RESEARCH ARTICLE

Lowering systolic blood pressure does not increase stroke risk: an analysis of the SPRINT and ACCORD trial data

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Abstract

Objective: Traditional neurology teaching states that when mean arterial pressure dips below a 60 mm Hg threshold, there is an increase in stroke risk due to cerebral hypoperfusion. The aim of this study was to determine whether intensive lowering of systolic blood pressure increases adverse cardiovascular outcomes by examining the association between achieved blood pressure values, specifically mean arterial pressure and pulse pressure, and risk of stroke. **Methods**: Data from participants in the Systolic Blood Pressure Intervention Trial (SPRINT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure (BP) trial were examined, using survival analysis to model minimal arterial pressure and average pulse pressure during the study period against risk of stroke, hypotension, and syncope, with death as a competing risk. **Results**: In both SPRINT and ACCORD participants, there was no increase in stroke risk with achieved mean arterial pressure values below 60 mm Hg. In SPRINT participants, achieved mean arterial pressure values greater than 90 mm Hg were associated with a 247% (HR: 3.47, 95% CI: 2.06–5.85) higher risk of stroke compared with participants in the 80–89 mmHg reference group. No association was found between low achieved pulse pressure values and greater stroke risk in either the SPRINT or ACCORD participants, as well as no association between mean arterial pressure and pulse pressure values and risk of syncope. **Interpretation**: Intensive lowering of systolic blood pressure does not increase risk of stroke in hypertensive patients, despite extremely low mean arterial pressure or pulse pressure values.

Introduction

Many observational studies indicate that increased systolic blood pressure (SBP) leads to an increased risk of cardiovascular disease.[1,2] Conversely, systolic blood pressure less than 115 mm Hg is associated with significantly lower risk of stroke.[3] A recent systematic review and metaregression analysis has also emphasized that strict and aggressive blood pressure control may be the most crucial therapeutic strategy for secondary stroke prevention; highlighting that systolic blood pressure reduction is linearly associated with the magnitude of risk reduction in recurrent cerebrovascular events.[4]

The Systolic Blood Pressure Intervention Trial (SPRINT) investigated the relationship between intensity of systolic blood pressure treatment and adverse outcomes, finding that, while intensive treatment reduced cardiovascular disease events and mortality but did not lead to differences in overall serious adverse events, selected adverse outcomes including hypotension, electrolyte abnormalities, and acute kidney injury or acute renal failure were increased in the intensive treatment group.[5] The Action

to Control Cardiovascular Risk in Diabetes (ACCORD) trial included a blood pressure (BP) intervention trial that employed a similar study design to SPRINT in a diabetic population.[6] Intensive blood pressure lowering was defined as targeting a reduction in systolic blood pressure below 120 mm Hg in both the SPRINT and ACCORD BP trials versus targeting a systolic blood pressure goal below 140 mm Hg. Although the benefits of reducing systolic blood pressure include lower cardiovascular disease and mortality in SPRINT and stroke in ACCORD BP, it remains unclear whether intensive systolic blood pressure lowering, in terms of achieved blood pressure values, may put a patient at risk for adverse outcomes, such as stroke and hypotension secondary to cerebral hypoperfusion.

While systolic blood pressure is a measured value of blood pressure, pulse pressure is a calculated value defined as the difference between systolic blood pressure and diastolic blood pressure. Pulse pressure depends upon ejected ventricular blood interacting with large arteries and pressure from reflected waves.[7] Compared with other measures of blood pressure, pulse pressure has been shown to be a more sensitive cardiovascular risk indicator.[8]

Mean arterial pressure is also a calculated value and believed to be a better measure of cerebral perfusion than systolic blood pressure.[9] Mean arterial pressure is defined as the diastolic blood pressure (DBP) plus one third of the pulse pressure and is influenced by such factors as ventricular ejection fraction and peripheral vascular resistance.[10] A mean arterial pressure value of less than 60 mm Hg may result in hypoperfusion of the brain leading to increased adverse outcomes.[11–13] While ACCORD BP and SPRINT reported on the relationship between systolic blood pressure and adverse outcomes, such as stroke and cardiac events, the relationship of these outcomes with calculated values, such as mean arterial pressure and pulse pressure, remains unclear. Following the publication of the SPRINT results, clinicians have debated the applicability of the findings to routine medical practice.[14] We hypothesized that intensive lowering of systolic blood pressure would increase adverse outcomes, investigating correlations between mean arterial pressure and pulse pressure with stroke, syncope, and hypotension.

Methods

Study population

After Institutional Review Board approval by the University of Tennessee Health Science Center, de-identified data were obtained through data sharing efforts from the National Heart, Lung, and Blood Institute (NHLBI) biorepository BioLINCC for both the SPRINT and the ACCORD BP trials.[5,6] The details regarding the methodology of each study have been previously reported.[5,6,15,16] In brief, both were randomized, controlled, open-label trials comparing the cardiovascular benefits of achieving a systolic blood pressure target below 120 mm Hg with a treatment target below 140 mm Hg.

Clinical characteristics and outcomes

Descriptive statistics were obtained for each cohort, including race, gender, BMI, baseline systolic and baseline diastolic blood pressure, and average years of follow-up. The primary outcome of interest was stroke. Secondary outcomes included hypotension and syncope.

