range of 11.8% to 25.6%, and 30-day RSRR was 20.9% (20.2% to 22.1%) with a range of 17.1% to 24.4%. The top 7 principal diagnoses for these readmissions were heart failure (4.8% of all readmissions), postoperative complications such as shock, hematoma, wound dehiscence, and infection (1.4%), arrhythmias (1.1%), sepsis (0.9%), pneumonia (0.8%), gastrointestinal bleed (0.6%), and mechanical device complications (0.5%). Adjusting for patient characteristics, the odds of each adverse outcome for a patient treated at a hospital 1 SD above the national average relative to that of a patient treated at a hospital 1 SD below the national average was statistically significant (**Figure 1**).

Since the Food and Drug Administration approval of TAVR in November 2011, there has been rapid expansion in the number of hospitals performing TAVR. Our results show marked variation in hospital performance with TAVR, with an IQR of 1.8% for 30-day RSMR. For perspective, the IQR for 30-day RSMR for isolated coronary artery bypass grafting, a commonly performed invasive cardiac procedure, is 1% (4).

We found that for an individual patient, the between-hospital variation translates to a >2-fold higher risk of dying within 30 days for a patient undergoing TAVR at a hospital 1 SD above the national average compared with undergoing TAVR at a hospital 1 SD below. The between-hospital variation was lower for 1-year mortality and 30-day readmission, but remained substantial. Some of this between-hospital variation can be attributed to clinical factors insufficiently captured by our adjustment model, but hospital and system factors are likely also important drivers of this variation. In addition, TAVR volume and duration of center experience were not assessed and could influence outcomes. As the importance of hospital and system factors was not investigated in this paper henceforth, the conclusions of this paper reflect the authors' opinion.

This study serves as an important benchmark for quality measurement and future performance improvement efforts for TAVR. Moving forward, as more centers and operators begin performing TAVR, and existing centers and operators become more proficient, it will be important to continue to monitor the extent of hospital variation to ensure the delivery of optimal outcomes for patients.

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Effect of Vitamin D Supplementation on Aortic Stiffness and Arterial Hemodynamics in People With Osteoarthritis and Vitamin D Deficiency

Increased aortic stiffness (aPWV), peripheral blood pressure (pBP), and central hemodynamic parameters independently predict cardiovascular events and all-cause mortality (1,2). Moreover, BP variability (BPV)

has been shown to be an independent predictor of cardiovascular risk (3). Data from intervention studies assessing the effects of vitamin D on aPWV and BP indices are sparse and inconclusive. There are no vitamin D intervention studies targeting visit-to-visit (VVV) BPV.

People with osteoarthritis (OA) represent a population enriched with vascular risk factors that may be amenable to benefit with treatment from vitamin D supplementation. Here, we present findings from a substudy of a clinical trial investigating the effect of vitamin D supplementation on musculoskeletal outcomes among older people with vitamin D deficiency and OA (principal trial study design previously published) (4). The aim of this substudy was to determine the effects of vitamin D supplementation on aPWV, pBP, central blood pressure (cBP), and VVV indices.

Participants were randomized to receive intervention (monthly capsule of 50,000 IU [1.25 mg] cholecalciferol) or identical inert placebo. Duplicate measures of supine aPWV (carotid-to-femoral tonometry), pBP (automatic oscillometry), and cBP (radial arterial tonometry) were recorded at baseline, and 6 and 12 months. VVV was quantified using the coefficient of variation ([standard deviation/mean BP]×100). Between-group differences in the change in outcomes were assessed across the 3 time points using mixed-effect model analysis (verified with generalized estimating equations) with maximum likelihood estimations for missing data. Changes in aPWV were also estimated after adjusting for changes in mean arterial pressure (MAP). The sample size allowed for a clinically significant difference of at least 0.5 m/s for aPWV and 4.5 mm Hg for peripheral and central systolic BP.

Participants (age 63 ± 7 years, 49% female) with vitamin D deficiency (43.12 ± 12.24 nmol/l) and knee OA were randomly assigned to intervention (n = 118) or placebo (n = 123). Baseline vitamin D, age, sex, BP indices, and aPWV were similar between groups. Fifty-one percent of intervention participants and 48% of placebo participants self-reported hypertension. Vitamin D increased with intervention compared with placebo (45.10 [95% confidence interval (CI): 40.20 to 49.93] nmol/l vs. 7.99 [95% CI: 4.32 to 11.66] nmol/l; $p < 0.001$).

