

Effect of Intensive Blood Pressure Treatment on Heart Failure Events in the Systolic Blood Pressure Reduction Intervention Trial

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Background—Acute decompensated heart failure (ADHF) was a frequent common outcome in SPRINT (Systolic Blood Pressure Intervention Trial). We examined whether there was differential reduction in ADHF events from intensive blood pressure [BP] treatment among the 6 key, prespecified subgroups in SPRINT: age ≥ 75 years, prior cardiovascular disease, chronic kidney disease, women, black race, and 3 levels of baseline systolic BP (≤ 132 versus >132 to <145 versus ≥ 145 mm Hg).

Methods and Results—ADHF was defined as hospitalization for ADHF, confirmed and formally adjudicated by a blinded events committee using standardized protocols. At 3.29 years follow-up, there were 103 ADHF events (2.2%) among 4683 standard arm participants and 65 ADHF events (1.4%) among 4678 intensive arm participants (Cox proportional hazards ratio, 0.63; 95% confidence interval, 0.46–0.85; P value = 0.003). In multivariable analyses, including treatment arm, baseline covariates that were significant predictors for ADHF included chronic kidney disease, cardiovascular disease, age ≥ 75 years, body mass index, and higher systolic BP. The beneficial effect of the intervention on incident ADHF was consistent across all prespecified subgroups. Participants who had incident ADHF had markedly increased risk of subsequent cardiovascular events, including a 27-fold increase ($P < 0.001$) in cardiovascular death.

Conclusions—Targeting a systolic BP < 120 mm Hg, compared with < 140 mm Hg, significantly reduced ADHF events, and the benefit was similar across all key, prespecified subgroups. Participants who developed ADHF had markedly increased risk for subsequent cardiovascular events and death, highlighting the importance of strategies aimed at prevention of ADHF, especially intensive BP reduction.

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Hypertension is the most prevalent risk factor for heart failure (HF) and precedes the diagnosis of HF in 75% to 85% of people who develop HF.¹ In addition, hypertension pathophysiology is closely linked to all key adverse outcomes in HF, including acute exacerbations, chronic symptoms, and mortality.¹ Although elevated systolic blood pressure (SBP) is associated with an increased risk of developing HF, and blood

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pressure (BP) reduction prevents incident HF, the optimal target for BP lowering for HF prevention has been uncertain.² In the recently reported SPRINT trial (Systolic Blood Pressure Intervention Trial), which was terminated early because of benefit, intensive BP reduction reduced the risk of the primary

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outcome (a composite of a myocardial infarction [MI], acute coronary syndrome not resulting in MI, stroke, acute decompensated HF [ADHF], or death from cardiovascular causes) by 25% and reduced total mortality by 27%.³ The risk for ADHF was reduced by 38% by intensive BP reduction in SPRINT.³

SPRINT included a highly diverse group of participants, including those in 13 key, prespecified subgroups: age (≥ 75 years and < 75 years); women and men; black race and non-black race; chronic kidney disease (CKD) and no CKD; prior cardiovascular disease (CVD) and no prior CVD; and the 3 tertiles of baseline SBP. Multiple lines of evidence suggest the potential for disparate responses to intensive BP lowering among participants in these subgroups. For example, in elderly patients in whom the risk of HF is the highest,⁴ arterial stiffening is common and may contribute to the elevation of SBP and the depression of diastolic BP (DBP).⁵ Although isolated elevation of SBP without a concomitant elevation of DBP is a known risk factor for incident HF in older adults,^{6,7} low DBP has been associated with adverse cardiovascular outcomes.⁸ This is important because myocardial perfusion depends on adequate DBP, and myocardial perfusion requirements are increased in hypertension, such that intensive DBP reduction could reduce myocardial perfusion and promote myocardial ischemia, adverse left ventricular (LV) dilation, and subsequent HF. Some studies have suggested that anti-hypertensive treatment can be associated with increased risk of coronary events at low levels of DBP, particularly in those with CVD.⁹

In women, hypertension contributes more to the population burden of HF than MI; the 5-year mortality after the onset of hypertensive HF in women is high, $\approx 69\%$.^{4,10,11} In addition, women develop concentric LV hypertrophy and maintain normal chamber size, whereas men most frequently develop eccentric LV hypertrophy with chamber dilation.^{12,13} Thus, treating to lower BP goals in SPRINT may produce divergent responses by sex because of differences in both ischemic heart disease burden and LV hypertrophic remodeling.

Compared with nonblacks, HF is more prevalent in blacks and has higher rates of death and morbidity.^{14–16} Among patients with CKD, HF is the leading cardiovascular complication, and its prevalence increases with declining kidney function.¹⁷ In both blacks and those with CKD, studies suggest that antihypertensive therapy may be of benefit in reducing cardiovascular events; however, there is uncertainty regarding the optimal range of BP lowering.^{15,16,18–22}

The purpose of this analysis was to determine the relative risk for developing ADHF among the prespecified subgroups in SPRINT, the impact of intensive BP treatment on development of ADHF among each of these subgroups, the predictors of incident ADHF, and the impact of assignment to the intensive BP treatment arm for subsequent outcomes among participants who developed ADHF in SPRINT.

