BP and its variability are important risk factors for CVD and kidney dysfunction [4–6]. Our analyses simultaneously took into account the dependency and association between repeated SBP measurements and time-to-event and allowed for evaluation of both direct and indirect (i.e. through SBP) effects of the intensive treatment [14–17]. When cumulative effect of SBP and its variability, both within individuals and between treatment groups, was taken into account, the initial beneficial effect of intensive treatment was lost during follow-up. Importantly, recent secondary analyses of ONTARGET and TRASCEND trials showed a higher predictive value for a composite mean SBP over time compared with baseline or event-preceding or time-updated SBP [18], which substantiates our approach. Based on experimental studies, high BP variability induces a chronic inflammatory state through activation of the myocardial angiotensin-converting enzyme, increasing the expression of monocyte-protein-1 and transforming growth factor-B, resulting in ventricular hypertrophy,

TABLE 2. Association of intensive treatment with serious adverse events during follow-up

Characteristic	Intensive treatment, $N = 4552$	Standard treatment, $N = 4516$	HR (CI 95%)	*P* value
All serious adverse events[a] *n* (%)	1748 (38.40)	1676 (37.11)	1.04 (0.98–1.12)	0.210
Specific conditions of interest				
Hypotension	110 (2.42)	64 (1.42)	1.71 (1.26–2.33)	0.001
Syncope	104 (2.28)	80 (1.77)	1.29 (0.96–1.73)	0.087
Bradycardia	86 (1.89)	70 (1.55)	1.22 (0.89–1.67)	0.222
Electrolyte abnormality	142 (3.12)	102 (2.26)	1.38 (1.07–1.79)	0.012
Injurious fall[b]	104 (2.29)	105 (2.33)	0.98 (0.75–1.29)	0.887
Acute kidney injury or acute renal failure[c]	192 (4.22)	114 (2.52)	1.68 (1.33–2.12)	0.000

Serious adverse events include conditions of interest classified as possibly or definitely related to the intervention by the SPRINT investigators. AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; *N*, numbers; SPRINT, Systolic Blood Pressure Intervention Trial.
[a]Defined as an event that was fatal or life threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalization, or was an important medical event that the investigator judged to be a significant hazard or harm to the participant that may have required medical or surgical intervention to prevent one of the other events listed above.
[b]An injurious fall was defined as a fall that resulted in evaluation in an emergency department or resulted in hospitalization.
[c]Acute kidney injury and acute renal failure were coded if the diagnosis was listed in the hospital discharge summary and was felt to be one of the top three reasons for admission or continued hospitalization. A few cases of AKI were noted in an emergency department if the participant presented for one of the other conditions of interest.

remodeling and dysfunction, perivascular fibrosis, endothelial injury, and kidney dysfunction [19–23].

Three recent studies investigating the association of visit-to-visit BP variability with primary SPRINT outcome and adverse events have led to conflicting results. Chang *et al.* [24] showed no association between BP variability with primary SPRINT outcome but a significant association with all-cause mortality. This study, however, included only the SBP measurements between 3 and 18 months of follow-up and discarded about 42% ($n = 238$) of the primary SPRINT outcomes. Moreover, they adjusted for multiple covariates disregarding the previous treatment randomization. Goyal *et al.* [25] showed SBP variability to be independently associated with higher risk of hyponatremia among SPRINT participants. In another post-hoc analysis among a subset of SPRINT participants with baseline CKD, DBP variability was associated with the primary outcome and with major SAEs [26].

The beneficial effect of intensive treatment was lost earlier among specific subgroups in our analyses; including CKD participants, women, and individuals of black ethnicity. Previous studies have observed larger SBP variability among these groups, linking it to a higher vascular risk among these individuals [23,27]. Their larger SBP variability might explain earlier loss of beneficial effect of intensive treatment among these individuals. Compared with older participants, individuals younger than 75 years lost the beneficial effect of intensive treatment earlier. Although SBP variability increases with age, younger individuals have shown a greater susceptibility to target organ damage resulting from SBP variability [27]. Moreover, older patients might respond better to medications such as diuretics due to their beneficial impact on outcomes such as congestive heart failure which is one component of the primary SPRINT outcome [28]. These factors might explain earlier loss of beneficial impact of intensive treatment among younger individuals in our study. We also observed that individuals with SBP more than 132 mmHg at baseline and during follow-up lost the beneficial impact of intensive treatment earlier compared with those with SBP of 132 or less. This could be attributed to a higher SBP variability among individuals with SBP more than 132 mmHg due to larger fluctuations in the number or dose of prescribed antihypertensive medications in this group. It is important to mention that the 95% CI for participants with prevalent CKD or CVD, women, black individuals was substantially wider than the comparison groups. However, the slope of the graphs for participants with prevalent CKD or CVD, women, black individuals were clearly larger compared with non-CKD, non-CVD, male, nonblack race subgroups, respectively (P interaction <0.0001) (Fig. 6, Supplemental Fig. 6, http://links.lww.com/HJH/B41).

