ORIGINAL RESEARCH

Effects of Intensive Systolic Blood Pressure Lowering on Cardiovascular Events and Mortality in Patients With Type 2 Diabetes Mellitus on Standard Glycemic Control and in Those Without Diabetes Mellitus: Reconciling Results From ACCORD BP and SPRINT

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***Background*—**Intensive systolic blood pressure (SBP) lowering significantly reduced cardiovascular disease (CVD) events in SPRINT (Systolic Blood Pressure Intervention Trial) but not in ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure).

***Methods and Results*—**SPRINT tested the effects of intensive (<120 mm Hg) versus standard (<140 mm Hg) SBP goals on CVD events and all-cause mortality. Using 2×2 factorial design, ACCORD BP tested the same SBP intervention in addition to an intensive versus standard glycemia intervention. We compared the effects of intensive SBP lowering on the composite CVD end point and all-cause mortality in SPRINT with its effects within each of the glycemia arms in ACCORD BP. Intensive SBP lowering decreased the hazard of the composite CVD end point similarly in SPRINT (hazard ratio: 0.75; 95% confidence interval, 0.64–0.89) and in the ACCORD BP standard glycemia arm (hazard ratio: 0.77; 95% confidence interval, 0.63–0.95; interaction *P*=0.87). However, the effect of intensive SBP lowering on the composite CVD end point in the ACCORD BP intensive glycemia arm (hazard ratio: 1.04; 95% confidence interval, 0.83–1.29) was significantly different from SPRINT (interaction *P*=0.023). Patterns were similar for all-cause mortality.

***Conclusions*—**The effects of intensive SBP control on CVD events and all-cause mortality were similar in patients without diabetes mellitus and in those with diabetes mellitus on standard glycemic control. An interaction between intensive SBP lowering and intensive glycemic control may have masked beneficial effects of intensive SBP lowering in ACCORD BP.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifiers: NCT01206062, NCT00000620. **(*J Am Heart Assoc*. 2018;7:e009326. DOI: 10.1161/JAHA.118.009326.)**

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Accompanying Table S1 and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009326

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Clinical Perspective

What Is New?

- Previous data showed that intensive systolic blood pressure lowering compared with standard systolic blood pressure control (goal <120 versus <140 mm Hg) was beneficial in patients without diabetes mellitus in SPRINT (Systolic Blood Pressure Intervention Trial) but not in those with type 2 diabetes mellitus in ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure).
- The results of the current analyses show that intensive systolic blood pressure lowering decreased the risk of cardiovascular disease events and all-cause mortality similarly in SPRINT participants and ACCORD BP participants on standard glycemic control but not in ACCORD BP participants on intensive glycemic control.

What Are the Clinical Implications?

- These findings support the current American College of Cardiology and American Heart Association guidelines of a systolic blood pressure goal of <130 mm Hg in patients both with and without type 2 diabetes mellitus.

Beginning in the 1960s, randomized controlled trials demonstrated the value of treating high diastolic blood pressure and, subsequently, high systolic blood pressure (SBP).[1,2] However, the treatment target for SBP has been uncertain.[3,4] Several recent meta-analyses support "intensive" SBP lowering in patients with and without diabetes mellitus, but these included randomized controlled trials that targeted a higher SBP goal (<140 mm Hg or even higher) for "intensive" SBP control or blood pressure medication trials that did not have a predefined SBP goal.[2,5–7] The recent American College of Cardiology/American Heart Association guidelines recommend an SBP goal of <130 mm Hg in patients with and without diabetes mellitus.[8]

Whether the SBP goal should be even lower, particularly <120 mm Hg, could be debated. Two large randomized controlled trials sponsored by the National Institutes of Health (NIH) tested an SBP goal of <120 mm Hg. Both studies compared the effects of intensive (SBP target <120 mm Hg) and standard (SBP target <140 mm Hg) SBP treatment targets on cardiovascular disease (CVD) events. The first of these trials was ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) in patients with type 2 diabetes mellitus (T2DM).[9] In addition to intensive versus standard SBP targets, in a 2×2 factorial design, ACCORD BP also tested intensive versus standard glycemic targets (glycated hemoglobin <6% versus 7.0–7.9%).[9] In the primary analysis that combined the intensive and standard glycemia arms, ACCORD BP showed a nonsignificant 12% decrease in the primary composite CVD end point, along with a nonsignificant 7% increase in all-cause mortality for the SBP intervention.[9]

In SPRINT (Systolic Blood Pressure Intervention Trial), which tested the same SBP targets in patients without diabetes mellitus,[10,11] the BP intervention was stopped early because intensive SBP lowering resulted in a substantial reduction in both the primary composite CVD end point and all-cause mortality.

Reasons for these discrepant findings remain widely debated. Because ACCORD BP had fewer participants than SPRINT[9,11] and the observed event rate was half the event rate assumed for power calculations in ACCORD BP,[9] it has been suggested that ACCORD BP was underpowered.[12] Nonetheless, despite the smaller sample size, the reported number of events and event rates in ACCORD BP[9] were higher than in SPRINT. ACCORD BP reported an interaction *P* value of 0.08 for comparison of the effects of intensive SBP control on the primary composite CVD end point in the standard glycemia versus intensive glycemia arms.[9] Another ACCORD BP report noted that compared with the combined standard SBP and standard glycemia group, intensive management of either SBP or glycemia alone improved major CVD outcomes.[13] These findings raise the possibility that potential interactions between the intensive glycemia and SBP interventions in ACCORD BP might have masked beneficial effects of the SBP intervention.

In this study, we compared the effects of intensive SBP lowering on the composite CVD end point and all-cause mortality in SPRINT with its effects within each of the glycemia arms in ACCORD BP. We hypothesized that an interaction between the ACCORD BP glycemic and SBP interventions masked the potential beneficial effects of intensive SBP lowering in ACCORD BP. Furthermore, we investigated whether the effects of the intensive SBP intervention changed following early discontinuation of the intensive glycemia intervention in ACCORD BP.

Methods

Limited data from the SPRINT and ACCORD BP data sets are available from National Heart, Lung, and Blood Institute (NHLBI) data repository[14] for reproducing or replicating the results of this analysis. The Statistical Analysis section provides details of analytical procedures.

The current study was based on a secondary analysis of the limited-access SPRINT BioLINCC data set obtained from the NIH and direct analyses of the ACCORD BP database. The SPRINT and ACCORD BP studies were approved by the institutional review board at each participating study site. All participants provided written informed consent.

Table 1. Baseline Characteristics by SBP Groups in SPRINT (n=9361) and ACCORD-BP Standard (n=2362) and Intensive Glycemia (n=2371) Arms*

	SPRINT		ACCORD-BP			
			Standard Glycemia		Intensive Glycemia	
	Standard SBP	Intensive SBP	Standard SBP	Intensive SBP	Standard SBP	Intensive SBP
	n=4683	n=4678	n=1178	n=1184	n=1193	n=1178
Age, y	67.9±9.5	67.9±9.4	62.7±6.7	62.8±6.8	62.8±6.8	62.6±6.4
Female sex, %	35.2	36.0	47.1	46.9	48.2	48.6
White race, %	57.7	57.7	59.5	58.7	55.9	61.0
Never smoked, %	44.2	43.8	45.4	45.9	44.8	43.4
SBP, mm Hg	140±15	140±16	140±15	138±16	139±15	139±16
DBP, mm Hg	78±12	78±12	76±10	76±10	76±10	76±10
Clinical atherosclerotic disease, %†	20.0	20.0	33.3	33.0	33.4	35.1
Antihypertensive agents (no./patient)	1.8±1.0	1.8±1.0	1.7±1.1	1.7±1.2	1.6±1.1	1.7±1.1
Duration of diabetes mellitus	NA	NA	9.0 (5.0, 15.0)	9.0 (5.0, 15.0)	10.0 (5.0, 16.0)	9.0 (5.0, 15.0)
Glycated hemoglobin%	Not reported	Not reported	8.3±1.0	8.3±1.0	8.3±1.0	8.3±1.0
Fasting plasma glucose, mg/dL	99±13	99±14	173±55	175±55	172±54	175±55
BMI, kg/m^2	29.8±5.7	29.9±5.8	32.1±5.2	32.3±5.6	32.1±5.5	32.1±5.6
Estimated MDRD GFR, mL/min/1.73 m^2	72±21	72±21	91±23	91±23	91±24	90±24
Urine albumin creatinine ratio, mg/g	9.4 (5.6, 21.8)	9.6 (5.7, 21.1)	16.0 (7.0, 56.0)	15.0 (7.0, 45.0)	14.0 (7.0, 42.0)	15.0 (7.0, 46.0)

Percentages are reported for categorical variables and mean±SD or median (25th, 75th percentiles) for continuous variables. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NA, not assessed; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

*All *P* values of comparison between standard and intensive SBP were ≥0.05 except SBP (*P*=0.03) in the ACCORD BP standard glycemia arm and white race (*P*=0.01) in the ACCORD BP intensive glycemia arm.

†Clinical atherosclerotic disease was defined in ACCORD as one or more of myocardial infarction, stroke, angina, coronary artery bypass grafting, percutaneous coronary intervention, or other revascularization procedure. Clinical atherosclerotic disease was defined in SPRINT as ≥1 of myocardial infarction, acute coronary syndrome, coronary revascularization, carotid revascularization, peripheral artery disease with revascularization, >50% stenosis of coronary/carotid/lower extremity artery; or abdominal aortic aneurysm ≥5 mm.