Statistical analysis

Baseline and follow-up blood pressure measurements from 9361 SPRINT participants and 4731 participants from the ACCORD BP trial were included in this analysis. Data from participants who withdrew consent were excluded. Mean arterial pressure was defined as (DBP + (SBP-DBP)/3), and pulse pressure was defined as the difference between systolic blood pressure and diastolic blood pressure. The minimal mean arterial pressure at any time during the study period and the mean pulse pressure over the follow-up visits, before the event occurred or before censoring, were divided into categories of 10 mm Hg increments, and total frequencies for each category are reported. Incidence of stroke, hypotension as a serious adverse event, and syncope were obtained for both intensive and standard groups at each level of mean arterial pressure and pulse pressure, and risk of these events was modeled with Cox proportional hazard models, taking into account competing risk of death using Fine & Gray's method. Additional analyses were performed with the time-varying effect of myocardial infarction and heart failure, nonmyocardial infarction cardiac events, and hypotension events. Mean arterial pressure values of 80–89 mm Hg and pulse pressure values from 50 to 59 mm Hg were used as references ranges. The models were adjusted for race, age, gender, treatment assignment, statin use, systolic blood pressure (only for analysis of pulse pressure), and history of bradycardia events. All variables used for adjustment were predefined. The proportional hazard assumptions were assessed with visual plots of complementary log survival versus log time. Because the generalized additive model is based on the log (odds ratio), and the spline term is also modeled on this scale, all figures are presented using log (odds ratio) plots. Statistical significance was defined as $P < 0.05$. Analyses were performed using SAS© software, Version 9.4. [NC, SAS Institute Inc.].[17]

Results

SPRINT

Descriptive statistics for the SPRINT trial study sample are displayed in Table 1. Mean systolic blood pressure was 139.7 mm Hg and mean diastolic blood pressure was 78.1 mm Hg. Throughout the median follow-up period of 3.2 years, there was a combined frequency of 365 (3.9%) cases of total death, 102 (1.1%) cases of cardiovascular disease death, 132 (1.5%) cases of stroke, 213 (2.3%) cases of myocardial infarction, 162 (1.7%) cases of heart failure, and 80 (0.9%) cases of acute coronary syndrome without myocardial infarction between the standard and intensive groups (Table 1). For the primary outcome, 62 (1.4%) stroke cases were in the intensive group and 70 (1.6%) cases were in the standard group. Regarding secondary outcomes, the intensive group experienced 110 (2.4%) hypotension cases and 107 (2.3%) syncope cases as compared to 66 (1.4%) and 80 (1.7%) cases in the standard group, respectively. The highest percentage of participants, 3807 (40.7%), had an average minimal mean arterial pressure between 70 and 79 mm Hg, and 3386 (36.2%) had an average pulse pressure in the 50–59 mm Hg range (Table 1).

Hazard ratios for stroke risk are presented in Table 2. There was no higher risk of incident stroke with a mean arterial pressure value below 60 mm Hg, compared with mean arterial pressure 80–89 mm Hg (HR: 0.44, 95%CI: 0.10–2.00; $P = 0.29$). However, the risk of stroke was greater with minimal mean arterial pressure values above 90 mm Hg (HR: 3.47, 95%CI: 2.06–5.85; $P < 0.0001$). On

Table 1. Participant characteristics (*N* %).

	SPRINT			ACCORD BP trial		
	Intensive	Standard	Total	Intensive	Standard	Total
N	4678	4683	9361	2361	2370	4731
Age (SD)	67.9 (9.5)	67.9 (9.4)	67.9 (9.4)	62.7 (6.8)	62.8 (6.6)	62.7 (6.7)
Race (*N*: %black)	1454 (31.1)	1493 (31.9)	2947 (31.5)	547 (23.2)	580 (24.5)	1127 (23.8)
Gender (%female)	1684 (36)	1648 (35.2)	3332 (35.6)	1128 (47.8)	1129 (47.6)	2257 (47.7)
Average follow-up year	3.2	3.2	3.2	4.6	4.7	4.7
Body mass index	29.9	29.8	29.9			
Baseline systolic blood pressure	139.7	139.7	139.7	139.0	139.4	139.2
Baseline diastolic blood pressure	78.22	78.04	78.1	75.9	76.0	76.0
Primary outcomes (*N*, %)	243 (5.2)	319 (6.8)	562 (6.0)	208 (8.8)	237 (10.0)	445 (9.4)
Total death	155 (3.3)	210 (4.5)	365 (3.9)	150 (6.4)	144 (6.1)	294 (6.2)
Cardiovascular disease death	37 (0.8)	65 (1.4)	102 (1.1)	60 (2.5)	58 (2.5)	118 (2.5)
Stroke	62 (1.4)	70 (1.6)	132 (1.5)	36 (1.5)	62 (2.6)	98 (2.1)
Heart attack	97 (2.1)	116 (2.5)	213 (2.3)	126 (5.3)	146 (6.2)	272 (5.8)
Heart failure	62 (1.3)	100 (2.1)	162 (1.7)	83 (3.5)	91 (3.8)	174 (3.7)
Acute coronary syndrome	40 (0.9)	40 (0.9)	80 (0.9)			
Adverse event						
Hypotension	110 (2.4)	66 (1.4)	176 (1.9)			
Syncope	107 (2.3)	80 (1.7)	187 (2.0)			
Minimal MAP (mean, SD)	74.5 (8.3)	81.9 (8.6)	78.2 (9.2)	70.04 (7.9)	79.28 (8.3)	74.7 (9.3)
<60	143 (3.1)	42 (0.9)	185 (1.98)	184 (7.8)	24 (1.0)	208 (4.4)
60–69	1153 (24.7)	350 (7.5)	1503 (16.1)	1039 (44.0)	264 (11.1)	1303 (27.5)
70–79	2331 (49.8)	1476 (31.5)	3807 (40.7)	899 (38.1)	966 (40.8)	1865 (39.4)
80–89	896 (19.2)	2029 (43.3)	2925 (31.3)	206 (8.7)	892 (37.6)	1098 (23.2)
90–99	155 (3.3)	786 (16.8)	941 (10.1)	33 (1.4)	224 (9.5)	257 (5.4)
Average pulse pressure (mean, SD)	53.4 (10.5)	60.1 (10.6)	57.3 (11.0)	55.5 (10.3)	62.4 (10.2)	58.9 (10.8)
<50	1747 (37.4)	776 (16.6)	2523 (27.0)	760 (32.2)	226 (9.5)	986 (20.8)
50–59	1682 (36.0)	1704 (36.4)	3386 (36.2)	895 (37.9)	768 (32.4)	1663 (35.2)
60–69	854 (18.3)	1413 (30.2)	2267 (24.2)	500 (21.2)	908 (38.3)	1408 (29.8)
70–79	304 (6.5)	603 (12.9)	907 (9.7)	155 (6.6)	340 (14.4)	495 (10.5)
≥80	91 (2.0)	187 (4.0)	278 (3.0)	51 (2.2)	128 (5.4)	179 (3.8)

