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Response to Letter Regarding Article, "Coronary Artery Calcium (CAC) to Guide a Personalized Risk-Based Approach to Initiation and Intensification of Antihypertensive Therapy"

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We thank Harbaoui and colleagues for their interest in our recent publication in *Circulation*. [1] Their letter raises important points, but also necessitates that we clarify others.

We agree that pulse pressure and diastolic blood pressure (BP) are important clinical parameters to consider when targeting intensive systolic BP goals among high risk adults. We have recently published on this very issue. [2] We also agree that some individuals with elevated coronary artery calcium (CAC) may be more susceptible to myocardial ischemia when undergoing intensive systolic BP reduction due to the baseline presence of wide pulse pressure and low diastolic BP (both of which could theoretically be associated with ischemia by further driving diastolic BP down below levels where auto-regulation of coronary perfusion can be maintained). It is important to note, however, that this concern is purely hypothetical at present. To shed further light on this issue, we do have a manuscript, currently in press at the journal *Hypertension,* which shows that persons with elevated CAC appear no more likely (10%) than those without any CAC (13%) to have baseline diastolic BP <60mmHg. [3] Nonetheless, there is a signal that those who have elevated CAC and who also happen to have low diastolic BP appear at higher risk for coronary heart disease events. [3]

Despite this, we would argue that to suggest pulse pressure, diastolic BP - or even a combination of both - mediate the entirety of the incremental prognostic significance of CAC is frankly inconsistent with the wealth of knowledge in this field. We point to the landmark CAC paper from the Multi-Ethnic Study of Atherosclerosis. [4] In this analysis, despite adjusting for a host of potentially confounding factors, including both systolic and diastolic BP (and, thus, indirectly pulse pressure), CAC remained very strongly associated with subsequent cardiac events. [4] As such, it is well know that CAC adds prognostic information over and above diastolic BP, pulse pressure, and many other risk factors. This is important for us to emphasize in our response to this letter because the focus of our paper was to test whether CAC may inform the risk-based allocation of hypertension treatment

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intensity. We think it does. Whether the few individuals who have elevated risk by CAC and who also happen to have low baseline diastolic BP should be treated less intensely than those persons with elevated CAC and normal diastolic BP is a matter for future studies. [3]

We must also challenge the authors' suggestion that the association between CAC and aortic stiffness by pulse wave velocity (PWV) is important enough to have been discussed in our initial manuscript. The correlation between CAC and PWV is modest at best, with a mere average increase of approximately 0.1 unit of CAC for every unit increase in PWV in the paper cited by Harbaoui and colleagues. [5]

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