Action to Control Cardiovascular Risk in Diabetes Blood Pressure

Details of the study population, interventions, and study procedures for ACCORD BP are provided in the supplement and published elsewhere.[15] In brief, ACCORD was a randomized controlled trial sponsored by the NHLBI to simultaneously examine the effects of glycemic control, SBP control, and treatment with fenofibrate on a background of statin on CVD outcomes in 10 251 participants aged ≥40 years with T2DM at high risk for CVD events and a glycated hemoglobin level ≥7.5%.[16] Using a double 2×2 factorial design, all 10 251 participants were randomly assigned to intensive (HbA1c [hemoglobin A1c] target <6.0%) or standard (HbA1c target 7.0–7.9%) glycemic therapy.[16] In addition, 4733 of the trial participants were randomly assigned to intensive (target <120 mm Hg) or standard SBP-lowering therapy (target <140 mm Hg; ACCORD BP trial).[9] Another 5518 participants were randomly assigned to receive fenofibrate or placebo on a background of simvastatin[17] (ACCORD Lipid trial). The current analysis was based on participants in the ACCORD BP trial.

ACCORD BP Intervention and Follow-up

Eligible participants were randomly assigned to either intensive or standard SBP control, stratified by clinical site. Details of the ACCORD BP measurement and intervention algorithm are provided in the supplement. In brief, participants in the intensive SBP group were seen at least once a month for 4 months, with additional monthly visits if needed for titration to their SBP goal, and every 2 months thereafter; participants in the standard SBP group were scheduled at months 1 and 4 and every 4 months thereafter.

Systolic Blood Pressure Intervention Trial

SPRINT participants were recruited between November 2010 and March 2013. Adults aged ≥50 years with SBP 130 to 180 mm Hg and high CVD risk were recruited. A major exclusion criterion was presence of diabetes mellitus. Further details of SPRINT inclusion and exclusion criteria were published elsewhere and are provided in the supplement.[10,11]

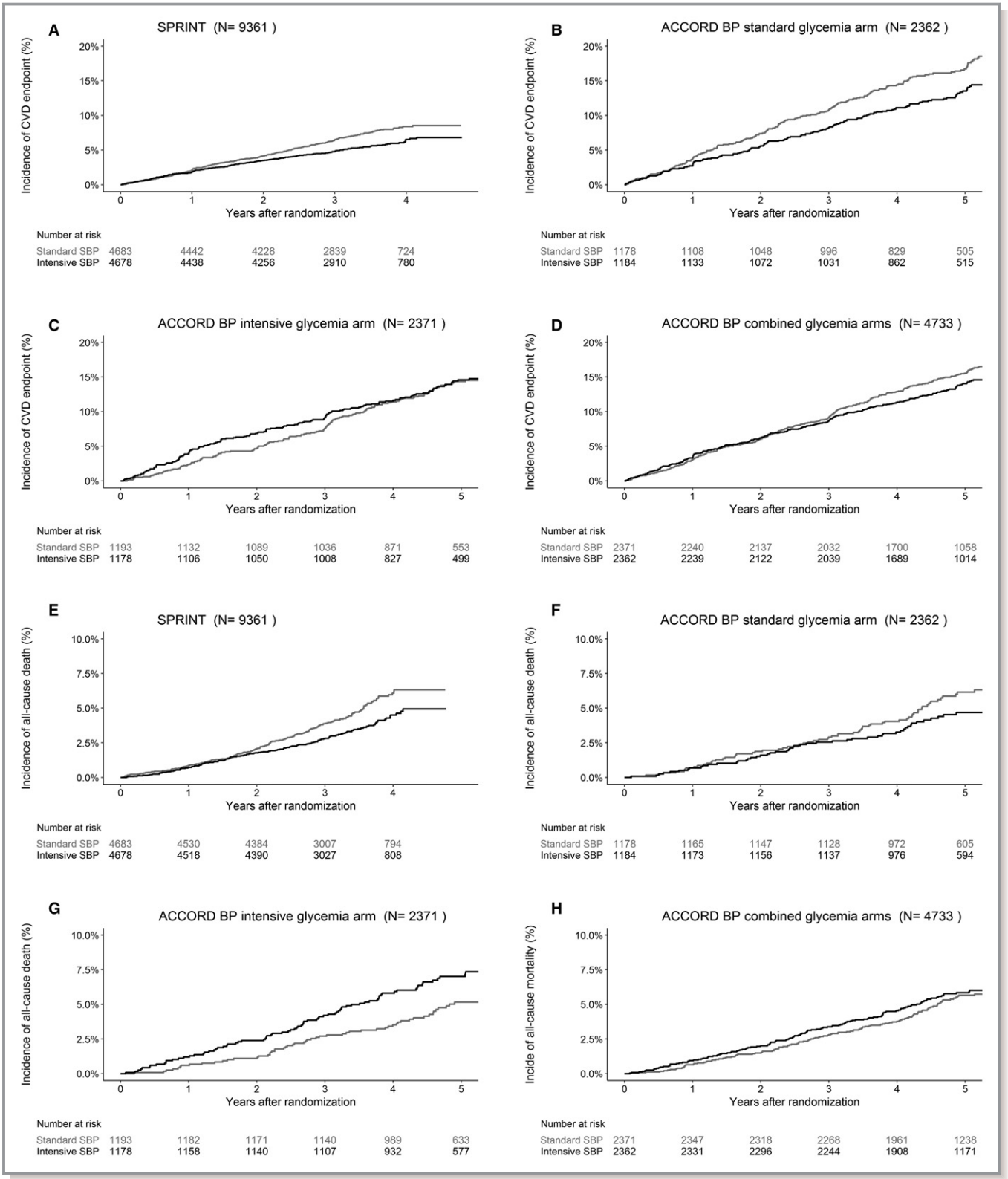

Figure 1. Cumulative incidence of composite CVD end point (A–D) and all-cause mortality (E–H) in intensive and standard SBP groups. A, Composite CVD end point in SPRINT. B, Composite CVD end point in ACCORD BP standard glycemia arm. C, Composite CVD end point in ACCORD BP intensive glycemia arm. D, Composite CVD end point in ACCORD BP combined glycemia arms. E, All-cause mortality in SPRINT. F, All-cause mortality in ACCORD BP standard glycemia arm. G, All-cause mortality in ACCORD BP intensive glycemia arm. H, All-cause mortality in ACCORD BP combined glycemia arms. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CVD, cardiovascular disease; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