Table 2. Incidence of stroke and hazard ratios for the risk of stroke (*n/N*, %, HR (95%CI), *P* value for difference).

	Intensive (*n* %)	Standard (*n* %)	Hazard ratio	*P* Value
SPRINT				
Having a low mean arterial pressure event	1 (0.8)	1 (2.9)	0.56 (0.14–2.35)	0.43
Minimal mean arterial pressure (per 5 mmHg)			1.29 (1.16–1.43)	<0.0001*
<60	1 (0.8)	1 (2.9)	0.44 (0.10–2.00)	0.29
60–69	15 (1.3)	5 (1.5)	0.58 (0.30–1.11)	0.10
70–79	26 (1.1)	25 (1.8)	0.81 (0.50–1.31)	0.39
80–89	15 (1.9)	19 (1.0)	Reference	
≥90	5 (5.9)	20 (2.9)	3.47 (2.06–5.85)	<0.0001*
Average pulse pressure (per 5 mmHg)			1.17 (1.06–1.28)	0.002*
<50	14 (0.8)	5 (0.7)	0.83 (0.48–1.43)	0.49
50–59	16 (1.0)	23 (1.4)	Reference	
60–69	11 (1.4)	22 (1.6)	1.07 (0.65–1.76)	0.80
70–79	16 (5.8)	13 (2.3)	2.00 (1.15–3.47)	0.014*
≥80	5 (6.0)	7 (4.1)	2.09 (0.96–4.55)	0.06
Having a hypotension event	9 (8.2)	3 (4.6)	0.34 (0.05–2.51)	0.29
Having a syncope event	107 (2.3)	80 (1.7)	0.28 (0.04–2.04)	0.21
ACCORD BP trial				
Having an low MAP event	3 (1.6)	2 (8.3)	1.47 (0.55–3.93)	0.45
Minimal mean arterial pressure (per 5 mmHg)			0.92 (0.75–1.13)	0.94
<60	3 (1.6)	2 (8.3)	2.90 (0.85–9.92)	0.09
60–69	13 (1.3)	11 (4.2)	2.27 (0.97–5.28)	0.06
70–79	15 (1.7)	29 (3.0)	1.88 (0.94–3.78)	0.08
80–89	4 (1.9)	13 (1.5)	Reference	
≥90	1 (3.0)	7 (3.1)	1.73 (0.55–5.48)	0.35
Average pulse pressure (per 5 mmHg)			1.18 (1.03–1.34)	0.013*
<50	4 (0.5)	3 (1.3)	0.30 (0.11–0.77)	0.013*
50–59	20 (2.2)	19 (2.5)	Reference	
60–69	6 (1.2)	12 (1.3)	0.48 (0.24–0.94)	0.032*
70–79	3 (1.9)	20 (5.9)	1.58 (0.79–3.17)	0.20
≥80	3 (5.9)	8 (6.3)	1.87 (0.71–4.90)	0.20

Competing risk model for stroke and death.

Adjustment with patient's sociodemographics and general clinical characteristics.

*indicates a statistically significant value (*P* < 0.05).

the other hand, average pulse pressure values between 70 and 79 mm Hg were associated with a doubling of the stroke risk compared with pulse pressure values between 50 and 59 mm Hg (HR: 2.00, 95%CI: 1.15–3.47; *P* = 0.014).

Incidence and risk of hypotension as a serious adverse event and syncope are reported in Table 3. Minimal mean arterial pressure levels below 60 mm Hg were associated with a 275% higher risk of hypotension (HR: 3.75, 95% CI: 1.76–8.01; *P* < 0.001), and minimal mean arterial pressure levels between 60 and 69 mm Hg were associated with a 78% higher risk of hypotension (HR: 1.78, 95%CI: 1.06–2.99; *P* = 0.028). Mean arterial pressure values greater than 90 mm Hg were associated with a 70% lower risk of hypotension (HR: 0.30, 95%CI: 0.09–0.97; *P* = 0.045). No statistically significant hazard ratios for risk of hypotension were found in any of the pulse pressure quintiles. Risk of syncope was not associated with either minimal mean arterial pressure or mean pulse pressure values.

