DBP <80 mm Hg and CHD in the setting of an observational study has been unduly extrapolated by the authors to a practical advice on BP treatment.

Lowering of BP to <80 mm Hg to 70 mm Hg in the treatment of hypertension is usually not a treatment goal. It is, however, rather often, an inevitable outcome of effective systolic lowering. There is indeed a dual problem with the aspiration to keep the diastolic pressure during treatment at ~80 mm Hg: 1) isolated systolic hypertension is common in the older population segment; and 2) DBP declines precipitously with age in normotensive and hypertensive subjects alike, and is further lowered by any pharmacological treatment of hypertension.

In the standard treatment arms of the SPRINT (Systolic Blood Pressure Intervention Trial) (2) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) (3) hypertension treatment trials, the achieved DBP was ~73 mm Hg and 70.5 mm Hg, respectively. Keeping in mind the standard deviation of the mean, this indicates that a significant fraction of patients treated to the standard goal of <140 over 90 mm Hg end up with a DBP <70 mm Hg. In older trials, where the treatment paradigm focused on DBP goal <90 mm Hg, the achieved SP was more than 140 mm Hg. Are we prepared to pay the systolic price?

The potential harm of excessive diastolic lowering in terms of CHD must be weighed against the expected rise in stroke and renal disease associated with uncontrolled systolic pressure. Treatment advice should be given based on interventional trials considering outcome on multiorgan endpoints, not on observational studies with a limited focus.

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REPLY: Diastolic Blood Pressure

Myocardial Damage and Coronary Ischemic Events

We appreciate the interest in our recent paper in the *Journal* (1). Dr. Marcus and colleagues express concerns that findings from our observational study should not be extrapolated to clinical care. We agree that our results cannot definitively prove causal effects; as with all observational studies, the possibility of residual confounding cannot be eliminated. We also agree with Dr. Marcus and colleagues that analyses from recent randomized trials (e.g., SPRINT [Systolic Blood Pressure Intervention Trial] and HOPE [Heart Outcomes Prevention Evaluation]-3) can help confirm our observational data and inform how our findings can be translated into clinical practice. We note that the former limitation and the latter suggestion were included in our original paper.

Nonetheless, placed in the context of the evidence to date, we maintain that our observational results are robust and compelling. For example, they meet the following Bradford Hill Criteria: 1) for strength, we found a 50% increased risk of coronary heart disease (CHD) (p value of <0.001) among those with diastolic blood pressure (DBP) <60 mm Hg after rigorous adjustment, results that make residual confounding as the sole explanation unlikely; 2) for consistency, our results are consistent with a wealth of prior data; 3) for temporality, we found an association of low DBP with cross-sectional elevations in high-sensitivity troponin and with temporal change in troponin over the following 6 years; 4) for biological gradient, the lower the DBP category is the stronger our findings are for myocardial damage and CHD; 5) for plausibility, our results are plausible given that we know coronary perfusion depends on diastolic driving pressure; and 6) for coherence, we showed for the first time coherence between epidemiologic findings (e.g., CHD events) and laboratory testing for ischemia (high-sensitivity troponin).

Consistent with this, our conclusions are supported by results from the HOT (Hypertension Optimal Treatment) trial, the only randomized trial evaluating specific DBP targets (2). The HOT trial demonstrated that, among participants with ischemic heart disease, those treated to a DBP target of 80 mm Hg had a higher rate of myocardial infarction (8.3 per 1,000 patient-years) than those

TABLE 1 Association Between Low DBP and Adverse Outcomes, After Further Adjustment for Heart Rate

	Cross-Sectional Analysis for Elevated hs-cTNT (≥14 ng/l)*			Prospective Proportional Hazards Analysis for Incident Outcomes†					
		Odds Ratio			CHD			Mortality	
Visit 2 Diastolic BP	n/N	(95% CI)	p Value	n/N	HR (95% CI)	p Value	n/N	HR (95% CI)	p Value
<60 mm Hg	39/1,087	2.47 (1.53–3.97)‡	<0.001‡	165/1,087	1.50 (1.20–1.86)‡	<0.001‡	345/1,087	1.41 (1.21–1.65)‡	<0.001‡
60–79 mm Hg	264/7,977	1.18 (0.89–1.55)	0.252	1,299/7,975	1.22 (1.07–1.39)	0.003	2,159/7,974	1.08 (0.98–1.20)	0.119
80–89 mm Hg	102/1,902	1.00 (reference)	—	350/1,902	1.00 (reference)	—	597/1,902	1.00 (reference)	—
≥90 mm Hg	50/599	0.72 (0.48–1.08)	0.111	129/599	0.89 (0.72–1.10)	0.288	238/599	1.01 (0.86–1.18)	0.921

Adjusted for age (years), race-center, gender, body mass index (kg/m^2), smoking (current; former; never), alcohol intake (current; former; never), hypertension medication use (yes, no), systolic blood pressure (BP), heart rate, diagnosed diabetes (yes, no), low-density lipoprotein cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl), current use of cholesterol-lowering medication (yes or no), and estimated glomerular filtration rate (ml/min/1.73m^2). *Logistic model for cross-sectional association between diastolic BP and baseline elevated high-sensitivity troponin T (hs-cTnT). †Cox model for prospective association between diastolic BP and incident events. ‡Significant values.

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio.

treated to a target of 85 mm Hg (6.8 pr 1,000 patient-years; relative risk: 1.22) (3).

Drs. Battista Danzi and Cuspidi suggest that heart rate may be an important factor in the association between low DBP and coronary ischemia. This important suggestion was also raised by Dr. Namasivayam and esteemed colleagues (4). While we do not have complex data such as systolic pressure-time loading, heart rate is available in the ARIC (Atherosclerosis Risk In Communities) study dataset. Thus, we performed additional analyses adding heart rate to our models. As can be seen in **Table 1**, the addition of heart rate did not appreciably alter our results, suggesting that the association between low DBP and adverse coronary outcomes is not mediated by heart rate.

Finally, the letter by Dr. Spence is a sobering reminder that, for some elderly patients, DBP measured by an arm cuff may actually be higher than central aortic DBP (the latter being the most relevant for coronary perfusion), a phenomenon that further helps to explain our results.

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Valve Thrombosis After Transcatheter Aortic Valve Replacement

Transcatheter aortic valve replacement (TAVR) is the standard of care for patients with severe aortic stenosis who are increased risk for open heart surgery. Currently more than 200,000 patients worldwide have received this therapy, and the majority of implanted valves have shown no evidence of structural degeneration with follow-up up to 5 years (1). However, recent reports of late structural degeneration including valve thrombosis (VT) at 8 years have raised safety concerns in light of the expansion of indications for use (2).

Given these considerations, we read with much interest the recent paper by Hannson et al. (3) assessing the VT using multidetector computed tomography. On multivariable analysis, a 29-mm transcatheter heart valve (THV) (relative risk: 2.89; 95% confidence interval: 1.44 to 5.80) and no post-