Methods

Study Population

The study population included all participants in SPRINT; the details of the design and primary results of SPRINT have been previously reported.^{3,23} Briefly, 9361 participants ≥ 50 years of age with SBP

≥ 130 mmHg, without a history of diabetes mellitus or stroke, and an increased risk of cardiovascular events were enrolled from November 2010 to March 2013. Increased cardiovascular risk was defined by 1 or more of the following: clinical or subclinical CVD other than stroke; CKD, excluding polycystic kidney disease; a 10-year risk of CVD of $\geq 15\%$ on the basis of the Framingham risk score; or an age of ≥ 75 years. Detailed inclusion and exclusion criteria were previously reported.²³ The study was approved by the institutional review board at each participating study site. All participants provided written informed consent.

The CVD subgroup included participants with clinical or subclinical CVD other than stroke. Clinical CVD was defined as previous MI, percutaneous intervention, coronary artery bypass grafting, carotid endarterectomy, or carotid stenting; peripheral arterial disease with revascularization; acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test or positive cardiac imaging study; at least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery; or abdominal aortic aneurysm ≥ 5 cm with or without repair. Subclinical CVD was defined as coronary artery calcium score ≥ 400 Agatston units within the past 2 years; ankle brachial index ≤ 0.90 within the past 2 years; or LV hypertrophy by ECG (based on computer reading), echocardiogram report, or other cardiac imaging procedure report within the past 2 years. CKD was defined as estimated glomerular filtration rate of 20 to < 60 mL/min per 1.73 m² of body surface area, calculated with the use of the 4-variable Modification of Diet in Renal Disease equation.³ People with symptomatic HF within the past 6 months or LV ejection fraction (by any method) $< 35\%$ at the time of randomization were not included in the study.

Study Measurements

Demographic data (age, race, ethnicity, and sex) and physical measurements (weight and height) were collected during participant screening and confirmed at the baseline randomization visit. SBP and DBP were recorded as the calculated average of 3 seated readings. Participants answering a self-administered questionnaire as Yes to the question “Do you now smoke cigarettes?” were considered current smokers.

Intervention

All participants provided written informed consent. Participants were randomly assigned to have SBP targeted to < 140 mmHg ($n=4683$) or < 120 mmHg ($n=4678$). Extensive details regarding the randomization and intervention have been previously reported.^{3,23,24}

Study Outcomes

Prespecified subgroups of interest for all outcomes were defined according to status with respect to CVD at baseline (yes versus no), status with respect to CKD at baseline (yes versus no), sex, race (black versus nonblack), age (< 75 versus ≥ 75 years), and baseline SBP tertiles (≤ 132 , > 132 to < 145 , and ≥ 145 mmHg).

Clinical and laboratory data were obtained at baseline and every 3 months for the first year, then every 6 months. Data regarding potential outcomes were assessed every 3 months using a structured interview to minimize ascertainment bias,²³ and a standard protocol, with centralized monitoring by the coordinating center, was used to obtain relevant information, including medical records, laboratory reports, and electrocardiograms. Deaths were investigated whenever clinic staff became aware of them.

All clinical events, including ADHF, were formally adjudicated by a Morbidity and Mortality committee using a standardized electronic form. Adjudicators were blinded to treatment assignment. ADHF was defined as hospitalization or emergency department visit requiring treatment with infusion therapy (diuretic or inotropic agents) for a clinical syndrome that presented with multiple signs and symptoms consistent with cardiac decompensation and inadequate cardiac pump function. A detailed manual of operations for adjudication was developed based initially on that used and validated in the Atherosclerosis Risk in Communities study.²⁵ All ADHF

events were new (incident) HF events. Positive symptoms supporting ADHF included new onset or increasing shortness of breath, peripheral edema, orthopnea, or paroxysmal nocturnal dyspnea. Positive signs supporting ADHF included hypoxia; pulmonary rales on clinical examination; pulmonary vascular congestion on chest x-ray; elevation of biomarker BNP (B-type natriuretic peptide) or pro-N-terminal BNP above diagnostic threshold; reduced LV ejection fraction or diastolic dysfunction; new or increased treatment specifically for ADHF, such as intravenous loop diuretic or inotrope; documented response to therapy; and evidence in the treating physician's notes that the primary reason for the hospitalization or emergency department visit was ADHF.

Confirmation of ADHF events relied on multiple pieces of key clinical data, as well as adjudicators' clinical judgment, guided by specific, prespecified definitions and operational rules. Identification of ADHF did not rely on any single piece of data, such as the presence of dyspnea, edema, a low LV ejection fraction, or an increased BNP value. For participants seen in the emergency department alone, positive adjudication as an ADHF event required unequivocal documentation in the medical record of administration of intravenous loop diuretic or inotrope and an appropriate response to therapy, regardless of the strength of the history, physical examination, and other evaluations supporting ADHF.

Chronic stable HF during a hospitalization, with no evidence of decompensation or augmentation of therapy for worsening HF, was not considered an end point in SPRINT. Reduced LV ejection fraction in the absence of symptoms, right-sided HF, and volume overload because of inadequate dialysis in patients with end-stage renal disease were not considered SPRINT HF end points.

The SPRINT BP intervention was stopped early at the recommendation of the data and safety monitoring board (and accepted by National Institutes of Health) on August 20, 2015, because of benefit in the intensive arm on the primary outcome. Data, in this article, were frozen on March 10, 2016, but only used adjudicated events that occurred on or prior to August 20, 2015, that included additional 6 events from the original report,³ 3 in each treatment arm.