When minimal mean arterial pressure and mean pulse pressure were assessed on a continuous scale, a 5 mm Hg increase in minimal mean arterial pressure demonstrated a 29% greater risk of stroke (HR: 1.29, 95%CI: 1.16–1.43) (Fig. 1), whereas a 5 mm Hg increase in mean pulse pressure showed a 17% higher stroke risk (HR: 1.17, 95%CI: 1.06–1.28) (Fig. 2). However, a 5 mm Hg increase in mean arterial pressure conferred a 20% reduction in hypotension risk (HR: 0.80, 95%CI: 0.70–0.90) (Table 3), but did not have any relationship to syncope risk. A 5 mm Hg increase in pulse pressure, meanwhile, was not associated with changes in either hypotension or syncope risk.

ACCORD

Descriptive statistics for the ACCORD data are also presented in Table 1. Mean systolic blood pressure was 139.2 mm Hg and mean diastolic blood pressure was 76 mm Hg. Throughout the median follow-up period of

Table 3. Incidence and risk of hypotension and syncope in SPRINT participants.

	Intensive (n %)	Standard (n %)	Hazard ratio	P value
Hypotension				
Having an low mean arterial pressure event	9 (6.2)	3 (7.1)	2.82 (1.48–5.35)	0.002*
Minimal mean arterial pressure (per 5 mmHg)			0.80 (0.70–0.90)	0.0002*
<60	9 (6.2)	3 (7.1)	3.75 (1.76–8.01)	<0.001*
60–69	36 (3.1)	15 (4.3)	1.78 (1.06–2.99)	0.028*
70–79	45 (1.9)	26 (1.8)	1.18 (0.75–1.83)	0.48
80–89	19 (2.1)	19 (0.9)	Reference	
≥90	1 (0.7)	3 (0.4)	0.30 (0.09–0.97)	0.045*
Average pulse pressure (per 5 mmHg)			0.93 (0.84–1.03)	0.14
<50	34 (2.0)	17 (2.2)	1.36 (0.89–2.07)	0.16
50–59	38 (2.3)	19 ()	Reference	
60–69	29 (3.4)	15 (1.1)	1.02 (0.68–1.53)	0.92
70–79	7 (2.3)	12 (2.0)	0.93 (0.53–1.64)	0.80
≥80	2 (2.2)	3 (1.6)	0.81 (0.31–2.13)	0.67
Syncope				
Having an low mean arterial pressure event	7 (4.8)	0 (0.0)	1.35 (0.63–2.87)	0.44
Minimal mean arterial pressure (per 5 mmHg)			0.99 (0.90–1.10)	0.92
<60	7 (4.8)	0 (0.0)	1.24 (0.54–2.82)	0.61
60–69	40 (3.5)	9 (2.6)	1.05 (0.67–1.63)	0.84
70–79	40 (1.7)	33 (2.2)	0.81 (0.55–1.20)	0.30
80–89	17 (1.9)	32 (1.6)	Reference	
≥90	3 (2.0)	6 (0.8)	0.84 (0.40–1.76)	0.65
Average pulse pressure (per 5 mmHg)			1.0 (0.91–1.10)	0.97
<50	30 (1.7)	12 (1.6)	1.25 (0.81–1.94)	0.32
50–59	38 (2.3)	22 (1.3)	Reference	
60–69	21 (2.4)	28 (2.0)	0.98 (0.67–1.43)	0.90
70–79	13 (4.4)	11 (1.8)	0.97 (0.59–1.58)	0.89
≥80	5 (5.4)	7 (3.7)	1.35 (0.69–2.65)	0.38

*indicates a statistically significant value (P < 0.05).

4.7 years, there was a combined frequency of 294 (6.2%) cases of total death, 118 (2.5%) cases of cardiovascular disease death, 98 (2.1%) cases of stroke, 272 (5.8%) cases of heart attack, and 174 (3.7%) cases of heart failure, in the standard and intensive groups. For stroke outcome, 36 (1.5%) cases of stroke were in the intensive group and 62 (2.6%) cases were in the standard group. The highest percentage of patients, 1865 (39.4%), had a minimal mean arterial pressure between 70 and 79 mm Hg, and 1663 (35.2%) had an average pulse pressure between 50 and 59 mm Hg (Table 1).

Hazard ratios for risk of stroke are shown in Table 2. There was no significantly higher stroke risk with minimal mean arterial pressure values below 60 mm Hg (HR: 2.90, 95%CI: 0.85–9.92, P = 0.09). There was a lower stroke risk with pulse pressure values below 50 mm Hg (HR: 0.30, 95%CI: 0.11–0.77; P = 0.013). Pulse pressure values between 60 and 69 mm Hg also showed a reduction in stroke risk by 52% (HR 0.48, 95%CI: 0.24–0.94; P = 0.032). When mean pulse pressure was assessed on a continuous scale, a 5 mm Hg increase in mean pulse pressure demonstrated an 18% higher risk of stroke (HR: 1.18, 95% CI: 1.03–1.34) (Fig. 3).

Discussion

Intensive lowering of systolic blood pressure in hypertensive patients did not demonstrate a higher stroke risk based upon our analysis of data from two large prospective, randomized clinical trials, both randomizing half the participants to an intensive systolic blood pressure goal of less than 120 mm Hg. These results suggest that the long-held idea that stroke risk increases below a mean arterial pressure threshold of 60 mm Hg may not be correct, and that mean arterial pressure values below this threshold may be safe. In SPRINT and ACCORD BP, there is no evidence that treating to a target systolic blood pressure less than 120 mm Hg increases the risk of stroke, even for those with achieved mean arterial pressure less than 60 mm Hg. Similar results were found in a small study (n = 115) reporting mean arterial pressure values below 70 mm Hg were not associated with higher stroke