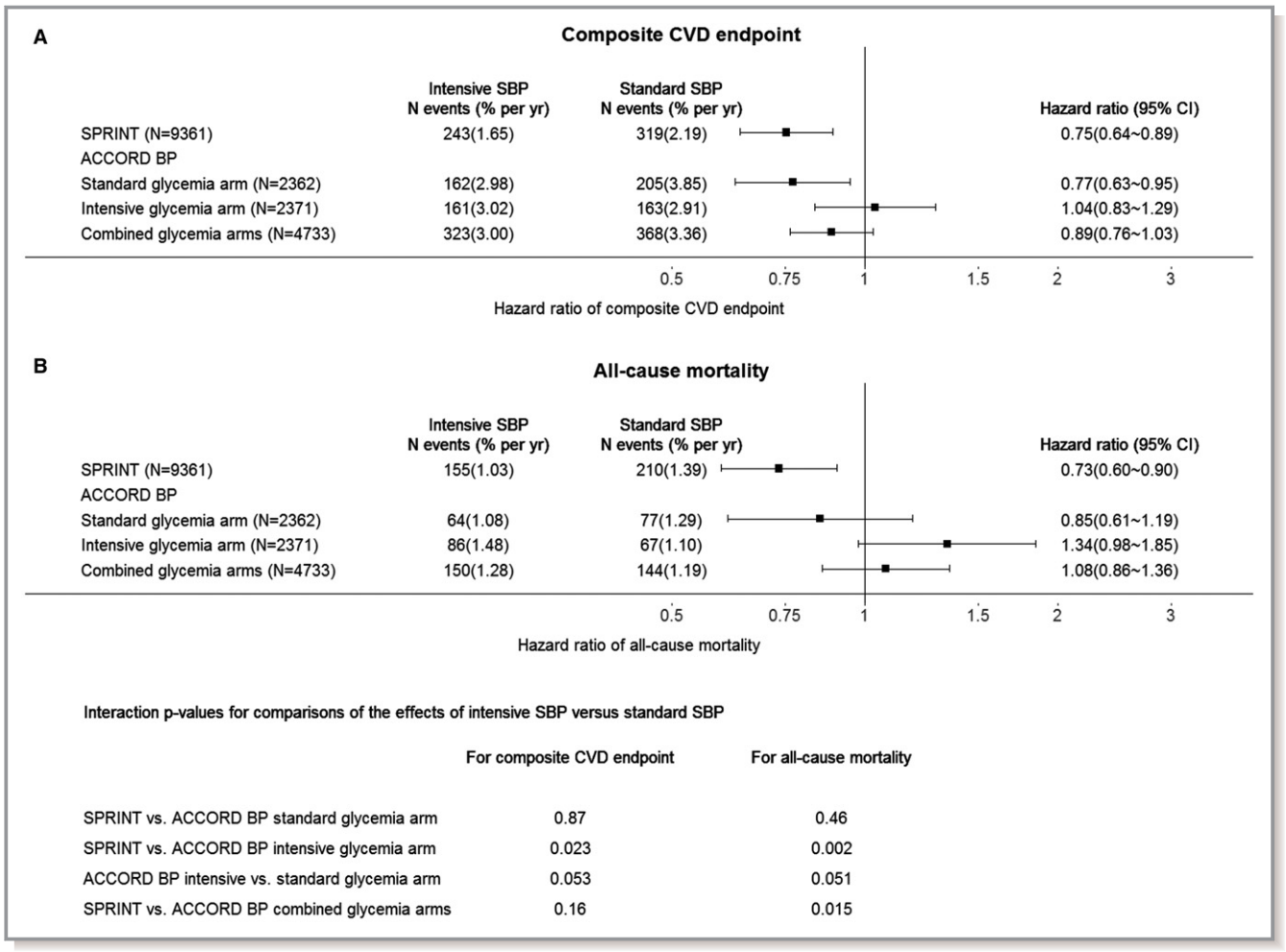

Figure 2. Effects of intensive SBP control on the composite CVD end point (A) and all-cause mortality (B) in SPRINT and ACCORD BP. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CI, confidence interval; CVD, cardiovascular disease; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

SPRINT SBP Intervention and Follow-up

Participants in both arms were seen monthly for the first 3 months and every 3 months thereafter. Additional monthly visits could be scheduled for drug titration to meet the assigned SBP goal. Blood pressure measurement and SBP goals were similar to those used in the ACCORD BP trial.[10,11] A decision to stop the SPRINT intervention was made August 20, 2015, because of beneficial effects of the intensive SBP reduction.[11] Only events and follow-up time that occurred on or before August 20, 2015, were included in this analysis.

Definition of CVD Outcomes

The primary end point in SPRINT was a composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from CVD causes. The primary CVD end point in ACCORD BP was similar to that of SPRINT except that it did not include acute decompensated heart failure or acute coronary syndrome. To match the SPRINT experience as closely as possible, we defined a modified composite CVD end point in ACCORD BP as a composite of the primary ACCORD BP CVD end point or congestive heart failure or unstable angina. In sensitivity analyses, we compared the SPRINT-protocol-defined[18] primary composite CVD end point in SPRINT participants with the ACCORD BP–protocol-defined[15] primary composite CVD end point in each of the glycemia arms in ACCORD BP.

Statistical Analysis

We compared patient characteristics and outcomes between the intensive SBP and standard SBP groups for the 9361 SPRINT participants, the 2362 ACCORD BP participants who were randomized to the standard glycemia arm, and the 2371 ACCORD BP participants who were randomized to the intensive glycemia arm. We summarized baseline participant characteristics by SBP group separately within each cohort. We present mean SBP with 95% confidence intervals (CIs) in

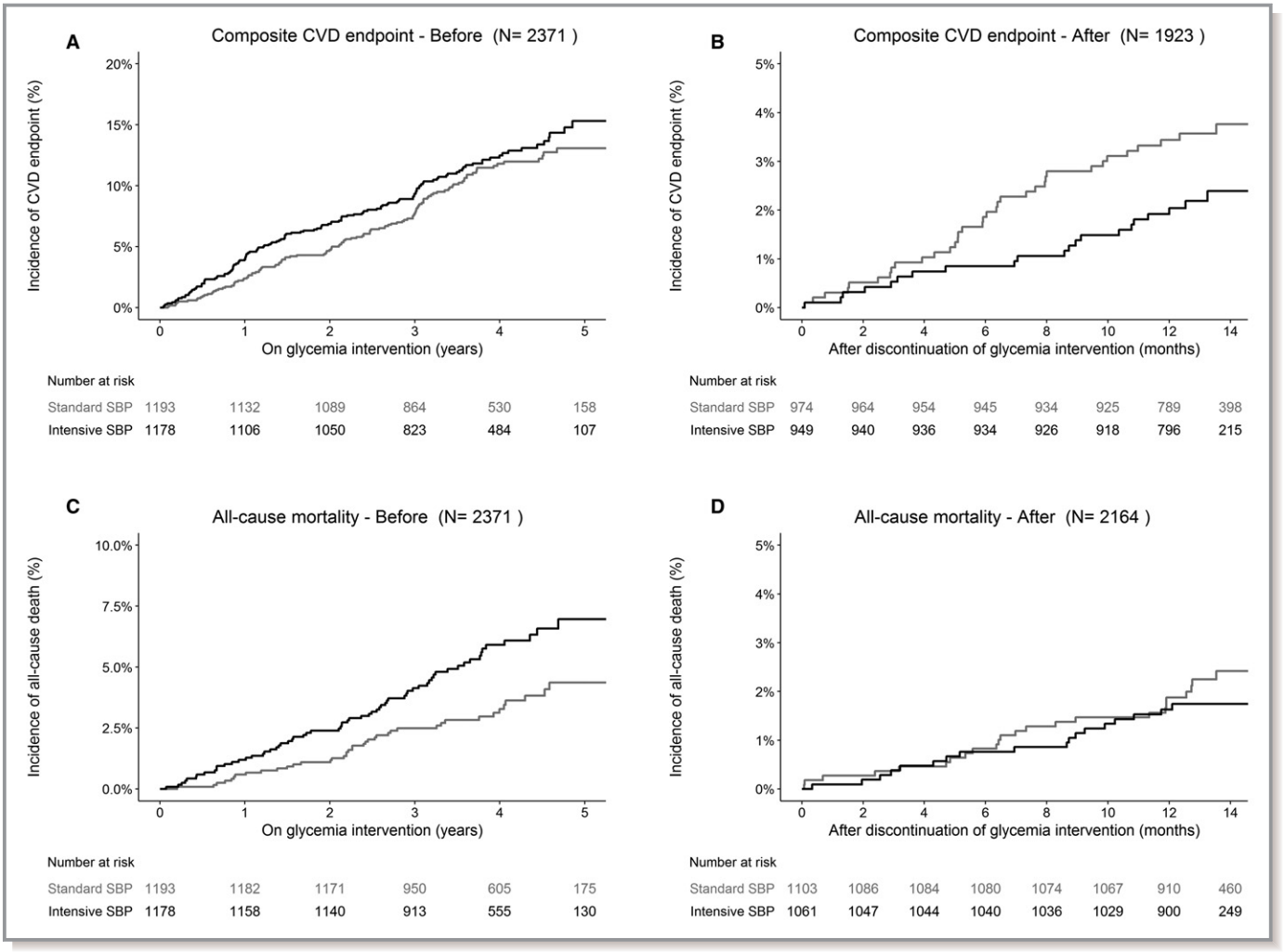

Figure 3. Cumulative incidence of the composite CVD end point and all-cause mortality in the intensive and standard SBP groups before and after intensive glycemia intervention was discontinued in the ACCORD BP intensive glycemia arm. A, Composite CVD end point before intensive glycemia intervention was discontinued. B, Composite CVD end point after intensive glycemia intervention was discontinued. C, All-cause mortality before intensive glycemia intervention was discontinued. D, All-cause mortality after intensive glycemia intervention was discontinued. Because the entire duration of the study is presented and the duration before intensive glycemia intervention was discontinued was much longer than the duration after intensive glycemia intervention was discontinued, the *x*- and *y*-axes scales are different for the before and after panels. Please see Figure S3 for graphic depiction of incidence of events during the first 14 months after randomization and the 14 months after discontinuation of the glycemia intervention. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CVD, cardiovascular disease; SBP, systolic blood pressure.

the intensive and standard SBP groups for each cohorts at baseline and at each follow-up visit.

We used time-to-event methods to evaluate the effects of the SBP intervention on the composite CVD end points and all-cause mortality in each cohort and to provide pairwise comparison of the effects of the SBP intervention across the 3 cohorts and between SPRINT and ACCORD BP after pooling across the 2 glycemia arms. Our primary analyses censored follow-up at the last outcome event ascertainment, with event rates expressed as number of events per patient-year. We used Kaplan–Meier curves to depict the cumulative incidence of the composite CVD end points and all-cause mortality over follow-up. We applied Cox proportional hazards regression analyses to estimate hazard ratios (HRs) between the groups with intensive and standard SBP goals. We combined all 3 cohorts into a single analysis and performed Cox regression with stratification of the baseline hazard by study cohort and by clinical site in SPRINT and by clinical center network in ACCORD BP. The Cox models were parameterized to estimate separate HRs within each cohort and a pooled HR across the 2 glycemia control interventions of ACCORD BP. Comparisons among these HRs to evaluate interactions between the SBP intervention and the 3 cohorts were performed using likelihood ratio tests. These comparisons were repeated after censoring the follow-up of the ACCORD BP patients at the termination of the glycemia intervention when this occurred

Table 2. Effects of Intensive SBP Lowering on the Composite CVD End Point and All-Cause Mortality During and After Intensive Glycemia Intervention Was Discontinued Within the Intensive Glycemia Arm in ACCORD BP in Time-Dependent Cox Regression Models

Outcome	HR (95% CI) and *P* Value for Intensive vs Standard SBP		Interaction *P* Value
	During Glycemia Intervention	Postglycemia Intervention	
Composite CVD end point	1.15 (0.90–1.46), *P*=0.259	0.64 (0.38–1.10), *P*=0.105	0.052
All-cause mortality	1.67 (1.13–2.45), *P*=0.010	0.79 (0.44–1.44), *P*=0.445	0.041

ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; SBP, systolic blood pressure.

before the patient's last outcome ascertainment. In sensitivity analyses, the Cox regressions comparing randomized SBP groups were repeated in the ACCORD BP participants using the ACCORD BP–protocol-defined primary composite CVD end point.