Statistical Analyses

All statistical analyses were conducted at the coordinating center with the use of SAS software, version 9.4 (SAS Institute). Continuous variables are presented as mean and standard deviation or median and interquartile range, and categorical variables are presented as number with percent. Baseline characteristics were compared among participants who did and did not experience ADHF during the trial, with the use of the χ^2 test, Wilcoxon rank-sum test, and 2-sample *t* tests where appropriate.

Time until first occurrence of ADHF was compared between the 2 treatment arms with the use of the intention-to-treat approach for all randomized participants. For this analysis, we used Cox proportional hazards regression with 2-sided tests at the 5% level of significance, with stratification by clinical site. Follow-up time was censored on the date of the last event ascertainment. Interactions between prespecified subgroups and the treatment arm were assessed with a likelihood ratio test for interaction. As a sensitivity analysis, baseline variables likely related to the development of ADHF were assessed in univariate models and added as a group to the primary analysis model.

Among the subset of participants experiencing HF during the trial, a Cox proportional hazards model, including baseline covariates and treatment arm, was used to examine which baseline covariates were predictive of recurrent ADHF. Only the first recurrence of ADHF was used in this analysis. Time to event was calculated as the number of days from the first ADHF to the first recurrence, and censoring time was calculated as the time from first ADHF to the last participant visit. The effect of ADHF on other clinical outcomes (all-cause mortality, CVD mortality, non-MI acute coronary syndrome, and stroke) was evaluated using a time-dependent Cox proportional hazards model, with a time-varying covariate for first ADHF event to model the effect of participants moving from the non-ADHF state to the ADHF state on these other clinical outcomes.²⁶

No adjustments were made for multiple testing. Nominal *P* values are reported throughout as simple guides to possible associations.

Results

A total of 9361 participants were enrolled between November 2010 and March 2013. The BP intervention was stopped early at the recommendation of the data and safety monitoring board (and accepted by National Institutes of Health) on August 20, 2015, because of benefit in the intensive arm on the primary outcome.³ The median follow-up at that time was 3.29 years of the planned average of 5 years. However, processing and adjudication of events that occurred prior to August 20, 2016, continued such that as of the date of this analysis (March 10, 2016), there were a total of 103 ADHF events among 4683 (2.2%) participants in the standard arm and 65 ADHF events among 4678 (1.4%) intensive arm participants (Cox proportional hazards ratio [HR] stratified by clinical site, 0.63; 95% confidence interval, 0.46–0.85; *P* value =0.003) for a risk reduction of 37%. Separation between groups in ADHF events was apparent at 6 months (Figure 1). The number needed to treat²⁷ to prevent an ADHF event during the median 3.29 years of the trial was 130.

Table 1 shows the baseline clinical characteristics for the cohort based on ADHF occurrence during the trial and by treatment arm. Patients who developed ADHF were older, had higher prevalence of baseline CKD, had clinical CVD, had increased albuminuria, and had lower estimated glomerular filtration rate and DBP at baseline irrespective of treatment arm. Race and sex were similar in the ADHF and no ADHF groups in both treatment arms. Univariate predictors for development of ADHF were randomization to the standard treatment arm, age ≥ 75 years, and subgroups with CKD and CVD (Table 2). In multivariable analyses that included treatment arm, the baseline covariates that were statistically significant predictors for development of ADHF included age ≥ 75 years, CKD, CVD, higher baseline SBP, body mass index, smoking status, and lower baseline DBP (Table 3). The effects of the intervention on the rate of ADHF events were consistent across the prespecified subgroups (Figure 2). There were no statistically significant interactions (*P* values ranged from 0.21 to 0.99) between treatment arm and subgroup with respect to the risk of ADHF events, and all subgroups had reduced risk of ADHF when assigned to the intensive BP intervention (Figure 2).

Clinical Outcomes After ADHF Events

Participants who were adjudicated as having an incident ADHF event had markedly increased risk of subsequent cardiovascular outcomes and death, regardless of treatment arm. Even after adjusting for treatment arm, sex, baseline age, baseline CKD, and baseline CVD, the HR for subsequent cardiovascular events and death among participants who experienced an initial ADHF event remained high (Table 4). Among the 168 participants who had an initial ADHF event, 48 participants (29%) had at least 1 recurrent ADHF event. There was no significant difference in this regard between treatment group: 29 of 103 (28%) standard arm and 19 of 65 (29%) intensive arm (HR, 0.93; 95% confidence interval, 0.50–1.67; *P* value =0.81). Black race and CKD sub group were the most significant baseline predictors of recurrent ADHF events (Table 5).