Smoothing log(OR) for Stroke, SPRINT
DF=2 P=0.0866
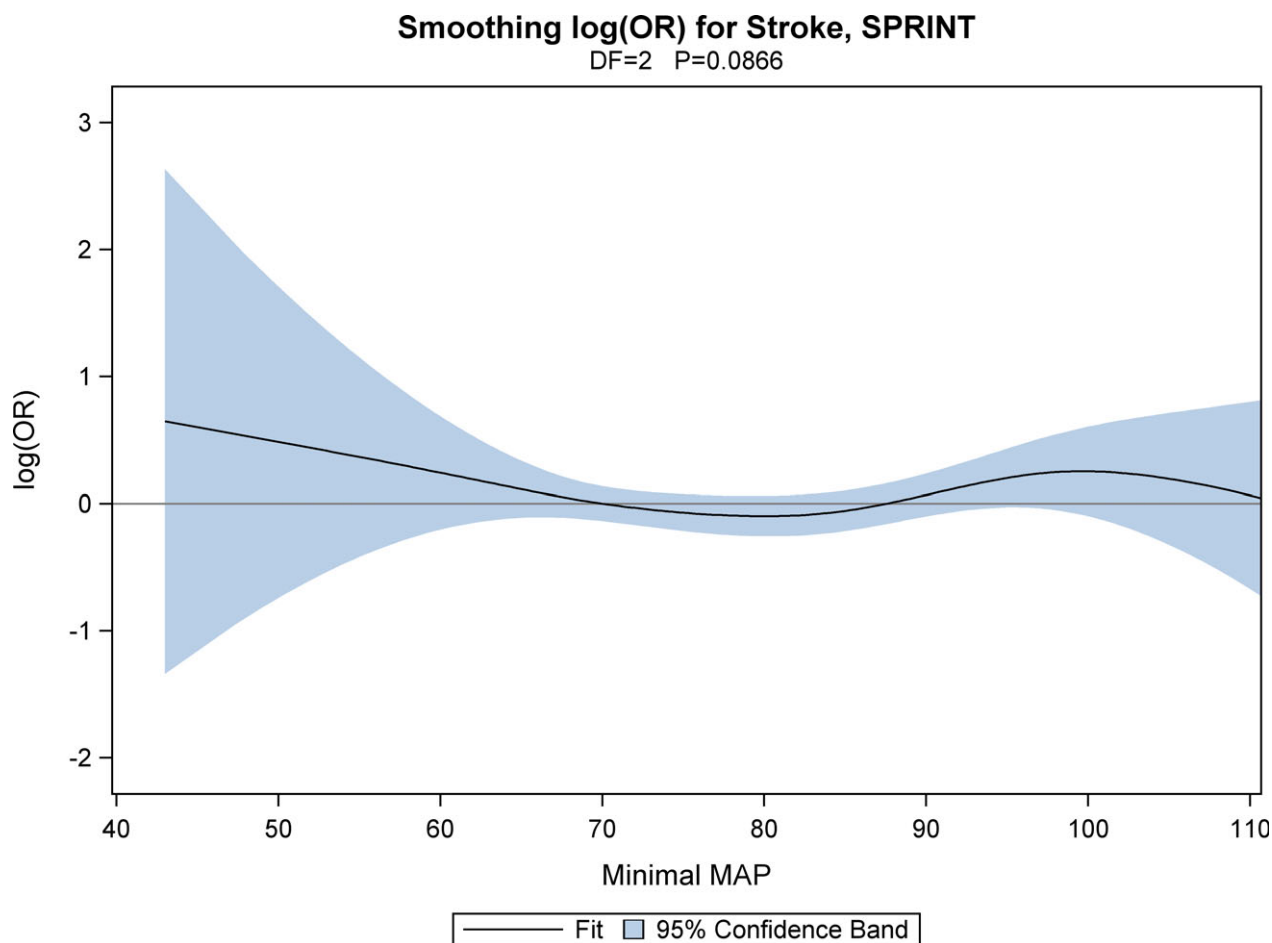
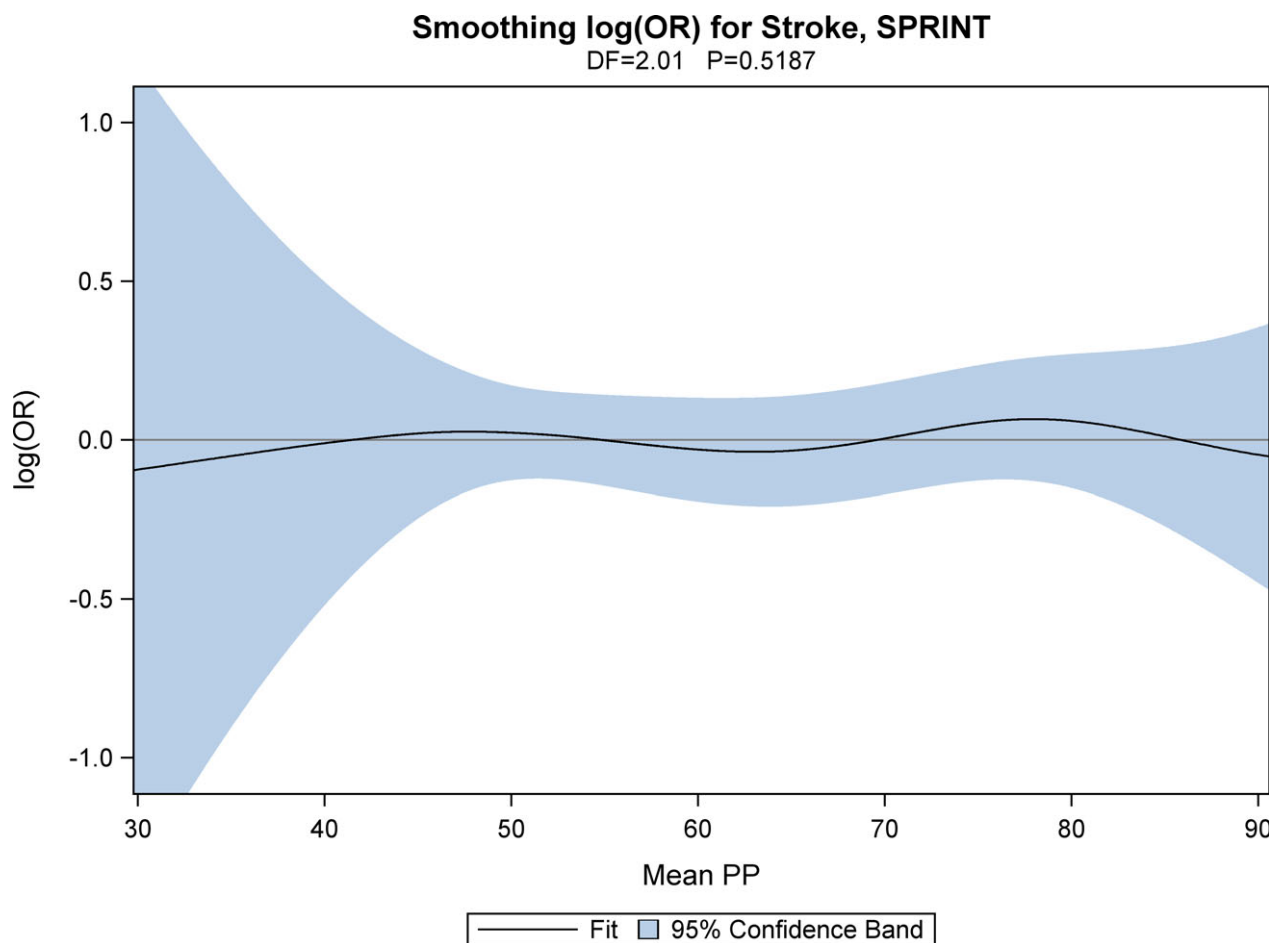**Figure 1.** Hazard ratios of stroke by levels of mean arterial pressure in SPRINT trial.