In addition to these analyses, which compared participants according to their randomized treatment assignment, we applied time-dependent Cox regression in the intensive glycemia arm of ACCORD BP to compare the HR for current exposure to the intensive versus standard SBP intervention before and after the early discontinuation of the glycemia intervention on February 5, 2008.

We also present Kaplan–Meier curves for the cumulative incidence of the composite CVD end point and all-cause death within the 2 SBP groups following the discontinuation of the glycemia intervention, with time 0 reset to the discontinuation date.

In addition, we performed a sensitivity analysis to compare the HR for the intensive versus standard SBP intervention in the first 14 months following initial randomization to the HR for the 14 months after discontinuation of the glycemia intervention in the intensive glycemia arm in ACCORD BP.

We performed all analyses in SAS v9.4 (SAS Institute) and R v3.4.3 (R Foundation for Statistical Computing). We used a 2-sided α=0.05 for hypothesis tests, without adjustment for multiple comparisons.

Results

The current analysis included 9361 SPRINT participants and 4733 ACCORD BP participants (Figure S1). Baseline demographic, clinical, and laboratory characteristics were similar in the intensive and standard SBP groups within SPRINT and within both ACCORD BP glycemia arms (Table 1). However, compared with the SPRINT participants, the ACCORD BP participants were younger, more often female, and had higher mean body mass index, mean estimated glomerular filtration rate, and median value of albuminuria (Table S1). Baseline blood pressure and number of antihypertensive medications were similar in both studies.

The intervention lowered SBP in SPRINT and ACCORD BP with similar average differences in SBP between the 2 SBP treatment groups in SPRINT, the ACCORD BP standard glycemia arm, and the ACCORD BP intensive glycemia arm (Figure S2).

Mean durations of follow-up in SPRINT and ACCORD BP were 3.22±0.85 and 4.95±1.19 years, respectively.

Intensive SBP Lowering and the Risk of CVD Events and All-Cause Mortality During the Entire Follow-up in Both Studies

Cumulative incidences of the composite CVD end points (Figure 1A–1D) and all-cause mortality (Figure 1E–1H) were lower in the intensive SBP group compared with the standard SBP group in SPRINT and in the ACCORD BP standard glycemia arm but not in the ACCORD BP intensive glycemia arm. HRs for the composite CVD end point in the intensive versus standard SBP groups in SPRINT (HR: 0.75; 95% CI, 0.64–0.89) and the ACCORD BP standard glycemia arm (HR: 0.77; 95% CI, 0.63–0.95) were virtually identical, with an interaction *P*=0.87 (Figure 2A). In contrast, the HR for the groups with intensive versus standard SBP goals in the ACCORD BP intensive glycemia arm (HR 1.04, 95% CI 0.83–1.29) was significantly different (interaction *P*=0.023) from that noted in SPRINT (Figure 2A).

All-cause mortality HRs for the SPRINT intensive versus standard SBP groups (HR: 0.73; 95% CI, 0.60–0.90) and ACCORD BP standard glycemia arm (HR: 0.85; 95% CI, 0.61–1.19) were also similar, with an interaction *P*=0.46 (Figure 2B). In contrast, the HR for all-cause mortality with intensive SBP lowering in the ACCORD BP intensive glycemia arm (HR: 1.34; 95% CI, 0.98–1.85) was significantly different (interaction *P*=0.002) from that in SPRINT (Figure 2B).

In sensitivity analyses, when the ACCORD BP–protocol-defined primary composite CVD end point (excluding heart failure and unstable angina) was used in ACCORD BP, the HRs for the intensive versus standard SBP comparisons were similar to those presented using the SPRINT-like definition for the CVD outcome (Figure S3).

CVD Events and All-Cause Mortality in the Combined Glycemia Arms in ACCORD BP

The cumulative incidence of CVD events (Figure 1D) and all-cause mortality (Figure 1H) in the combined glycemia arms in ACCORD BP reflected the summation of the effects of intensive SBP intervention on the cumulative incidence of

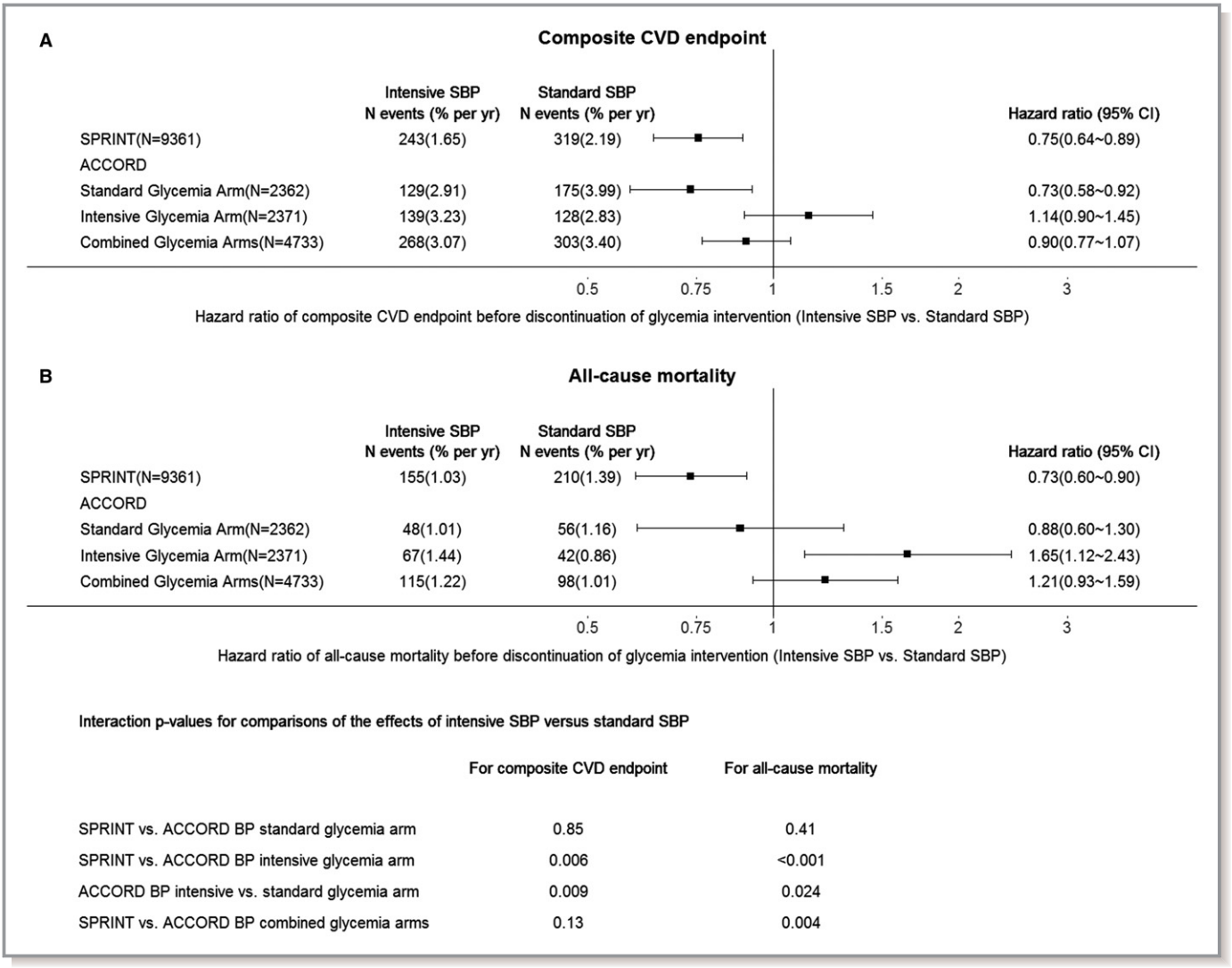

Figure 4. Effects of intensive SBP control on the composite CVD end point (A) and all-cause mortality (B) in SPRINT and before the glycemia intervention was discontinued in ACCORD BP. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CI, confidence interval; CVD, cardiovascular disease; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

CVD events in the standard and intensive glycemia arms (Figure 1B, 1C, 1F, and 1G). Similarly, the HRs for composite CVD end point and all-cause mortality with intensive SBP lowering in the combined glycemia arms reflected the summation of the HRs for these events within each glycemia arm (Figure 2A and 2B).