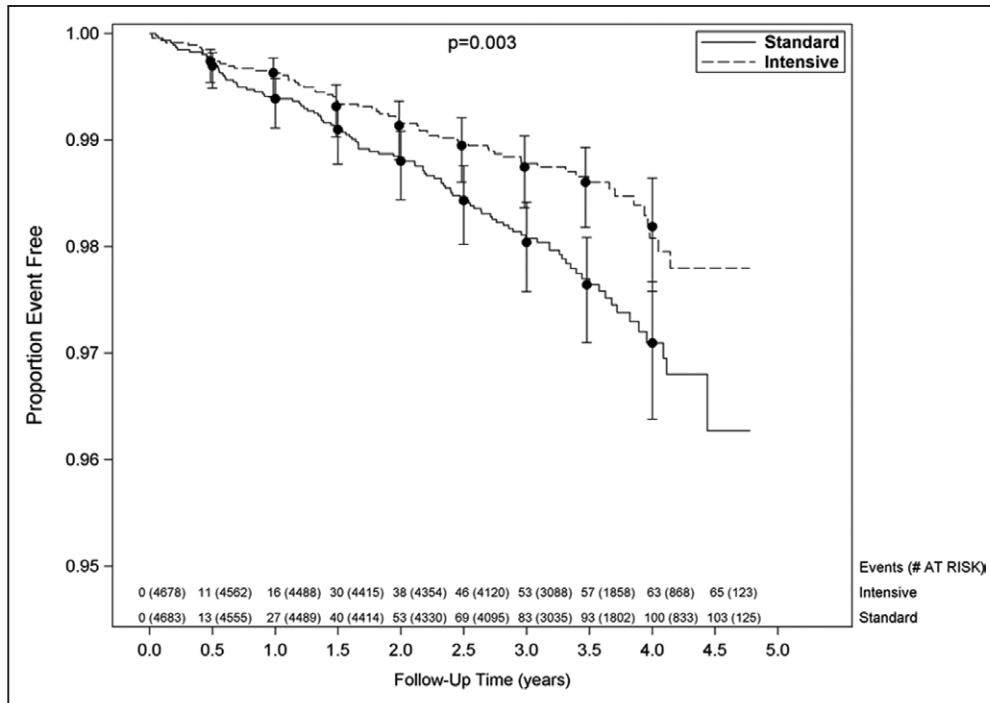


Figure 1. Kaplan–Meier curves for the SPRINT (Systolic Blood Pressure Reduction Intervention Trial) acute decompensated heart failure outcome by treatment group. Vertical bars indicate 95% confidence intervals. *P* value is from a Cox proportional hazards model stratified by clinical site. Number at risk and number of events is shown every 6 months.

Discussion

ADHF was one of the most frequent outcomes in the SPRINT trial, which was terminated early because of a 25% reduction in the primary outcome, a composite of cardiovascular events, including ADHF.³ The present report, which includes 6 additional ADHF events adjudicated since the main trial outcome report, showed that among participants with systolic hypertension who were aged ≥ 50 years and at high risk for cardiovascular events, treatment that targets an SBP of < 120 mmHg, as compared with < 140 mmHg, resulted in a 36% lower rate of ADHF. The beneficial effect of the intervention on the ADHF event rate became apparent early, at 6-month follow-up, and increased with duration of follow-up. The beneficial effect was consistent across all the key prespecified subgroups, including age ≥ 75 years or < 75 years, with or without prior CVD, with or without CKD, women or men, black race or nonblack race, and the tertiles of baseline SBP. In multivariable analyses that included treatment arm, most subgroup characteristics except black race and female sex were significant independent predictors of development of ADHF. Finally, participants who had an initial ADHF event had markedly increased risk of subsequent events, including recurrent ADHF. In comparison to participants without an initial ADHF event, these participants had 27-fold higher risk of cardiovascular death, 16-fold higher risk of MI, and 10-fold higher risk of all-cause death, even after adjustment for relevant covariates. These data highlight the importance of preventing ADHF in high-risk hypertensive patients by optimal BP reduction.

The robustness of the current results from SPRINT is supported by the large magnitude of the risk reduction, the early separation of groups during follow-up, and the consistency of the effect across all key prespecified subgroups. The results are further supported by including only ADHF events, use of a formal, robust, blinded adjudication process, and the finding

of markedly worsened prognosis after a positively adjudicated ADHF event.

These results from the large SPRINT trial significantly extend our knowledge of the impact of BP lowering on HF prevention in older people with systolic hypertension. Several prior trials in older patients with systolic hypertension showed large reductions in new HF events (64% in the HYVET study [Hypertension in the Very Elderly Trial], 50% in the SHEP trial [Systolic Hypertension in the Elderly Program Trial], and 36% in the Syst-Eur [Systolic Hypertension In Europe]) resulting from SBP reductions to 140 to -45 mmHg.^{28–30} HYVET included 3845 participants aged ≥ 80 years (mean age, 83.6 years; mean BP, 173/91 mmHg), and of whom 11.8% had a history of CVD. SHEP included 4736 people aged ≥ 60 years with mean baseline BP of 170/77 mmHg. Syst-Eur included 4695 people aged ≥ 60 years, with mean baseline BP of 174/86 mmHg. The particularly large reduction in HF events in HYVET likely reflects the older age of the participants compared with the other 2 trials. A larger benefit was also observed in participants aged > 80 years in the SHEP trial.

Although the benefits of lowering SBP to the 140 to 145 mmHg range for preventing HF events was well established by previous trials,^{27–29} there has been a paucity of information regarding the potential benefit and risk of lowering BP further. Data regarding the effect of BP reduction to < 130 mmHg on HF events have come primarily from observational studies and have been variable. Analysis from ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) suggested that BP control to $< 130/80$ mmHg conferred additional protection against stroke and renal disease but not MI or HF.³¹ ACCORD (Action to Control Cardiovascular Risk in Diabetes) was the only previous large randomized trial that specifically addressed the potential benefit of lowering SBP to < 130 mmHg (the target was 120 mmHg). The effects on HF outcomes in SPRINT and

