

# Effect of Vitamin D Supplementation on Arterial Stiffness and Central Blood Pressure Indexes: Demystifying the Evidence

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Vitamin D deficiency is highly prevalent, with potentially significant consequences for human health.<sup>1</sup> Numerous epidemiological studies have associated vitamin D deficiency with cardiovascular disease and hypertension.<sup>2</sup> However, randomized controlled studies have shown no effect of vitamin D supplementation on blood pressure (BP).<sup>3,4</sup> Prior studies assessed BP using a peripheral cuff over the brachial artery, either at a single time point or over 24 hours. Newer measures of central BP and arterial stiffness are more potent predictors of adverse cardiovascular outcomes than brachial BP.<sup>5,6</sup> Thus, could the prior vitamin D–BP trials have used the wrong BP end points?

Arterial stiffness is defined as restricted expansion of the arterial wall because of structural and functional changes within the vessel. Pulse-wave velocity (PWV), measured noninvasively, is a standard measure of arterial stiffness.<sup>7</sup> Central BP is the aortic systolic pressure that the left ventricle meets during systole and is influenced by peripheral vascular resistance, arterial stiffness, and magnitude of pressure wave reflections. Clinical trial data exist that support the use of central aortic BP and PWV as targets of antihypertensive therapy.<sup>8,9</sup>

Data about the effects of vitamin D supplementation on PWV and central BP have been limited.<sup>10,11</sup> Two studies in this issue of *JAHA* address this need, by examining the potential benefits of vitamin D supplementation on arterial stiffness and

central BP.<sup>12,13</sup> In BEST-D (Biochemical Efficacy and Safety Trial of Vitamin D), 305 community-dwelling older adults living in the United Kingdom were randomized to receive vitamin D 4000 IU, vitamin D 2000 IU, or placebo for 12 months. The primary end point in BEST-D was plasma 25-hydroxyvitamin D, and the main findings have been published previously.<sup>14</sup> Tomson et al,<sup>12</sup> in this issue of *JAHA*, examine the effects of vitamin D supplementation on a set of prespecified secondary outcomes related to BP. As in prior studies, they found that vitamin D supplementation in BEST-D had no effect on systolic BP measured using a peripheral BP cuff. At the end of 12 months, PWV was significantly higher in the 4000 IU vitamin D arm (10.1 m/s) compared with the placebo arm (9.6 m/s), but these values did not differ from baseline values (10.0 and 9.7 m/s, respectively). The authors did not directly report changes in central BP, but augmentation index, a measure of enhanced wave reflection, did not change with vitamin D supplementation. In a randomly selected subset of 177 participants (n=117 in the vitamin D arm, and n=60 in the placebo arm), echocardiographic measures of systolic and diastolic function and NT-proBNP (N-terminal pro-B-type natriuretic peptide) were assessed. There were no differences in any of the aforementioned parameters after 12 months of vitamin D supplementation between the groups.

Another trial, ViDA (Vitamin D Assessment Study),<sup>15</sup> randomized 5108 participants to monthly vitamin D supplementation (100 000 IU) versus placebo. The median follow-up was 3.3 years. In the main trial, there was no significant difference in the incidence of cardiovascular events (hazard ratio, 1.02; 95% confidence interval, 0.87–1.20).<sup>15</sup> In the ViDA substudy<sup>13</sup> reported in this issue of *JAHA*, Sluyter et al noted no effect of monthly high-dose vitamin D (100 000 IU) supplementation on brachial or central BP parameters, measured in a random subset of 517 participants (≈10% of the overall trial population). Median follow up was 1.1 years. In addition, no effect was noted on PWV or augmentation index. However, the authors conducted a further subgroup analysis involving 150 vitamin D–deficient participants (n=71 in the vitamin D arm, and n=79 in the placebo arm). The authors reported modest reductions in PWV ( $P=0.02$ ), augmentation index ( $P=0.03$ ), and central systolic BP ( $P=0.03$ ) in this subgroup. Furthermore, there was a moderate negative correlation of PWV (–0.29),

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*J Am Heart Assoc.* 2017;6:e007466 DOI: 10.1161/JAHA.117.007466.

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augmentation index (−0.23), and central systolic BP (−0.25) with change in 25-hydroxyvitamin D levels.

These data are interesting, and the positive findings were based on a clinically relevant subgroup (eg, those with established vitamin D deficiency), for whom supplementation would be expected to have the most benefit. On the other hand, the limitations of subgroup analyses are well known.<sup>16,17</sup> False-positive findings are common, particularly in post hoc analyses of randomized controlled trials that were negative overall.<sup>18</sup> The present data are based on a subgroup of a subgroup, further suggesting the need for cautious interpretation. A different question relates to the approach for measuring arterial stiffness. Noninvasive methods using oscillometric methods to capture PWV and central BP have limitations, as described.<sup>19</sup> Use of applanation tonometry with application of a generalized transfer function has been suggested as a reliable alternative.<sup>19</sup>

In conclusion, there is no clear evidence that high-dose vitamin D supplementation improves PWV, augmentation index, and/or central BP. These negative findings are in line with larger trials that focused on traditional BP. The present studies represent important contributions to the existing literature,<sup>10</sup> adding to the growing evidence that vitamin D supplementation does not influence BP or related measures. Future trials of vitamin D supplementation should include vitamin D-deficient participants and focus on different aspects of cardiovascular disease, such as metabolism and inflammation, considering the evidence supporting immunomodulatory roles of vitamin D supplementation.<sup>20</sup>

## Disclosures

Wang has received assay support from Diasorin, Inc. Arora has no relationships to disclose.

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**Key Words:** Editorials • arterial stiffness • pulse-wave velocity • vitamin D