Effects of Intensive SBP Lowering on the Composite CVD End Point and All-Cause Mortality Before and After Discontinuation of the Glycemia Intervention in the Intensive Glycemia Arm of ACCORD BP

Incidence of the CVD composite end point and all-cause deaths in the intensive and standard SBP groups before and after discontinuation of the glycemia intervention within the intensive glycemia arm of ACCORD BP are depicted in Figure 3. In a time-dependent Cox regression (Table 2) performed in participants randomized to the intensive glycemia arm of ACCORD BP, the HR for the effects of intensive SBP lowering was 1.15 (95% CI, 0.90–1.46) on the glycemia intervention and 0.64 (95% CI, 0.38–1.10) after the intensive glycemia intervention was discontinued (interaction P=0.052). Similar results were obtained for all-cause mortality, with HRs of 1.67 (95% CI, 1.13–2.45) before and 0.79 (95% CI, 0.44–1.44) after discontinuation of the intensive glycemia intervention (interaction P=0.041). In sensitivity analyses, results were similar when CVD events and all-cause deaths in the first 14 months during intensive glycemia intervention were compared with CVD events and all-cause

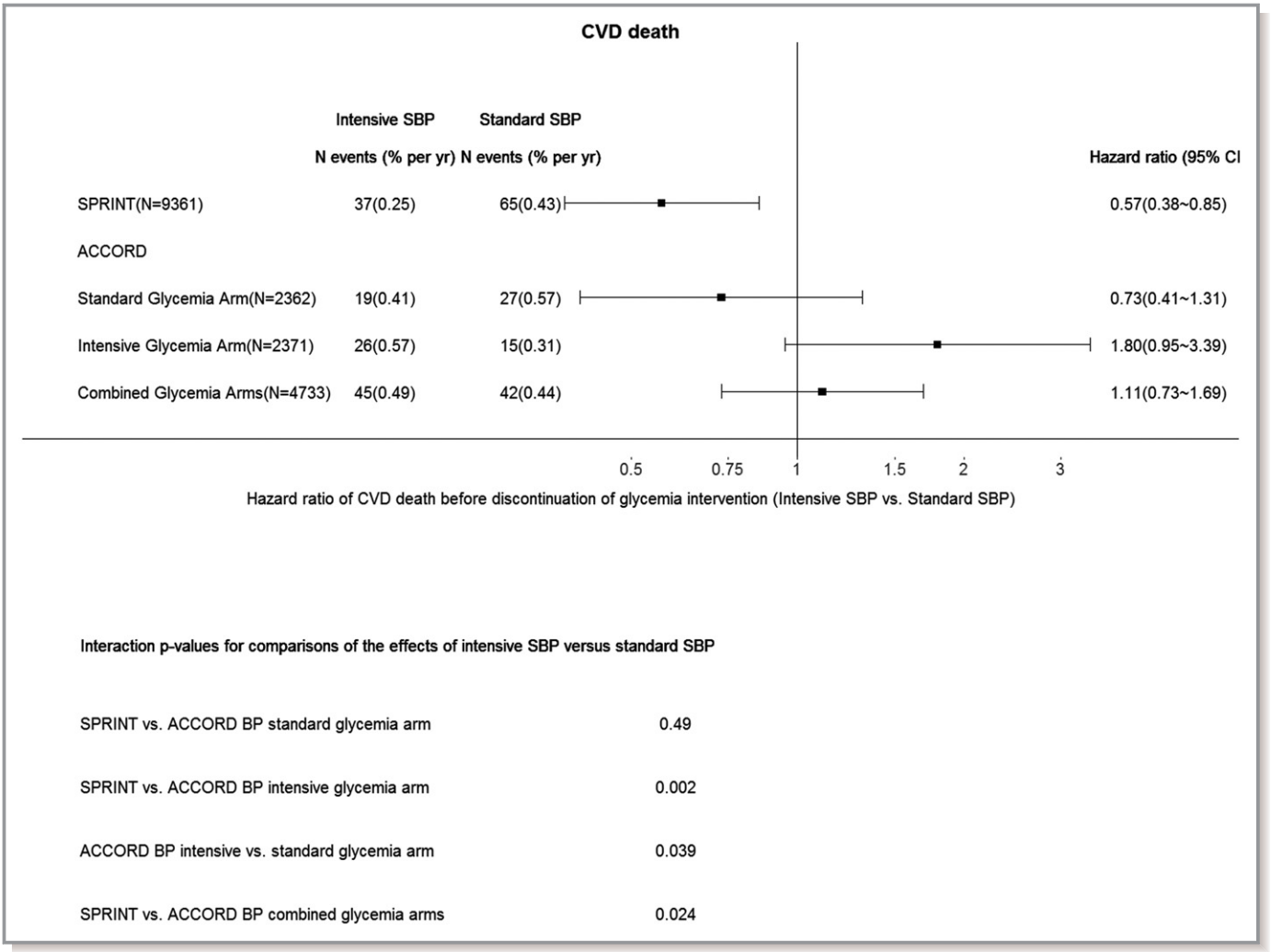

Figure 5. Effects of intensive SBP control on CVD death in SPRINT and before the glycemia intervention was discontinued in ACCORD BP. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CI, confidence interval; CVD, cardiovascular disease; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

deaths in the first 14 months after discontinuation of the intensive glycemia intervention (Figure S4).

Comparison of the Effects of Intensive SBP Lowering on the Risk of CVD Events and All-Cause Mortality in SPRINT and in ACCORD BP Before Discontinuation of the Intensive Glycemia Intervention

The HRs of intensive SBP lowering for the composite CVD end point or all-cause mortality in SPRINT were not different from those in the standard glycemia arm of ACCORD BP before discontinuation of the intensive glycemia intervention (Figure 4A and 4B). The HRs of intensive SBP lowering for the composite CVD end point and all-cause mortality during the glycemia intervention in the intensive glycemia arm were significantly different from SPRINT (interaction P=0.006 for the composite CVD end point and P<0.001 for all-cause mortality).

Comparison of the Effects of Intensive SBP Lowering on the Risk of Individual Components of the Primary Composite CVD End Point in SPRINT and in ACCORD BP Before Discontinuation of the Intensive Glycemia Intervention

In general, intensive SBP lowering was associated with reductions in CVD death (Figure 5), congestive heart failure (Figure 6), and myocardial infarction/coronary heart disease events (Figure 7) in SPRINT and in the ACCORD BP standard glycemia arm but was associated with increases in these events in the ACCORD BP intensive glycemia arm. In contrast, intensive SBP lowering was associated with reductions in

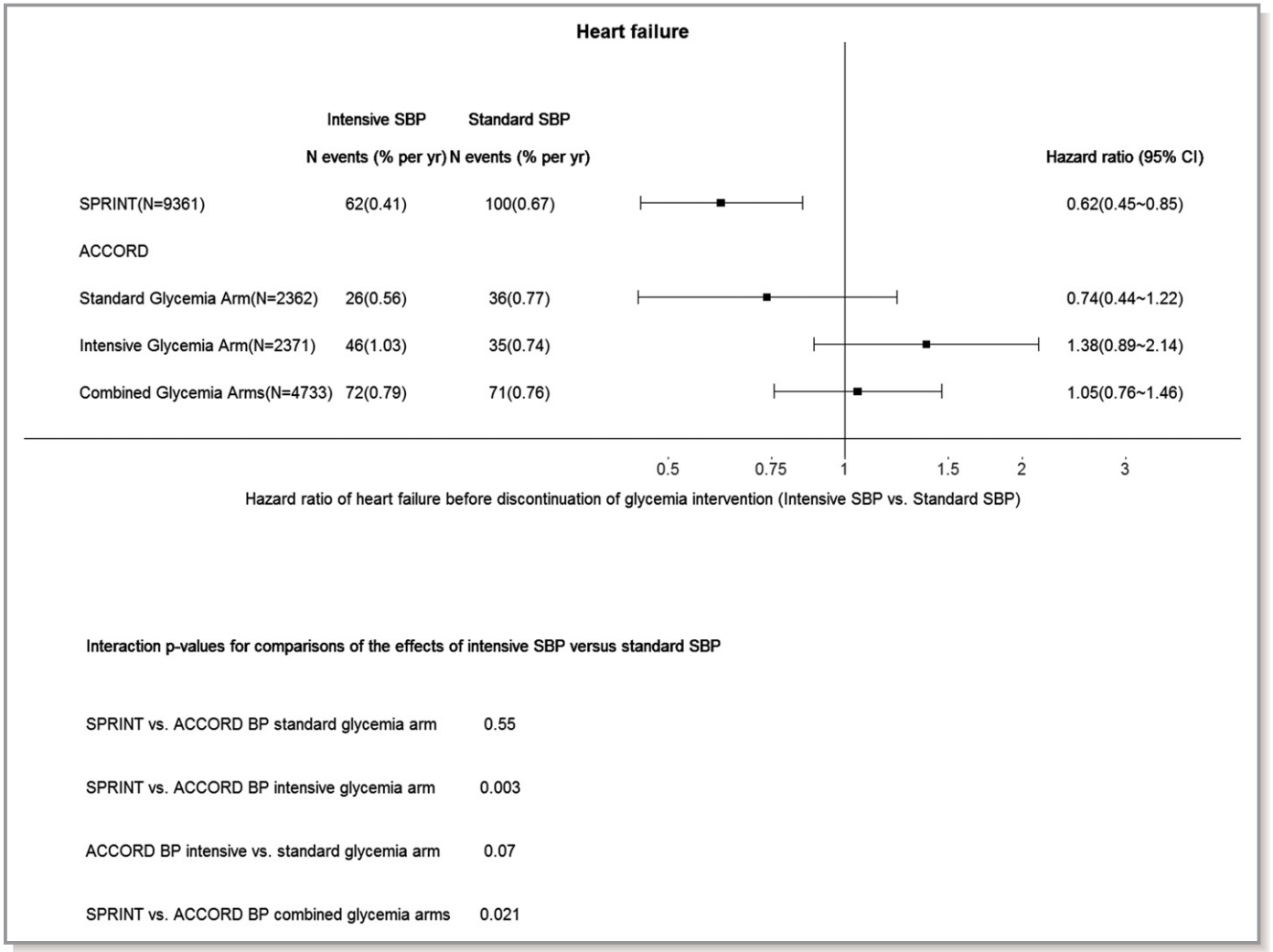

Figure 6. Effects of intensive SBP control on heart failure in SPRINT and before the glycemia intervention was discontinued in ACCORD BP. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CI, confidence interval; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

stroke across SPRINT and both ACCORD BP glycemia arms (Figure 8).