Table 1. Baseline Clinical Characteristics By On-Trial ADHF Occurrence

Characteristics	Intensive Treatment		Standard Treatment	
	No ADHF (N=4613)	ADHF (N=65)	No ADHF (N=4580)	ADHF (N=103)
Age ≥75 y, n (%)	1282 (28%)	35 (54%)	1261 (28%)	58 (56%)
Chronic kidney disease, n (%)	1289 (28%)	41 (63%)	1264 (28%)	52 (51%)
Cardiovascular disease, n (%)	914 (20%)	26 (40%)	897 (20%)	40 (39%)
Subclinical	241 (5%)	6 (9%)	235 (5%)	11 (11%)
Clinical	754 (16%)	25 (36%)	749 (16%)	34 (33%)
Framingham 10-year CVD risk score	25±13	33±18	25±12	33±16
Framingham risk ≥15%, n (%)	3502 (76%)	54 (83%)	3458 (76%)	89 (86%)
Female sex, n (%)	1661 (36%)	23 (35%)	1618 (35%)	30 (29%)
Age, y	68±9	75±11	68±9	74±10
Race or ethnic group, n (%)				
Black race	1357 (29%)	22 (34%)	1395 (31%)	28 (27%)
Hispanic	499 (11%)	4 (6%)	476 (10%)	5 (4.9%)
Other	98 (2.1%)	0 (0%)	77 (1.7%)	1 (1%)
White	2659 (56%)	39 (60%)	2632 (56%)	69 (67%)
Smoking status, n (%)				
Never	2022 (44%)	28 (43%)	2035 (45%)	37 (36%)
Former	1947 (42%)	30 (46%)	1946 (43%)	50 (49%)
Current	632 (14%)	7 (11%)	585 (13%)	16 (16%)
BMI, kg/m ²	30±6	30±6	30±6	30±6
Systolic BP, mm Hg	140±16	142±16	140±15	141±19
Diastolic BP, mm Hg	78±12	73±14	78±12	74±13
Heart rate, beats per minute	66±11	66±16	66±12	67±12
SBP tertile, n (%)				
≤132 mm Hg	1567 (34%)	16 (25%)	1523 (33%)	30 (29%)
>132 mm Hg to <145 mm Hg	1468 (32%)	21 (32%)	1517 (33%)	32 (31%)
≥145 mm Hg	1578 (34%)	28 (43%)	1540 (34%)	41 (40%)
Creatinine, mg/dL	1.1±0.3	1.4±0.5	1.1±0.3	1.2±0.4
eGFR MDRD, mL/min per 1.73 m ²	72±21	56±24	72±21	63±22
Ratio of urinary albumin to creatinine	41±166	230±552	39±134	133±494
Total cholesterol, mg/dL	190±42	187±37	190±41	181±42
LDL, mg/dL	113±36	111±32	112±35	104±34
HDL, mg/dL	53±14	53±15	53±15	50±13
Triglycerides, median [Q1, Q3], mg/dL	106 [76, 148]	112 [80, 143]	106 [77, 152]	116.0 [90, 157]

(Continued)

Table 1. Continued

Characteristics	Intensive Treatment		Standard Treatment	
	No ADHF (N=4613)	ADHF (N=65)	No ADHF (N=4580)	ADHF (N=103)
Fasting glucose, mg/dL	99±14	99±13	99±13	100±11
ACE inhibitors, n (%)	1736 (38%)	27 (42%)	1652 (36%)	41 (40%)
Angiotensin II antagonists, n (%)	979 (21%)	14 (22%)	969 (21%)	23 (22%)
Beta blockers, n (%)	1455 (32%)	27 (42%)	1359 (30%)	40 (39%)
CCBs, n (%)	1344 (29%)	33 (51%)	1368 (30%)	37 (36%)
Thiazide diuretics, n (%)	1774 (39%)	12 (19%)	1838 (40%)	35 (34%)
Statin use, n (%)	1946 (43%)	32 (51%)	2025 (45%)	51 (50%)
Aspirin use, n (%)	2362 (51%)	44 (68%)	2286 (50%)	64 (62%)

Subclinical cardiovascular disease includes ≥50% stenosis of a coronary, carotid, or lower extremity artery; abdominal aortic aneurysm ≥5 cm with or without repair; coronary artery calcium score ≥400 Agatston units; low ankle brachial index (≤0.90); left ventricular hypertrophy by computer electrocardiogram (ECG) reading, echocardiogram report, or other cardiac imaging procedure. Clinical cardiovascular disease includes myocardial infarction; acute coronary syndrome with or without resting ECG changes, ECG changes on graded exercise test, or positive cardiac imaging study; coronary revascularization; carotid endarterectomy or carotid stenting; peripheral arterial disease with revascularization. ACE indicates angiotensin-converting enzyme; ADHF, acute decompensated heart failure; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, the Modification of Diet in Renal Disease; and SBP, systolic blood pressure.

the ACCORD trial are directionally consistent,^{3,32} although HF event reduction in the ACCORD trial was smaller in magnitude and not statistically significant (HR, 0.94; 95% CI, 0.70–1.26). Several important differences between these trials should be noted. ACCORD recruited patients with diabetes mellitus only, while SPRINT specifically excluded these patients. In addition, the event rate in the standard-therapy group in ACCORD was almost 50% lower than expected. This lower event rate was likely because of several factors. First, inclusion criteria directed participants with dyslipidemia into the ACCORD lipid trial, leaving participants who were at lower risk for cardiovascular events to be enrolled into the BP trial. Second, the sample size of ACCORD was only half that of SPRINT (4733 versus 9361) and excluded people with CKD and those aged >79 years and so may not have been adequately powered to examine HF. SPRINT enrolled an older cohort (mean age 68 versus 62 years in the ACCORD trial), with 28% of participants aged ≥75 years and mandated inclusion of significant proportions of patients with preexisting CVD and CKD. ACCORD also used a factorial design that included comparisons of standard and intensive glycemic and lipid treatment targets in the same trial. Thus, differences in results between SPRINT and ACCORD could be because of differences in study design, study population, and treatment interactions. As a result of these issues, the lower power in ACCORD was such that the confidence limits for HF events could not exclude a benefit. Consistent with