outcomes but might be a good marker for neurological deficits.[18] However, due to the small number of events for this mean arterial pressure threshold in both studies, caution is still warranted, and further research to help elucidate this relationship is needed.

While low mean arterial pressure values were not associated with stroke outcome, higher mean arterial pressure values were associated with a greater risk of stroke in SPRINT. These results have been found in other studies. Sesso et al. reported that in men younger than 60 years, higher average mean arterial pressure values were strongly associated with cardiovascular disease risk (events included myocardial infarction, angina pectoris, stroke, and cardiovascular death). Comparing men in the highest versus lowest quartiles of average mean arterial pressure (≥97 vs. <88 mm Hg), the RR of cardiovascular disease was 2.52. Strong positive associations for this group were also found in the second quartile of mean arterial pressure (>88 to <93 mm Hg).[19] We did find that low mean arterial pressure levels were

associated with an increased risk for hypotension as a serious adverse event but were not associated with syncope.

Our results also provide evidence that low pulse pressure is not associated with greater stroke risk. In fact, pulse pressure values below 50 mm Hg or between 60 and 69 mm Hg offered a protective effect for stroke in patients in the ACCORD trial. However, pulse pressure values between 70 and 79 mm Hg resulted in greater stroke risk in SPRINT participants. A study examining pulse pressure and adverse cardiovascular events found similar results using univariate analysis, with the third (60< to ≥70 mm Hg) and fourth (>70 mm Hg) quartiles of pulse pressure associated with an increased risk of fatal and nonfatal stroke compared with the first quartile reference group (pulse pressure ≤ 50 mm Hg). After multivariate analysis, the fourth quartile of pulse pressure continued to show a significant increase in nonfatal stroke compared to the first quartile.[20] Therefore, pulse pressure may be a useful clinical marker for adverse

Smoothing log(OR) for Stroke, SPRINT
DF=2.01   P=0.5187

[Figure: plot of log(OR) vs Mean PP, with Fit line and 95% Confidence Band]