Discussion

The results of these post hoc comparisons of the effects of intensive SBP lowering on CVD events and all-cause mortality between SPRINT and ACCORD BP indicate that the effects of intensive SBP lowering were similar in SPRINT and the ACCORD BP standard glycemia arm. In contrast, the effects of intensive SBP lowering were significantly different between SPRINT and the ACCORD BP intensive glycemia arm. Furthermore, the apparent increased risk of CVD events and all-cause mortality with intensive SBP lowering during the intensive glycemia intervention appeared to dissipate after discontinuation of the glycemia intervention.

The reasons for the lack of statistical significance between the primary composite CVD end point in the ACCORD BP trial intensive versus standard SBP treatment arms[9] remain widely debated, given the highly significant findings observed in SPRINT.[11] A participant-level pooled meta-analysis of SPRINT and ACCORD BP participants suggested that in the combined cohort, intensive SBP lowering decreased the risk of CVD events.[19] These results, however, were primarily driven by the SPRINT data.[19] Differences in blood pressure measurement techniques,[20] differences in the achieved SBP separations,[21] and differences in selection criteria[22] have also been proposed as potential explanations. Although these explanations are possibilities, other potential explanations merit consideration. Perhaps the most widely cited reason for the discordant results is a lack of statistical power in ACCORD BP.[12,19] However, the total numbers of CVD and death events were actually higher in ACCORD BP because of a higher event

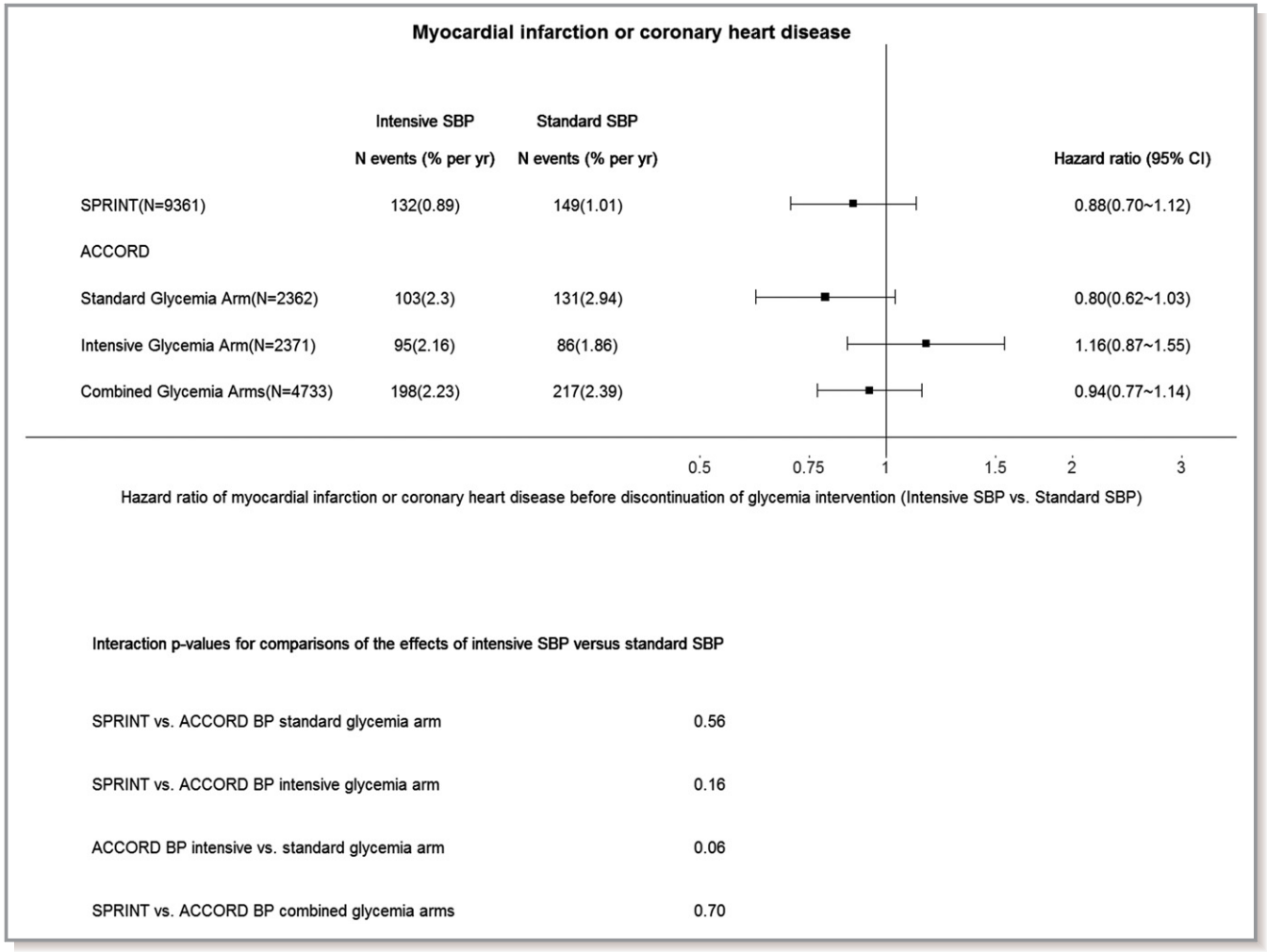

Figure 7. Effects of intensive SBP control on myocardial infarction/coronary heart disease events in SPRINT and before the glycemia intervention was discontinued in ACCORD BP. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CI, confidence interval; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

rate and longer duration of follow-up. Consequently, a lack of statistical power in ACCORD BP compared with SPRINT does not appear to provide a sufficient explanation for the divergent results.

An alternative explanation is that there was an interaction between the intensive glycemia intervention and the intensive SBP lowering intervention in ACCORD BP that may have masked the potential beneficial effects of the SBP intervention. This hypothesis is supported by 2 aspects of the results of the current analysis. First, intensive SBP lowering appeared to reduce the risk of CVD events and all-cause mortality in the standard glycemia arm but not in the intensive glycemia arm of the ACCORD BP trial. In an analysis of the combined glycemia arms, these competing effects resulted in a nonsignificant decrease in CVD event risk and a nonsignificant increase in all-cause mortality risk. Second, as suggested by Table 2 and Figure 3, apparent deleterious effects of intensive SBP lowering in the intensive glycemia arm of ACCORD BP appeared to dissipate after discontinuation of the intensive glycemia intervention.

Biological plausibility exists for an interaction between intensive glycemic control and intensive SBP control. Compared with patients without diabetes mellitus, adults with T2DM have diminished myocardial glucose extraction and utilization despite similar levels of plasma insulin and higher plasma glucose levels.[23] This may limit the ability of the myocardium in patients with T2DM to withstand ischemia and may contribute to the increased CVD morbidity and mortality in these patients.[23] Therefore, in the setting of intensive glycemic control in T2DM, intensive SBP lowering compared with standard SBP control might result in worse CVD outcomes. This premise is supported by analysis of the individual components of the primary composite CVD end point; intensive SBP lowering appeared to increase cardiac