Table 2. Univariate Baseline Predictors of Acute Decompensated HF

Baseline Variables	Hazard Ratio	95% Confidence Interval	P Value
Randomized to intensive blood pressure arm	0.63	0.46–0.85	0.003
Chronic kidney disease	2.71	1.97–3.73	<0.001
Age ≥75 y	2.93	2.12–4.10	<0.001
History of cardiovascular disease	2.37	1.70–3.29	<0.001
Female	0.83	0.58–1.19	0.31
Black race	1.01	0.68–1.50	0.94
Seated systolic blood pressure (10 unit increase)	1.09	0.99–1.20	0.082
Seated diastolic blood pressure (10 unit increase)	0.73	0.64–0.85	<0.001
Body mass index, kg/m ²	1.01	0.98–1.04	0.48
Current smoker	1.20	0.73–1.81	0.49

HF indicates heart failure.

this finding, the recently published SPRINT SENIOR study, which included 2636 elderly participants who were age ≥75 years (mean age, 79.9 years), showed a significantly lower rate of the primary composite outcome, ADHF events, and all-cause mortality in the intensive treatment group compared with the standard treatment group (the mean SBP in the intensive treatment group was 123.4 mmHg versus 134.8 mmHg in the standard treatment group). The overall serious adverse event rate was comparable by treatment group, including among the frailest participants. There were no differences between treatment groups in injurious falls, orthostatic hypotension, or syncope.²⁴

Table 3. Multivariable Model: Baseline Predictors of Acute Decompensated HF

Baseline Variables	Hazard Ratio	95% Confidence Interval	P Value
Randomized to intensive blood pressure arm	0.60	0.44–0.82	0.001
Chronic kidney disease	2.14	1.54–2.99	<0.0001
Age ≥75 y	2.35	1.59–3.48	<0.0001
History of cardiovascular disease	2.02	1.43–2.81	<0.0001
Female	0.72	0.49–1.03	0.077
Black race	1.31	0.85–1.98	0.22
Seated systolic blood pressure (10 unit increase)	1.16	1.04–1.30	0.008
Seated diastolic blood pressure (10 unit increase)	0.80	0.68–0.95	0.012
Body mass index, kg/m ²	1.04	1.02–1.07	0.002
Current smoker	1.66	1.01–2.65	0.038

HF indicates heart failure.

The present results are consistent with the findings of 2 recent meta-analyses. The first included 613825 subjects and showed that every 10 mmHg reduction in SBP reduced the risk of major HF events by 28%.³³ The proportional reductions per 10 mmHg decrease in SBP were greater for stroke and HF than for coronary heart disease, and there was a trend toward decreased HF events even with baseline SBP <130 mmHg.³³ The second meta-analysis included 35 hypertension treatment trials with HF events and showed a strong, significant correlation between the extent of SBP and DBP reduction and the reduction in HF events.³⁴ The relation between BP reduction and reduction in events was stronger for HF than for mortality and coronary events.

In the present study, both higher baseline SBP and lower baseline DBP were associated with higher ADHF risk. Because coronary perfusion occurs predominantly during diastole, excessively DBP could potentially pose a risk in patients with coronary artery disease.³⁵ Similarly, a recent study demonstrated that among adults with an SBP ≥120 mmHg, low DBP, particularly <60 mmHg, was associated with subclinical myocardial damage and coronary artery disease events.³⁶ However, in both the main SPRINT and the SPRINT SENIORS trials, ADHF events were lower in the intensive arm compared with those in the standard arm, despite lower DBPs (SPRINT, 68.7 versus 76.3 mmHg; SPRINT SENIORS, 62.0 versus 67.2 mmHg).^{3,24} In the SHEP trial, although the incidence of CVD events was higher among participants in the treatment arm whose DBPs were lowered to <70 mmHg compared with those ≥70 mmHg, the incidence of CVD events was still lower than in the participants in the placebo arm.⁹ Finally, in a recent meta-analysis, the reduction in HF events was related to the degree of DBP reduction.³⁴

Participants who developed ADHF in SPRINT had markedly increased risk of subsequent all-cause mortality, cardiovascular mortality, cardiovascular events, and readmission for recurrent ADHF. These results are similar to findings from multiple other studies^{37–39} and support the validity of adjudicated ADHF events in SPRINT. Among baseline characteristics, black race was a significant predictor of ADHF recurrence in SPRINT. Assignment to the intensive BP treatment arm appeared to have a neutral effect on recurrence of ADHF events (and other subsequent cardiovascular outcomes). However, because the trial was stopped early because of benefit, the duration of follow-up was much shorter than planned, and the number of recurrent HF events was relatively small. In addition, after an ADHF event, there were usually marked changes in medications to treat the ADHF. These factors likely confounded any ability to discern an effect of initial SPRINT treatment assignment on recurrent ADHF events. However, the grave prognosis of participants who developed ADHF strongly emphasize the importance of measures to prevent incident ADHF, including intensive BP reduction.

