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COMMENTARY

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New evidence for the diastolic J-curve effect challenges the safety of intensive blood pressure control

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1 | INTRODUCTION

The recently published Systolic Blood Pressure Intervention (SPRINT) study has revolutionized the concept of the effective treatment of hypertension.[1] The findings showed that aggressive systolic blood pressure (SBP) control to <120 mm Hg was associated with significant reduction of the primary composite outcome of myocardial infarction (MI), other coronary syndromes, stroke, heart failure (HF), or death from cardiovascular (CV) causes in both older men and women and even those 75 years and older.[2] These findings have prompted plans to revise the blood pressure (BP) treatment guidelines according to SPRINT. However, aggressive treatment of SBP to <120 mm Hg could also reduce diastolic BP (DBP) to ≤70 or <60 mm Hg. Such lowering of DBP could reduce coronary blood flow, particularly in high-risk patients with preexisting coronary artery disease (CAD), and hypertension with or without left ventricular hypertrophy (LVH) and cause myocardial ischemia, MI, or CV death due to the J-curve effect.[3–5] In a recent paper I wrote regarding the impact of SPRINT on the future treatment of hypertension, I alluded to the possibility of adverse CV events from the aggressive control of BP due to the J-curve effect from the low DBP.[6] This prediction is supported by two recent publications[7,8] reporting on the myocardial damage from the J-curve effect due to low DBP by measuring serial blood levels of high-sensitivity cardiac troponin T (hs-cTnT). This commentary addresses these two publications as well as other recent studies questioning the long-term safety of aggressive SBP and DBP control.

2 | CONTROVERSIES REGARDING THE AGGRESSIVE CONTROL OF BP

SPRINT is a unique and provocative study showing CV benefits of aggressive SBP control to <120 mm Hg in older patients with hypertension including those ≥75 years and older.[1,2] The SPRINT enrolled 9361 nondiabetic patients with hypertension who were 50 years and older with a baseline SBP ≥130 mm Hg and randomized to aggressive SBP control of <120 mm Hg or to standard SBP control of <140 mm Hg. After a follow-up of 3.26 years, the study was prematurely terminated due to significant CV benefits seen in the aggressive SBP control group compared with the standard SBP control group, which included patients 75 years and older.[1,2] The actual BP levels at the end of the study were 121.4/68.7 mm Hg in the aggressive BP control group and 136.2/76.3 mm Hg in the standard BP control group. This was associated with a significant reduction of the primary composite outcome of MI, other coronary syndromes, stroke, HF, or CV death (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.64–0.89 [*P*<.001]). However, these benefits were associated with serious adverse events of hypotension, syncope, electrolyte abnormalities, acute kidney injury, or acute renal failure in 4.7% in the intensive care group vs 2.5% in the standard care group (*P*<.001). The CV and stroke benefits of SPRINT have been reported elsewhere and by other large studies and reviews with less intensive BP controls and fewer adverse effects.[9–14] The findings from these studies are summarized in Table 1. In the substudy of diabetic patients with hypertension from the INVEST study by Cooper-Dehoff and colleagues,[9] patients were randomized to a tight SBP control group (SBP <130 mm Hg), a usual SBP control group (SBP: 130 to <140 mm Hg), or an uncontrolled SBP group (SBP ≥140 mm Hg). After 2.6 years of follow-up, the CV event rate in the tight, the usual, and the uncontrolled SBP groups were 12.7%, 12.6%, and 19.8%, respectively. In this study, the incidence of CV events was not different between the tight and the usual SBP control groups. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of diabetic patients with hypertension by Cushman and colleagues,[10] aggressive SBP control to <120 mm Hg was not better than standard SBP control of <140 mm Hg in preventing CV events except stroke. From the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) of high-risk patients, Mancia and colleagues[11] reported that the adjusted risk of CV events was reduced by treating to a BP of <140/90 mm Hg but not to <130/80 mm Hg after a mean of 4.7 years of follow-up. In a review by Chrysant and

TABLE 1 Levels of systolic blood pressure below which cardiovascular events could increase

Author	Study Type	Patients, No.	Age, y	SBP, mm Hg	Risks		
					CHD	Stoke	CV Death
Cooper-Dehoff[9]	RCT	6400	50	130	Yes	No	Yes
Cushman[10]	RCT	4733	62	119	Yes	No	Yes
Mancia[11]	RCT	12,554	67	130 to <140	Yes	No	Yes
Chrysant[12]	Rev	25,392	62	136	Yes	No	Yes
Sim[13]	Retro	398,419	64	137	Yes	–	Yes
Xie[15]	Rev-Met	44,989	62	133	Yes	–	Yes
Emdin[16]	Rev-Met	100,354	61	140	Yes	No	Yes

CHD, coronary heart disease; CV, cardiovascular; RCT, randomized control trial; Rev-Met, review/meta-analysis; Retro, retrospective; SBP, systolic blood pressure.

