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The Role of Heart Rate in Diastolic Coronary Perfusion and Subclinical Myocardial Ischemia

We read with interest the paper by McEvoy et al. (1) describing the association between low diastolic blood pressure and adverse clinical and subclinical (elevated troponin level) cardiovascular outcomes. The authors postulate that low diastolic blood pressure impairs coronary perfusion and thus causes adverse cardiac events. This mechanism is certainly plausible, but we wonder whether heart rate could have had an influence on the observed results. Heart rate affects diastolic pressure-time index, which is more important than diastolic pressure alone in determining coronary perfusion (2). Diastolic perfusion index is strongly influenced by heart rate and cardiac ejection duration, as demonstrated in large cohorts of both cardiology outpatients (3) and healthy volunteers (4). Additionally, the role of systolic pressure-time loading and its relationship to diastolic pressure-time index and overall myocardial oxygenation (i.e., myocardial demand-supply ratio) (2–4) is important to consider, and is itself strongly affected by heart rate and cardiac ejection duration. The findings of McEvoy et al. (1) highlight an important clinical issue—maintenance of adequate diastolic blood pressure to facilitate coronary perfusion. We would be interested to know to what extent heart rate interacted with their findings.

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In the Treatment of Hypertension, Lowering of Diastolic Pressure to <70 mm Hg Is Often Unavoidable

In the treatment of hypertension, lowering of diastolic pressure to <70 mm Hg is often unavoidable. McEvoy et al. (1) examined the association of diastolic blood pressure (DBP) with coronary heart disease (CHD), stroke and death using the ARIC (Atherosclerosis Risk In Communities) study cohort. They noted increased CHD risk of 1.5, 1.2, and 1.2 for DBP <60, 70, and 80 mm Hg, respectively. A similar relationship was seen in subjects treated for hypertension at baseline. The authors concluded that in the treatment of hypertension it may be prudent to ensure that DBP levels do not fall to <70 mm Hg. In our opinion, the linkage between

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