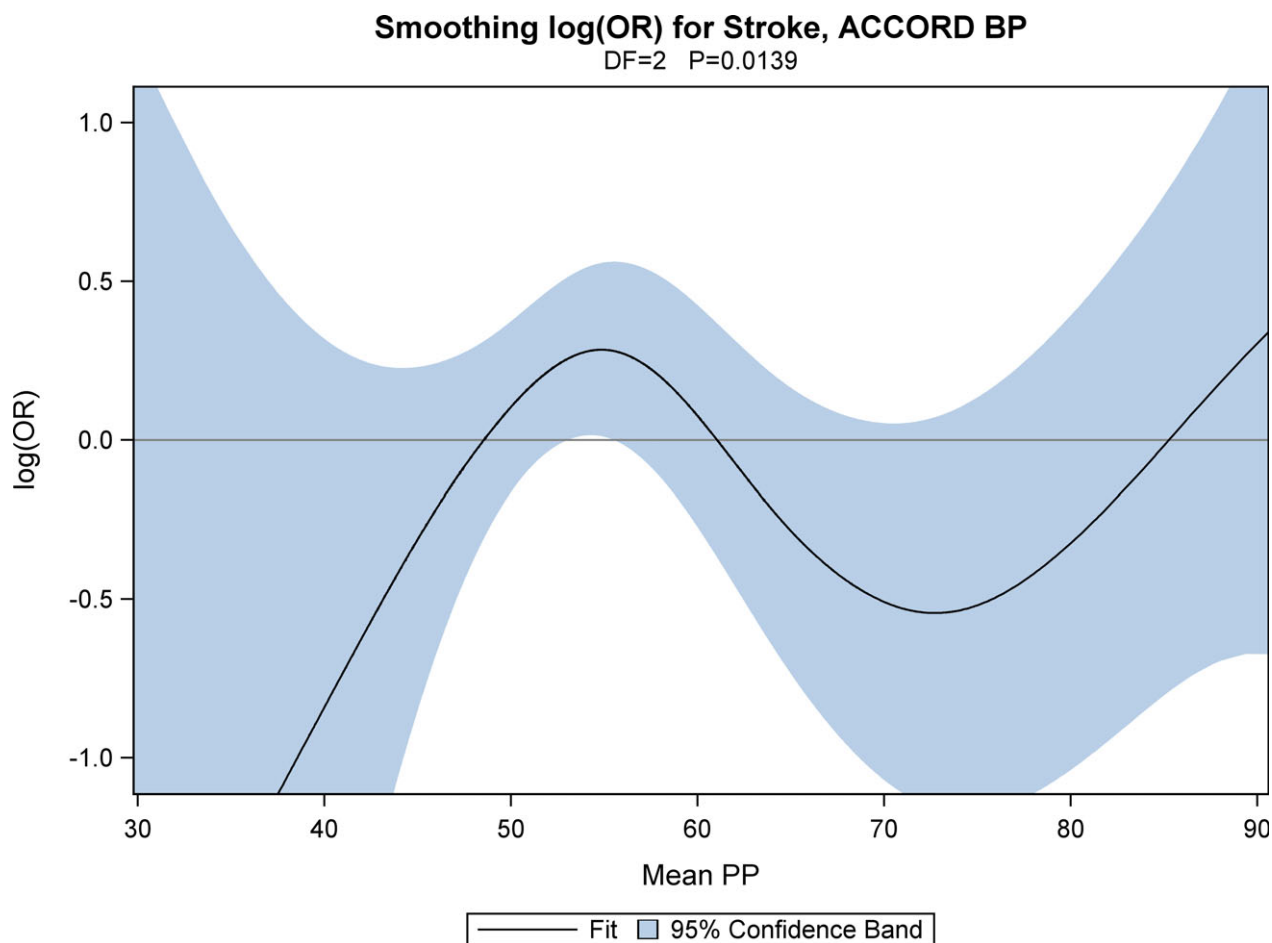**Figure 2.** Hazard ratios of stroke by levels of pulse pressure in SPRINT trial.

cardiovascular outcomes, as it is easily calculated in an office/hospital setting and may help identify high-risk patients.[20]

Pulse pressure may also be a convenient, noninvasive way to examine left ventricular ejection volume, which is often difficult to measure.[21] Because higher pulse pressure values may indicate significant systolic hypertension,[22] it is feasible that these higher pulse pressure values would also indicate increased stroke risk. It is worth noting, however, that pulse pressure may be a more significant marker in older individuals, as systolic blood pressure and diastolic blood pressure diverge with increasing age. While systolic blood pressure increases continuously until death, diastolic blood pressure increases up to ~60 years and then decreases with age.[19] Because pulse pressure is calculated from the difference between these two measurements, pulse pressure values will inevitably widen in older populations.

Similar to our findings, data from a recently published study by Beddhu et al. also demonstrate that lowering systolic blood pressure can be beneficial, even across varying levels of baseline diastolic blood pressure.[23] The authors conclude that low levels of diastolic blood pressure at baseline should not deter the use of intensive treatments for hypertension.

While an important strength of this study is the use of two well-known, large sample size cohorts from NIH-sponsored randomized clinical trials, there are also several limitations. Because this was a secondary analysis of primary data, we lack fine details about patients included in these datasets. Our analyses consist of various end-state outcomes, with blood pressure measurements taken at the time of each study visit. No data are available for the intervening periods between visits. Therefore, we do not have any information on the amount of time each patient spent in their identified mean arterial pressure and pulse pressure levels, just that at some point in time their calculated blood pressure values were within these ranges. In addition, there is a potential for ascertainment bias regarding hypotension serious adverse event data, and

Smoothing log(OR) for Stroke, ACCORD BP
DF=2 P=0.0139

Figure 3. Hazard ratios of stroke by levels of pulse pressure in ACCORD BP trial.

results should be interpreted with caution. Unlike the primary outcome data (i.e., stroke), which was collected at specified physician visits that were identical in number between the intensive and standard group, serious adverse event data (i.e., hypotension) were collected at any visit, including visits to adjust blood pressure medications. Because the intensive group had a greater number of these types of visits than the standard group, it is possible that the intensive group had a greater opportunity to report serious adverse events such as hypotension. Furthermore, due to the very small number of hypotensive events recorded (nine cases in the intensive group vs. three cases in the standard group at mean arterial pressure levels less than 60 mm Hg), caution is warranted.

The use of two different high-risk populations makes it difficult to directly compare cohorts, as SPRINT enrolled hypertensive patients with no known diabetes mellitus or prior stroke, while ACCORD BP enrolled patients with diabetes, many of whom also had other comorbidities. Thus, we did not conduct a pooled analysis, and results

may not be generalizable to healthier populations. Additionally, data were not available for either study regarding stroke subtype (i.e., ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage), therefore we were unable to assess potential differences in these subtypes.