The study has several strengths, including the large sample size, a diverse population at high risk for cardiovascular events, a large proportion of participants aged ≥75 years who have previously been under-represented in hypertension trials, and designation of key subgroups prior to trial launch. Another strength of the study is that because ADHF was a component of the composite primary trial outcome, robust procedures were undertaken to ensure validity of the ADHF events in

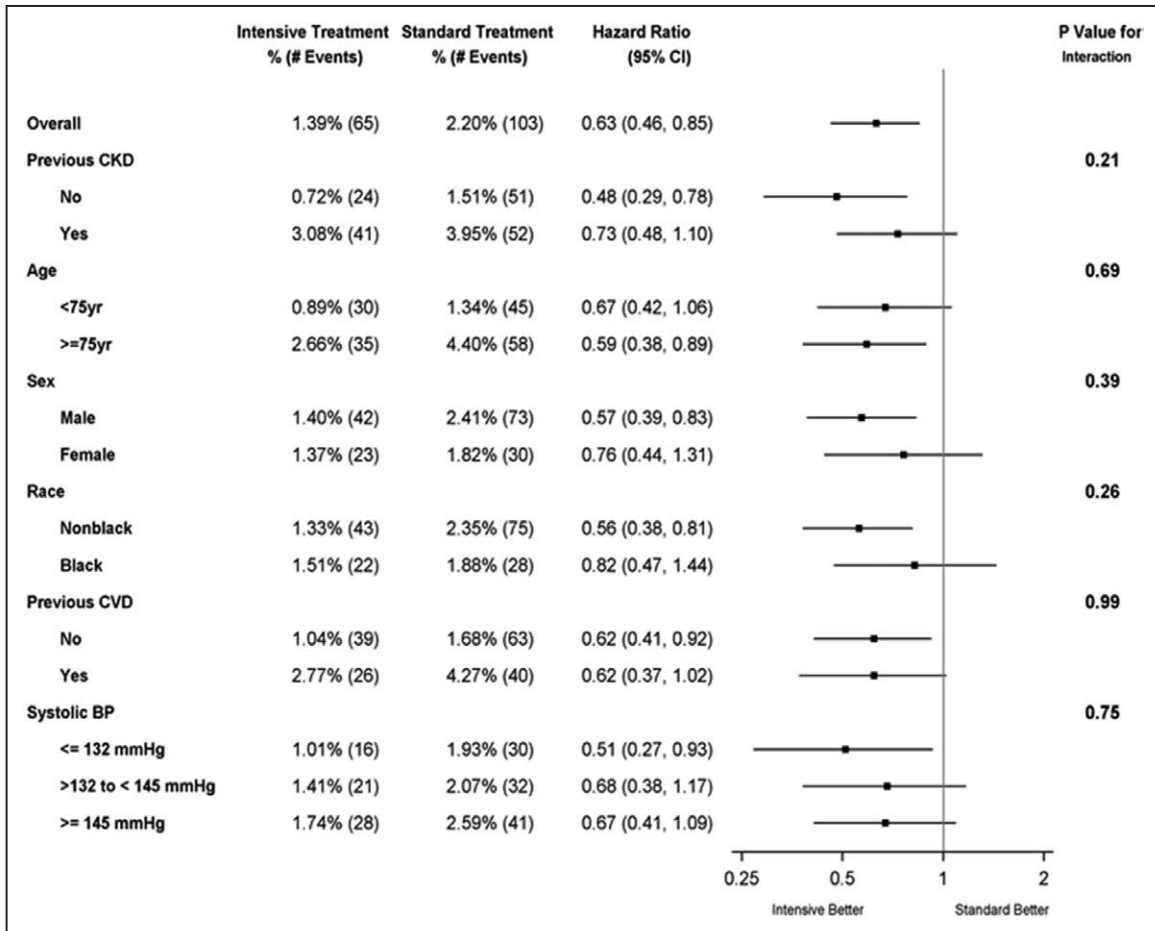


Figure 2. Forest plot of acute decompensated heart failure according to subgroups. The dashed vertical line represents the hazard ratio for the overall study population. The box sizes are proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision). The subgroup of no previous chronic kidney disease (CKD) includes some participants with unknown CKD status at baseline. Black race includes Hispanic black and black as part of a multiracial identification. BP indicates blood pressure; CI, confidence interval; and CVD, cardiovascular disease.

SPRINT, including protocols for capture of events and obtaining medical records from field sites; regularly scheduled participant queries to ascertain events; formal review by an events adjudication committee; formal event definitions that required fulfillment of multiple, specific criteria; inclusion of acute, decompensated HF that resulted in hospitalization or emergency department visit with intravenous diuretic or inotrope infusion and appropriate response to therapy; and exclusion of chronic, stable HF, which is a more challenging and variable event for trial adjudication.