Chrysant of diabetic patients with hypertension, the best reduction of CV events was achieved with a nadir SBP and DBP of 136 mm Hg and 85 mm Hg, respectively.[12] Similar results were reported by Sim and colleagues[13] from a large retrospective study of hypertensive patients. In this study, patients with a calculated SBP nadir of 137 mm Hg had the lowest incidence of CV mortality and end-stage renal disease. Further increase or decrease of SBP from this level was associated with a higher incidence of adverse events. In addition, from a large review and meta-analysis, Xie and colleagues,[15] reported that reduction of BP to 133/76 mm Hg was associated with greater reduction in major CV events, MI, and stroke than BP 140/81 mm Hg. However, more intensive treatment had no clear beneficial effects on HF, CV death, total mortality, or end-stage renal disease. Similar results were reported by Emdin and colleagues[16] from a large review and meta-analysis of diabetic patients with hypertension. Patients with an SBP <140 mm Hg had a lower incidence of CV events, coronary heart disease (CHD), and stroke than patients with an SBP ≥140 mm Hg.

3 | MECHANISM OF CV EVENTS WITH LOW DBP: THE J-CURVE EFFECT

The J-curve effect demonstrates a relationship between a range of BPs, mostly DBPs, and the incidence of CV complications which are the lowest when the DBP reaches a lowest point (nadir), after which any further increase or decrease of DBP is associated with a higher incidence of adverse CV events, including myocardial ischemia, chest pain, MI, and even death. The J-curve phenomenon seen with low DBP is due to the fact that coronary perfusion occurs during the diastolic phase of the cardiac cycle. Because the extraction of oxygen by the myocardium is complete, any further decrease in DBP, and, consequently, coronary blood flow, will result in myocardial ischemia despite the fact that the myocardium is protected through its autoregulatory mechanism from coronary pressures down to 45 mm Hg.[3] The presence of CAD and hypertension with or without LVH will shift the coronary autoregulation pressure upwards.[4] Studies in hypertensive patients with LVH have shown ischemic T-wave changes when the DBP was reduced to 85 to 90 mm Hg, confirming the presence of the J-curve effect.[5] Other studies in hypertensive patients with diabetes mellitus have shown a J-curve effect for DBPs ranging from 70 to 80 mm Hg.[16–19] A recent study by McEvoy and colleagues[7] provides new evidence regarding the damaging myocardial effects of low DBP through the J-curve effect. They analyzed the data from the Atherosclerosis in Communities (ARIC) study cohort of 11 565 patients with a mean age of 57 years at baseline followed for 21 years. They found that the DBP at baseline was independently associated with progressive myocardial damage, as assessed by the estimated annual changes of hs-cTnT during the 6 years of follow-up between visits 2 and 4 (Table 2). The hs-cTnT was higher for DBP <60 mm Hg, 60 to 69 mm Hg, and ≥100 mm Hg compared with the reference DBP 80 to 89 mm Hg. In addition, the incidence of CHD, stroke, and death were higher for baseline DBP <60 mm Hg compared with reference DBP 80 to 89 mm Hg. However, the incidence of CHD was still higher for DBPs 60 to 69 mm Hg and 70 to 79 mm Hg compared with a reference DBP of 80 to 89 mm Hg (Table 3).The ARIC study is a prospective observational cohort of 15 792 adults sampled from four US communities followed annually for 21 years.[20] Several studies have shown that hs-cTNT ≥14 ng/L is a sensitive index of myocardial damage and adverse CV events in asymptomatic patients.[21–23] In addition, one recent study correlated the SBP and DBP levels from 22 672 patients from the Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) registry.[24] The analysis of data has shown a J-curve effect of SBP ≥140 mm Hg and DBP ≥80 mm Hg and SBP <120 mm Hg and DBP <70 mm Hg, respectively. These BP levels were associated with a higher incidence of the primary composite outcome of CV death, MI, or stroke.[24]

4 | DISCUSSION

The results of the SPRINT study are impressive and provocative and deserve closer scrutiny. Achieving intensive SBP reductions will inevitably lead to lower DBP, which may result in myocardial damage long term through the J-curve effect.[7] For example, in a secondary

TABLE 2 Association of DBP with elevated hs-cTnT ≥14 ng/L

Visit 2 DBP, mm Hg	OR (95% CI)	*P* Value	Annual Changes (Visits 2 and 4)	*P* Value
<60	2.24 (1.22–4.10)	<.01	1.46 (0.51–2.40)	<.002
60–69	1.52 (1.00–2.32)	<.05	0.95 (0.28–1.61)	<.005
70–79	1.02 (0.71–1.47)	0.9	0.85 (0.27–1.44)	<.004
80–89	1.00 (reference)	–	0 (reference)	-
90–99	1.06 (0.61–1.83)	.84	−0.84 (−1.47 to 0.0)	.06
≥100	1.54 (0.63–3.78)	.34	−0.99 (−2.58 to 0.58)	.21

Adjusted for age, race, sex, body mass index, smoking, alcohol intake, systolic blood pressure, blood pressure medications, diabetes mellitus, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, cholesterol-lowering medications, and estimated glomerular filtration rate. CI, confidence interval; DBP, diastolic blood pressure; hs-cTnT, high-sensitivity cardiac troponin T; OR, odds ratio.