Another limitation to this study is inherent to the use of Cox Proportional Hazard models. While this statistical test has its strengths in that it allows for modeling the relationship of survival time through hazard function using many covariates at the same time, the test relies on an assumption that the hazards are proportional to each other, and the covariates investigated have a constant impact on this hazard over time. If time-dependent variables are included without appropriate modeling, this assumption can be violated, and significant effects in the early or late follow-up period can be missed.[24] In sensitivity analysis, we included other cardiovascular disease events before stroke as time-varying variables, assuming that patients who experienced another cardiovascular disease event may have an altered risk of stroke later. The results from these models were similar.

Smoothing log(OR) for Stroke, ACCORD BP
DF=2   P=0.4924
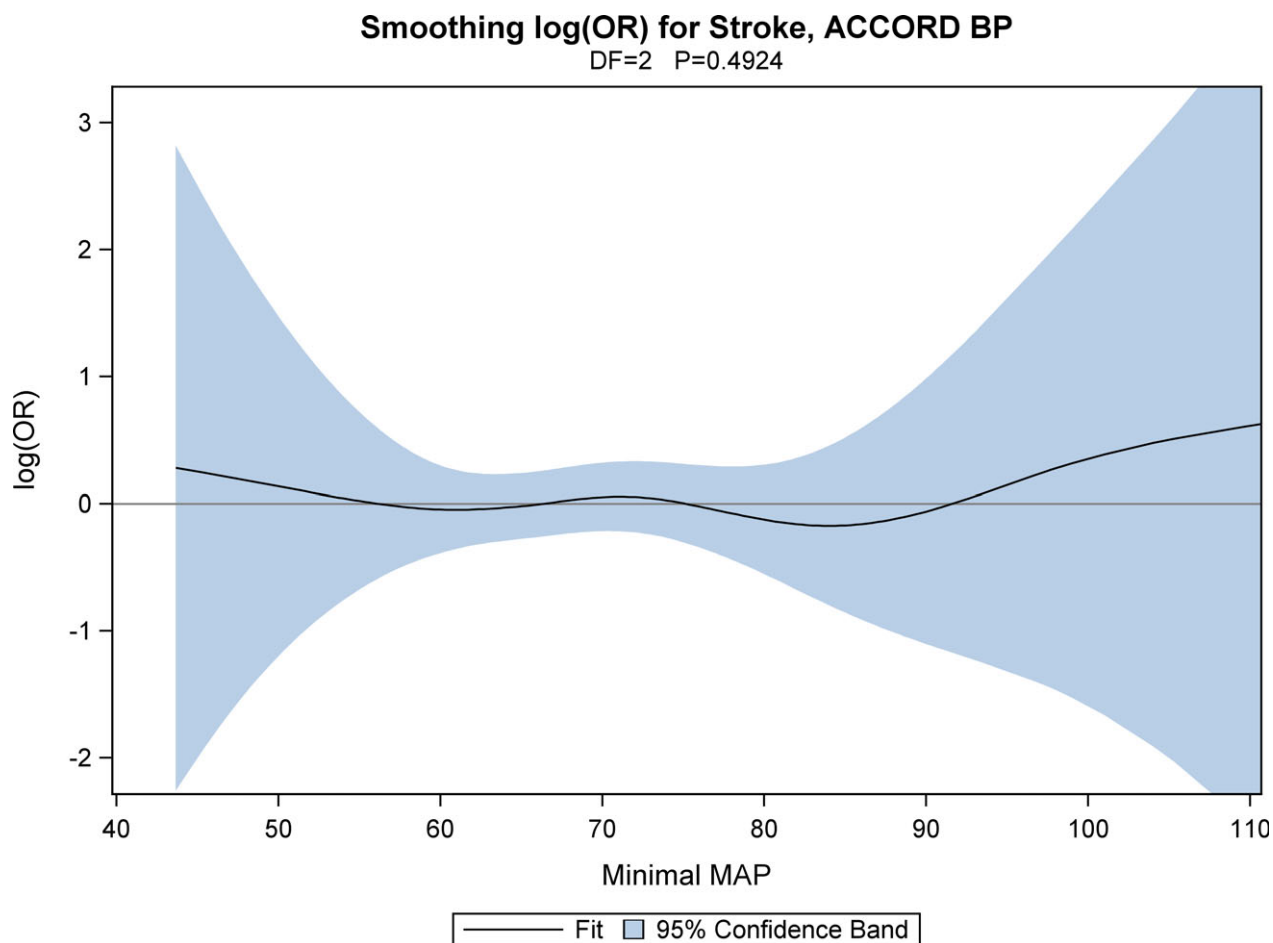
Figure 4. Hazard ratios of stroke by levels of mean arterial pressure in ACCORD BP trial.

These findings highlight a research effort that was made possible through data sharing requirements and the NEJM SPRINT Challenge. We conclude that, while intensive lowering of systolic blood pressure in patients is unlikely to induce harm by leading to stroke despite low mean arterial pressure and pulse pressure values, there exists a small increased risk of hypotension. This information may reassure clinicians in treating their hypertensive patients to the lower blood pressure levels that were targeted in ACCORD BP and SPRINT without concern for lowering mean arterial pressure or pulse pressure.

Acknowledgments

Conflict of Interest

The authors report no conflicts of interest.

Author Contributions

E. C. O'Conor drafted the manuscript and tables and interpreted data analyses; J. Wang ran data analyses and drafted figures; K. D. Gibney and G. R. Young assisted with drafting and editing manuscript; X. Yu, A. W. Alexandrov, T. Jones, K. C. Johnson, W. C. Cushman, and J. W. Tsao oversaw data analyses and helped draft manuscript. All authors approved the final manuscript.

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