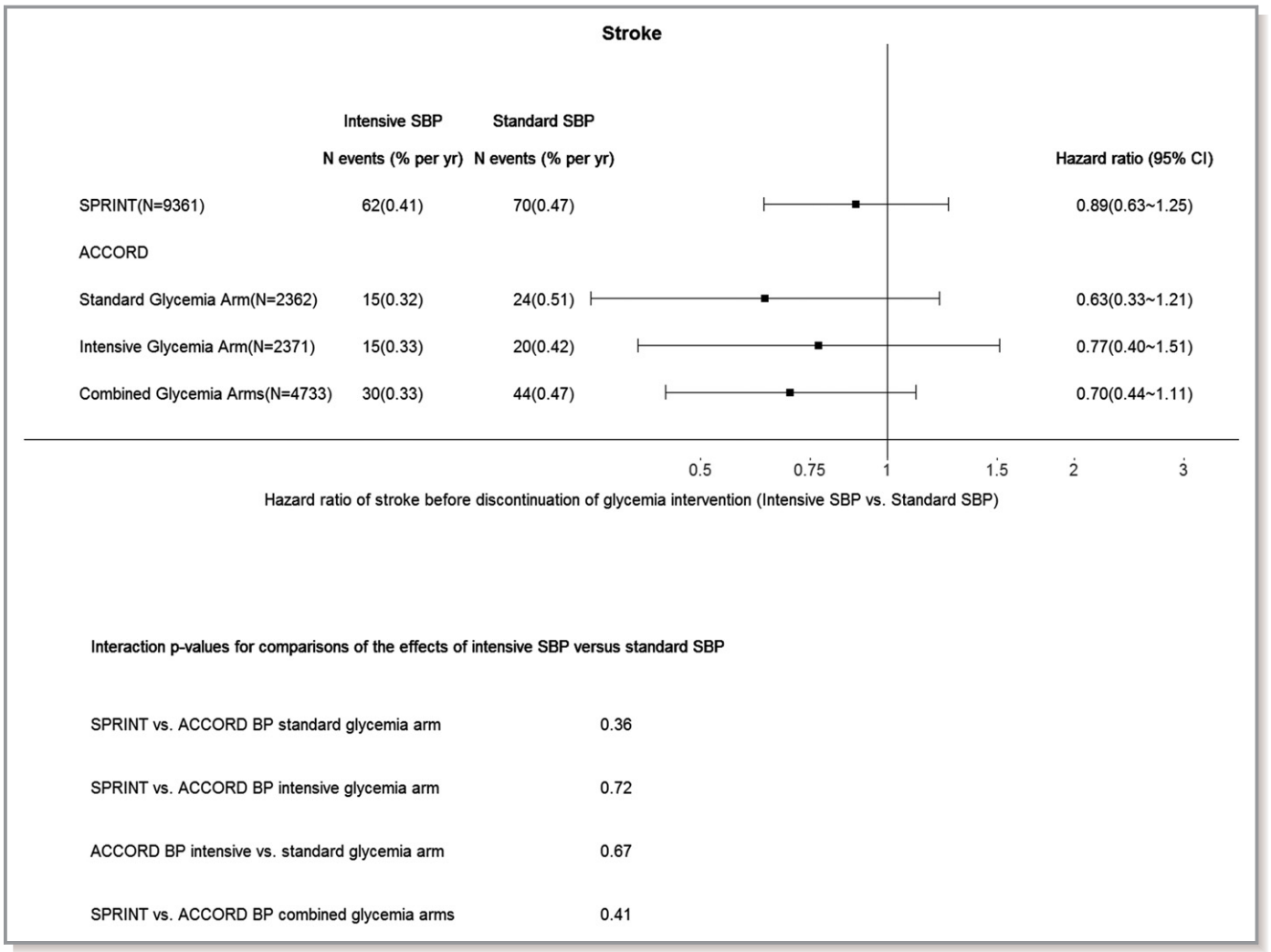

Figure 8. Effects of intensive SBP control on stroke in SPRINT and before the glycemia intervention was discontinued in ACCORD BP. ACCORD BP indicates Action to Control Cardiovascular Risk in Diabetes Blood Pressure; CI, confidence interval; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

events but not stroke. Consequently, the myocardium might be uniquely susceptible to intensive SBP lowering in the setting of intensive glycemic control.

A previous ACCORD BP report noted that, compared with the combined standard SBP and standard glycemia group, intensive management of either SBP or glycemia alone improved major CVD outcomes.[13] We noted similar findings for CVD event rates during the entire period of follow-up. The major difference between the current and previous reports is that the current analysis used SPRINT as the external reference point and compared CVD events and all-cause mortality in the standard and intensive glycemia treatment arms separately. In addition, we examined the effects of intensive SBP lowering before and after discontinuation of the intensive glycemia intervention within the intensive glycemia arm of ACCORD BP. Because intensive glycemia treatment is no longer recommended because of its increased all-cause mortality risk,[24] we believe that the benefits from intensive SBP lowering in the standard glycemia arm of ACCORD BP are clinically relevant for the management of hypertension in patients with T2DM. The current analysis supports intensive SBP lowering for CVD protection in patients with T2DM on standard glycemic control.

A limitation of the current study is that it was based on post hoc analyses. The ACCORD BP trial was analyzed using a prespecified factorial design in which the analysis of the effect of the intensive SBP intervention was based on an overall intensive versus standard SBP comparison in which the results were aggregated across both the intensive and standard glycemic control groups. This type of analysis assumes minimal or no interaction between the treatments being studied. Nonetheless, our post hoc analysis cannot fully exclude the possibility that the interactions between the SBP and glycemic control interventions in ACCORD BP were due to chance.

In conclusion, results of the current analyses support the possibility that intensive SBP lowering offers similar

beneficial effects in patients without diabetes mellitus and in patients with T2DM on standard glycemic control. There appears to be an interaction between intensive SBP lowering and intensive glycemic control that resulted in increased CVD events and all-cause mortality and that dissipated after discontinuation of the intensive glycemia intervention. This interaction between intensive SBP lowering and intensive glycemic control is the likely explanation for the discordant results noted between SPRINT and the combined glycemia arms of ACCORD BP. Taken together, these randomized comparisons support intensive SBP lowering in patients without diabetes mellitus and in patients with T2DM on standard glycemic control, as suggested by recent guidelines.[8]

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Disclosures

None.

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Supplemental Material

Table S1. Comparison of baseline characteristics between SPRINT and ACCORD BP.

	SPRINT N=9361	ACCORD BP N=4733	P value
Age, (year)	67.9 ± 9.4	62.7 ± 6.7	<0.001
Female sex, (%)	35.6	47.7	<0.001
White race, (%)	57.7	58.8	0.22
Never smoked, (%)	44.0	44.8	0.38
Systolic blood pressure, (mmHg)	139.7 ± 15.6	139.0 ± 15.3	0.01
Diastolic blood pressure, (mmHg)	78.1 ± 11.9	75.8 ± 10.0	<0.001
Clinical atherosclerotic disease* (%)	20.1	33.7	<0.001
Antihypertensive agents, (no./patient)	1.8 ± 1.0	1.7 ± 1.1	0.95
Duration of diabetes, (year)	NA	11.0 ± 7.8	
Glycated hemoglobin, (%)	Not reported	8.3 ± 1.0	
Fasting plasma glucose, (mg/dl)	98.8 ± 13.5	173.7 ± 54.6	<0.001
Body-mass index, (kg/m^2)	29.9 ± 5.8	32.1 ± 5.5	<0.001
Estimated MDRD GFR#, ($ml/min/1.73\ m^2$)	71.7 ± 20.6	90.5 ± 23.1	<0.001
Urine albumin creatinine ratio, (mg/g)	9.5(5.6,21.4)	15.0(7.0,47.0)	<0.001

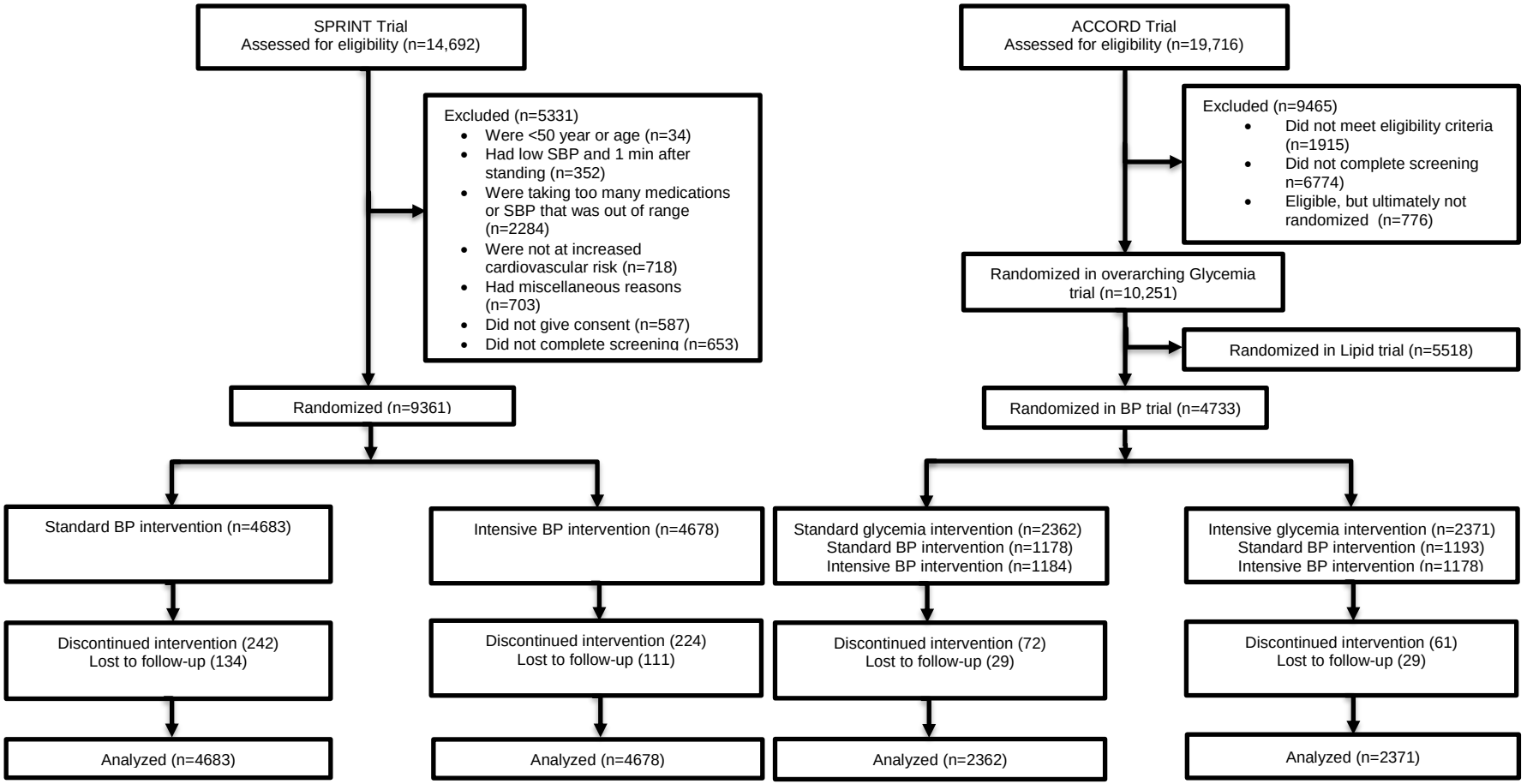
Results are presented as a percent (for binary variables) or as mean ± SD (for continuous variables other than ACR) or as median with interquartile range (for ACR).