Intensive BP lowering could lead to adverse events altering the efficacy of this intervention during follow-up. Our study showed less benefit for intensive treatment among individuals who experienced SAEs during follow-up (Fig. 6m and n). Although the proportion of participants who suffered SAEs was similar between the intensive and standard treatment groups, type of adverse event was different. More severe adverse events including hypotension, electrolyte abnormalities, and acute kidney injury occurred more often in the intensive treatment group. In addition to cumulative SBP and its variability, development of SAEs could partly explain loss of initial beneficial effect for intensive treatment over time. A secondary analysis of SPRINT among participants with normal renal function at baseline showed a 1.2 ratio for developing CKD per preventing one cardiovascular event [29]. The risk for mortality and CVD among patients with renal dysfunction is between 1.2–1.8 and 1.9–2.9, respectively [30]. Projecting the SPRINT eligibility criteria to the 1999–2006 National Health and Nutrition Examination Survey showed that intensive treatment prevents 107 500 deaths per-year but increases the number of patients with SAEs to 222 600 per-year [12]. Notably, SAEs occurred in the majority of SPRINT participants who suffered the primary outcome (96.3%). In the intensive treatment group, SAEs were associated with SPRINT primary outcome three times more than the SAEs in the standard group. If SAEs increase the risk of primary outcome, the harms of intensive hypertension treatment might offset its potential benefits.

New guidelines for management of BP, redefine the therapeutic target as BP less than 130/80 mmHg [31,32]. For primary prevention, the guidelines recommend pharmacology treatment among individuals with BP more than 130/80 mmHg and cardiovascular risk more than 10% or those with cardiovascular risk less than 10% but BP more than 140/90 mmHg. In secondary prevention settings, pharmacology treatment is recommended for BP more than 130/80. However, our results in the subgroup of SPRINT participants with CVD history showed earlier loss of beneficial impact of intensive SBP treatment over time than for non-CVD participants.

Despite the observed increasing tendency in the hazard ratios over time, as the SPRINT terminated after median 3.26 years of follow-up (range 0–4.5 years), our findings are only applicable to this time-window. 96.3% of patients who developed a primary outcome suffered SAEs during follow-up. This led to small number of events and limited power for the analyses among participants without SAEs.

Concerns have been raised that the BP measurements in SPRINT might not be directly comparable with those of other trials and not readily applicable to clinical settings. The measurement of BP in the SPRINT was unattended at the majority of study sites [33]. Assessment of 24-h ambulatory BP monitoring in a subset of SPRINT participants, demonstrated that daytime ambulatory SBP was higher than clinic SBP, the agreement between daytime ambulatory SBP and clinic SBP was poor, and the difference in ambulatory SBP between the two SPRINT treatment groups was lower than the difference measured by clinic SBP [34]. Although a subsequent analyses of the SPRINT reported that the SPRINT results were insensitive to whether or not BP measurements were made in an attended manner [35], it has been suggested that treatment arms in SPRINT could translate into clinic SBP of 132 versus 144 mmHg [36,37].

Major strength of our study is the use of a robust statistical model which allows us to maintain the initial SPRINT randomization in our analyses. In addition, our approach allows for evaluation of the cumulative impact of SBP and its variability (both intraindividual and between groups) as well as SAEs on the primary SPRINT outcome,

taking into account that hazard ratios may change over time [38]. An additional benefit of using joint model analysis is that postrandomization BP measurements are treated as an outcome (and not as a covariate), the joint likelihood of the BP measurements and the time to the primary endpoint are also completely specified, thus providing valid estimates of the treatment effect. During development of the statistical model and for construction of different SBP trajectories over time, we specifically took into account the initial decrease in SBP at the beginning of follow-up. As model specification and goodness of fit are fundamental for the validity of our results, supplemental statistical material details all the steps we followed for development of our statistical models.

Finally, we are aware that our results may be considered controversial, however, they are in line with what was originally published by the SPRINT group (Fig. 4 original publication in *The New England Journal of Medicine*) [13], which showed that intensive treatment did not significantly reduce cardiovascular risk in patients with CKD, younger participants, women, black individuals, CVD, and those with baseline SBP more than 132 mmHg. These groups are the same ones in which we have found that the protective benefit of intensive treatment is lost early during follow-up. Thus, loss of beneficial effect occurred earlier in those who did not significantly benefit from intensive treatment in the original SPRINT. These findings further increase confidence in the validity of our results.

In conclusion, intensive SBP treatment lowered the risk for the primary SPRINT outcome at the start of follow-up. However, the initial beneficial effect was lost during follow-up in the overall population and particularly among participants with prevalent CKD or CVD, women, black individuals, younger participants, those with baseline SBP more than 132 mmHg, and patients who suffered SAEs.

Our results call for caution regarding universal recommendations for intensive BP treatment, particularly among specific subgroups. In addition to potential adverse effects from intensive treatment, the impact of cumulative SBP as well as intraindividual SBP variability should not be dismissed. As the tenet of medicine 'Primum non nocere' must prevail, longer term clinical trials, with focus on sustained beneficial effects of intensive interventions over time and on patient safety are needed. cJM analysis is a novel and not frequently considered approach for assessment of clinical trial data. This method adds a time-varying perspective which approaches the conditions encountered in daily clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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