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Reply

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We sincerely thank Nagai *et al.* [1] for their commentary, which articulates a pathophysiologic mechanism for how increased SBP variability may increase the risk for diabetic foot ulcers. Specifically, in large vessels, increased SBP variability leads to increased oscillatory shear stress. The shear stress activates an inflammatory cascade that accelerates atherosclerotic plaque formation and subsequent development of peripheral arterial disease. Foot ulcers occur when a relatively minor trauma cannot be healed due to the resulting, downstream ischemia. Supporting this pathophysiologic mechanism are data associating increased SBP variability with increased intima-media thickening, increased lipid arc, decreased vessel wall elasticity, and decreased aortic distensibility [2–4]. The commentary does not address how SBP variability may drive microvascular complications beyond that imposed by upstream, macrovascular disease.

Nagai *et al.* commentary [1] adds to our nascent theory that increased SBP variability may be a novel risk factor for diabetic foot ulcers and major amputation [5,6]. It provides evidence for biologic plausibility. However, we agree with Dr Nagai's team that further evidence is needed before claiming causation. Specifically, our findings should be replicated in different populations using prospective study designs. Ideally, such investigations would control for potential confounders, such as smoking and medication adherence, that our original study was unable to address.

One way to further assess causation would be to conduct a clinical trial using calcium channel blockers to blunt SBP variability and potentially reduce the risk of diabetic foot ulcers. Prior epidemiologic and pathophysiologic studies may inform the design of such a trial. Specifically, both typesets of studies suggest a trial of calcium channel blockers would be most effective in patients who have not yet developed peripheral arterial disease. Epidemiologically, we found that calcium channel blockers were associated with a reduced risk of foot ulcerations, but only for patients who were not diagnosed with peripheral vascular disease [5]. For patients with established peripheral vascular disease, SBP variability no longer predicted major amputation rates. Pathophysiologically, this is

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Conflicts of interest

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consistent with the understanding of vascular disease. Calcium channel blockers have been shown to: blunt SBP variability; reduce the rate of intima-media thickening; and negate the association between SBP variability and decreased vessel elasticity [7–9]. In other words, calcium channel blockers may delay the onset of peripheral vascular disease but are unlikely to reverse or ameliorate existing peripheral vascular disease. Studying calcium channel blockers in those most likely to benefit – patients who have not yet developed peripheral vascular disease – would help inform efforts to tailor medical care to specific patient populations. It may provide clinicians with an additional tool to reduce the risk of diabetic foot ulcers at a time when the negative impact of ulceration is increasing relatively unchecked. We hope this discourse provides a good example of how to combine data from both ends of the scientific spectrum, pathophysiologic and epidemiologic, to advance our understanding and care of patients with diabetic foot ulcers.

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