* Clinical atherosclerotic disease was defined in ACCORD as one or more of myocardial infarction, stroke, angina, CABG, PTCI, or other revascularization procedure. Clinical atherosclerotic disease was defined in SPRINT as one or more of MI, ACS, coronary revascularization, carotid revascularization, PAD with revascularization, >50% stenosis of coronary/carotid/lower extremity artery; or AAA ≥5 mm

#Estimated by 4-variable MDRD equation

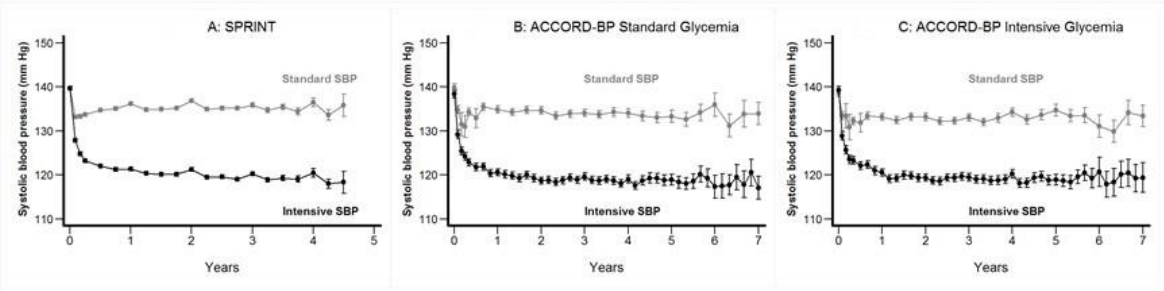
SPRINT – Systolic Blood Pressure Intervention Trial, ACCORD BP – Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial, MDRD – Modification of Diet in Renal Disease, GFR – glomerular filtration rate, CABG – Coronary Artery Bypass Grafting, PTCI – Percutaneous Coronary Intervention, MI – Myocardial Infarction, ACS – Acute Coronary Syndrome, PAD – Peripheral Artery Disease, AAA –Abdominal Aortic Aneurysm

Figure S1. CONSORT flowdiagram for SPRINT and ACCORD BP participants.



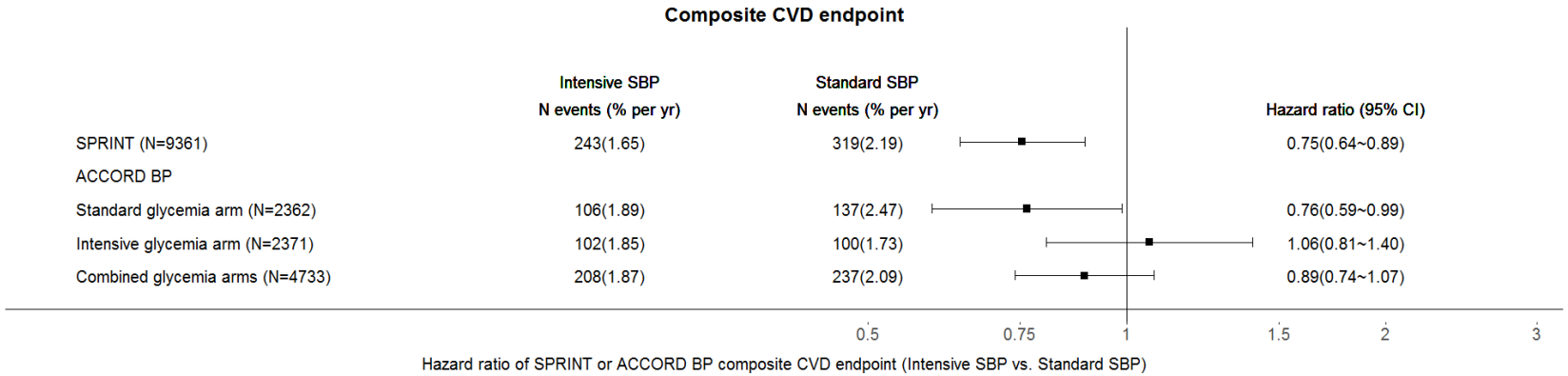
SBP – systolic blood pressure, CVD – cardiovascular disease, SPRINT – Systolic Blood Pressure Intervention Trial, ACCORD– Action to Control Cardiovascular Risk in Diabetes

Figure S2. **Follow-up mean SBP (95% CI) by SBP groups in SPRINT and ACCORD BP standard and intensive glycemia arms.**



SBP – systolic blood pressure, SPRINT – Systolic Blood Pressure Intervention Trial, ACCORD BP – Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial

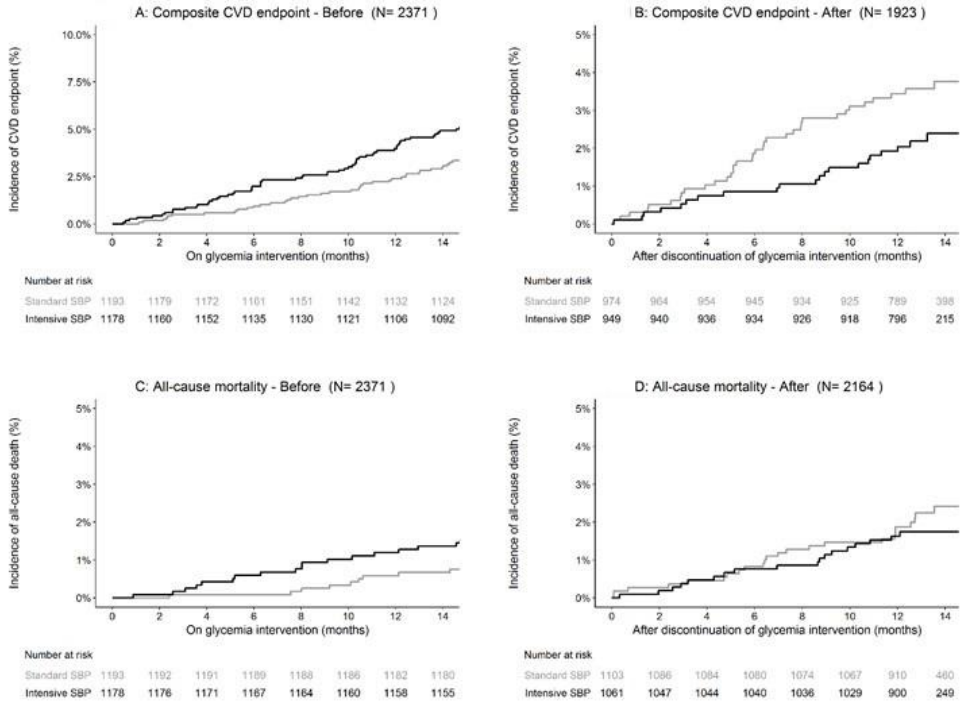
Figure S3. Effects of intensive SBP control on SPRINT protocol-defined primary CVD endpoint in SPRINT and ACCORD BP protocol-defined primary CVD endpoint in ACCORD BP.



Interaction p-values for comparisons of the effects of intensive SBP versus standard SBP	
SPRINT vs. ACCORD BP standard glycemia arm	0.94
SPRINT vs. ACCORD BP intensive glycemia arm	0.038
ACCORD BP intensive vs. standard glycemia arm	0.09
SPRINT vs. ACCORD BP combined glycemia arms	0.20

SBP – systolic blood pressure, CVD – cardiovascular disease, SPRINT – Systolic Blood Pressure Intervention Trial, ACCORD BP – Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial

Figure S4. **Cumulative incidence of composite CVD endpoint and all-cause mortality in intensive and standard SBP groups in the first 14 months during intensive glycemia intervention and in the first 14 months after discontinuation of the intensive glycemia intervention.**



A: CVD events during glycemia intervention
B: CVD events after discontinuation of the intensive glycemia intervention
C: All-cause during glycemia intervention
D: All-cause deaths after discontinuation of the intensive glycemia intervention
SBP – systolic blood pressure, CVD – cardiovascular disease