Potential limitations include that this is a secondary analysis and that there is uncertainty regarding generalizability of the findings to populations not included in the trial, including those with diabetes mellitus, prior stroke, low risk for cardiovascular events, age <50 years, and people residing in nursing homes or assisted-living facilities. Lowering BP in individuals with diabetes mellitus is an area of significant current controversy, with particular debate surrounding who should be offered therapy and the BP targets to be achieved. A recent meta-analysis of treatment trials in people with type 2 diabetes mellitus who had

Table 4. Subsequent Clinical Outcomes Based on Initial ADHF Occurrence

Outcome	No ADHF (n=9193)	ADHF (n=168)	Hazard Ratio	Lower 95% CI	Higher 95% CI	P Value
	N (%)	N (%)				
Death from any cause, n (%)	323 (3.5)	44 (26.2)	9.5	6.7	13.1	<0.001
Death from cardiovascular causes, n (%)	79 (0.9)	26 (15.5)	26.8	16.2	43.0	<0.001
Myocardial infarction (MI), n (%)	180 (2.0)	38 (22.6)	15.7	9.9	24.0	<0.001
Non-MI acute coronary syndrome, n (%)	75 (0.8)	7 (4.2)	9.9	3.7	21.6	<0.001
Stroke, n (%)	122 (1.3)	16 (9.5)	4.0	1.4	8.8	0.003

Data are adjusted for treatment arm, sex, baseline age (in years), baseline chronic kidney disease, and baseline cardiovascular disease. ADHF was a time-dependent covariate in these models. ADHF indicates acute decompensated heart failure; and CI, confidence interval.

Table 5. Multivariable Model Showing Predictors of Recurrence of ADHF Among 168 Participants Experiencing a First ADHF

Baseline Variables	Hazard Ratio	95% Confidence Interval	P Value
Intensive blood pressure treatment arm	0.93	0.50–1.67	0.81
Subgroup with age ≥ 75 y	0.98	0.51–1.90	0.94
Female sex	0.79	0.40–1.52	0.49
Black race	2.14	1.07–4.22	0.029
Subgroup with CVD history	0.78	0.42–1.42	0.43
Subgroup CKD	1.99	1.04–3.93	0.042
Seated systolic blood pressure (10 unit increase)	1.11	0.92–1.33	0.26
Seated diastolic blood pressure (10 unit increase)	1.12	0.85–1.44	0.41
Body mass index, kg/m ²	1.03	0.98–1.08	0.31
Current smoker	0.34	0.08–0.98	0.081

ADHF indicates acute decompensated heart failure; CKD, chronic kidney disease; and CVD, cardiovascular disease.

SBP ≤ 135 mmHg in the intensive BP group and ≤ 140 mmHg in the standard BP group found a 10% (95% confidence interval, 2%–17%) reduction in total mortality.⁴⁰ In addition, a secondary analysis of the ACCORD results showed that, as compared with the combined standard glycemia and BP arm, intensive BP treatment alone reduced major cardiovascular outcomes by 26% without an additional benefit from combining the 2 intensive treatments.⁴¹ However, although the beneficial effect of intensive BP reduction on cardiovascular outcomes seems to be potentially similar between the populations with and without diabetes mellitus, the optimal BP target in diabetes mellitus is still uncertain. Our data do not include a prediabetes mellitus subgroup, which is another group of significant interest.

Although the subgroups examined in this article were pre-specified in the SPRINT protocol, the study was not powered to detect an interaction between treatment arm and any subgroup. Thus, we have presented unadjusted *P* values, along with HRs and confidence intervals, as simple guides to possible associations. Our finding that black race was not a significant predictor of incident ADHF may have been because of the somewhat lower (4 years) average age compared with that of nonblacks.

Because new outpatient HF was not included as an event, we may have underestimated the effect of the intervention on overall incident HF.

Conclusions

ADHF was one of the most frequent cardiovascular outcomes in SPRINT. In patients at high risk for cardiovascular events, targeting an SBP of < 120 mmHg, as compared with < 140 mmHg, significantly reduced the risk of developing ADHF by 36%. This benefit was similar across all key, predetermined subgroups. Participants who developed ADHF had a markedly increased risk for subsequent death and cardiovascular events, even during the truncated duration of follow-up because of

early trial termination. These findings highlight the importance of strategies aimed at the prevention of ADHF, especially intensive BP reduction.

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Disclosures

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CLINICAL PERSPECTIVE

This article from the large SPRINT trial (Systolic Blood Pressure Reduction Intervention Trial) reports the incidence, predictors, and outcomes of participants who developed acute decompensated heart failure, one of the main trial outcomes, during the 3.5 years of follow-up before the trial was prematurely terminated because of benefit. This is the first report from a prospective, randomized trial of the effect of intensive blood pressure reduction (to 120 mmHg or less) in older people with systolic hypertension. The robustness of the current results from SPRINT is supported by the large magnitude of the risk reduction, the early separation of groups during follow-up, and the consistency of the effect across all key prespecified subgroups. The trial addresses several points of controversy, including the optimal level of blood pressure reduction and whether benefit is similar across multiple, predefined subsets of patients, including elderly, women, minorities, patients with preexisting cardiovascular or kidney disease, and by 3 different levels of baseline blood pressure. The results are potentially paradigm shifting for the prevention of heart failure through intensive blood pressure management.

Effect of Intensive Blood Pressure Treatment on Heart Failure Events in the Systolic Blood Pressure Reduction Intervention Trial

Bharathi Upadhy, Michael Rocco, Cora E. Lewis, Suzanne Oparil, Laura C. Lovato, William C. Cushman, Jeffrey T. Bates, Natalie A. Bello, Gerard Aurigemma, Lawrence J. Fine, Karen C. Johnson, Carlos J. Rodriguez, Dominic S. Raj, Anjay Rastogi, Leonardo Tamariz, Alan Wiggers and Dalane W. Kitzman
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