analysis of SPRINT by Williamson and colleagues[2] of elderly participants (≥75 years), DBP fell from a mean baseline of 71.5 mm Hg to 62 mm Hg from the intensive treatment of SBP. This is of potential concern due to the J-curve effect of low DBP and CAD events.[16–19] In their recent study, McEvoy and colleagues[7] present strong evidence that low DBP is associated with increased levels of hs-cTnT, an index of structural heart damage. Although the SPRINT study did not show evidence for a J-curve effect, subclinical cardiac damage cannot be excluded. If the study was not stopped prematurely, adverse cardiac effects could have been demonstrated. Other large studies and reviews have shown that similar benefits could be obtained with similar or higher SBPs and DBPs.[9–14] However, it should be recognized that the method used to measure BP in SPRINT was by an automatic device in the absence of a doctor or nurse to avoid the white-coat effect. Consequently, the BPs in SPRINT would likely be higher than those reported. Additionally, the results of SPRINT cannot be compared with those of these studies, since most of these studies included patients with diabetes and the results could be different between diabetic and nondiabetic patients with hypertension. This was demonstrated by Weber and colleagues[25] in their subanalysis of the data from the Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) study. From this analysis of 10 705 patients with diabetes and hypertension, SBP reduction ≤140 mm Hg in 6459 patients with diabetes was associated with a 49% (*P*<.001) lower incidence of the primary composite end point of CV death or nonfatal MI or stroke. However, further SBP reductions to <120 mm Hg did not result in a further decrease of outcomes, except for stroke. In contrast, in the nondiabetic cohort of 4246 patients, the primary composite end point fell steadily to 45% (*P*=.041) to SBP <120 mm Hg. These results are different from their previous analysis of the total patient cohort, which showed no difference in the primary composite outcome between SBP <140 mm Hg and SBP <130 mm Hg, with the exception of stroke, which was steadily lower down to SBP <120 mm Hg.[26] It is of interest that an analysis of several studies by Lackland and colleagues[27] showed that the risk ratio of stroke incidence was 0.68 (95% CI, 0.60–0.79) for SBP 140 to 149 mm Hg vs ≥150 mm Hg, 0.63 (95% CI, 0.52–0.73) for SBP 130 to 139 mm Hg vs ≥140 mm Hg, and 0.68 (95% CI, 0.57–0.83) for SBP <130 vs ≥130 mm Hg. These results are intriguing since stroke incidence has been shown to be lower with lower BPs. If the results of SPRINT were to be applied clinically to qualified hypertensive patients, they would significantly increase the number of patients who require treatment. A recent analysis from the National Health and Nutrition Examination Survey from 2007–2012 found that an additional 16.8 million US adults met the SPRINT eligibility criteria (6.6 million with SBP 130–139 mm Hg and 10.2 million with SBP ≥140 mm Hg). This analysis demonstrates that SBP lowering to ≤120 mm Hg would substantially increase the percentage of US adults who would benefit from SBP reduction.[28] This would result in significant increases in both the number of patients requiring treatment and the costs of care, since most SPRINT patients were taking an average of three medications.

5 | CONCLUSIONS

The SPRINT study demonstrating CV benefits in nondiabetic patients with hypertension is a landmark finding, and, although not definitive, will most likely result in a revision of current BP treatment guidelines with target SBP levels >120 mm Hg. This new revision could be closer to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the American Heart Association guidelines of 2003 and 2007.[29,30] These guidelines recommend reduction of SBP and DBP

TABLE 3 Association of DBP with CHD, stroke, and mortality

	CHD		Stroke		Mortality	
Visit 2 DBP, mm Hg	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
<60	1.49 (1.20–1.85)	.001	1.13 (0.79–1.61)	.52	1.32 (1.13–1.55)	<.001
60–69	1.23 (1.05–1.44)	.01	1.03 (0.80–1.32)	.83	1.10 (0.98–1.23)	.12
70–79	1.20 (1.05–1.37)	.01	1.07 (0.86–1.32)	.55	0.99 (0.89–1.10)	.89
80–89	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
90–99	0.93 (0.74–1.16)	.52	1.20 (0.87–1.66)	.27	1.01 (0.85–1.19)	.92
≥100	0.76 (0.50–1.17)	.21	1.50 (0.90–2.50)	.12	1.03 (0.76–1.40)	.84

Adjustments similar as in Table 2. CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio.

to <140 and <90 mm Hg in persons 50 years and older with uncomplicated hypertension and to <130 and <80 mm Hg for patients with diabetes mellitus, chronic kidney disease, or CAD.[29,30] More relaxed BP control should be reserved for patients 75 years and older. Similar recommendations have been published recently.[31] It should be stated that aggressive SBP control in the main SPRINT study and the elderly substudy[1,2] showed no reduction in MI or stroke. Therefore, before new guidelines are written and applied clinically, these findings should be clarified. Such relaxed guidelines will alleviate the high BP burden and costs of care and will prevent the incidence of CV events from a possible J-curve effect from very low DBPs.

CONFLICT OF INTEREST

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