There was no significant between-group difference in the change in aPWV (Table 1). The difference attenuated after adjustment for changes in MAP (−0.10 [95% CI: −0.47 to 0.26] m/s vs. 0.05 [95% CI: −0.33 to 0.42] m/s; $p = 0.56$). Post-hoc analysis among participants with high baseline aPWV (>10 m/s; intervention n = 34 vs. placebo n = 33) showed a near significant intervention effect (intervention: −1.77 m/s [95% CI: −2.57 to −0.97] vs. placebo: −0.72 m/s [95% CI: −1.50 to 0.07]; $p = 0.065$). However, this attenuated after adjustment for changes in MAP ($p = 0.14$). There were no significant between-group differences for changes in any of the pBP, cBP, or VVV indices (Table 1).

This is the longest vitamin D intervention trial, to our knowledge, assessing the effect on aPWV, and the results are concordant with previous studies of considerably shorter duration. Importantly, when accounting for the BP effect on aPWV by adjusting for changes in MAP, the treatment effect decreased from −0.26 to −0.10 m/s. It is also the longest trial to test the effects on cBP indices, and the results confirm negative effects in smaller studies of select patient populations. Our findings also add novel information on VVV and confirm recent work showing no effect of vitamin D on pBP.

Despite being the longest study to date, limitations include a relatively short follow-up and lack of data on cardiovascular events, as well as mineral metabolism markers that could have affected results (i.e., calcium). Lastly, findings may not be generalizable to people with severe vitamin D deficiency.

In conclusion, we found no effect of vitamin D supplementation on aPWV, BP, or VVV among older people with vitamin D deficiency and OA.

TABLE 1 Changes in Aortic Stiffness, Peripheral and Central Hemodynamic Parameters, and Overall VVV BPV by Study Arm

	Intervention (n = 118)	Placebo (n = 123)	p Value*
aPWV, m/s	−0.26 (−0.62 to 0.10)†	0.06 (−0.30 to 0.43)	0.22
Peripheral SBP, mm Hg	−3.00 (−5.60 to −0.40)	−2.94 (−5.59 to −0.30)	0.98
Peripheral DBP, mm Hg	−1.47 (−3.00 to 0.06)	−0.53 (−2.09 to 1.03)	0.40
MAP, mm Hg	−2.08 (−3.93 to −0.24)	−1.48 (−3.36 to 0.39)	0.66
Peripheral PP, mm Hg	−2.48 (−4.35 to −0.61)	−0.95 (−2.76 to 0.85)	0.25
Central SBP, mm Hg	−2.77 (−5.42 to −0.11)	−2.90 (−5.59 to −0.22)	0.94
AP, mm Hg	−0.84 (−1.86 to 0.17)	−0.16 (−1.17 to 0.86)	0.35
Central PP, mm Hg	−2.10 (−4.03 to −0.18)	−0.93 (−2.81 to 0.95)	0.40
AIx@75	0.54 (−1.75 to 0.68)	0.77 (−0.45 to 1.99)	0.14
Visit-to-visit BPV†			
Peripheral systolic BP	6.90 ± 4.49	6.07 ± 4.67	0.21
Peripheral diastolic BP	7.16 ± 4.14	6.52 ± 4.08	0.28
Mean aortic pressure	6.64 ± 3.93	5.84 ± 4.20	0.17
Central systolic BP	7.21 ± 4.39	6.91 ± 5.34	0.67

Values are beta coefficients (95% confidence intervals) or coefficient of variation ± SD. *p Value for the interaction between group and time (mixed-effects linear regression). †BPV indices were calculated among those participants who completed all 3 visits, and represent the absolute values over the 12-month follow-up period.

AIx@75 = augmentation index adjusted for heart rate; AP = augmentation pressure; aPWV = aortic stiffness; BP = blood pressure; BPV = blood pressure variability; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure; VVV = visit-to-visit.

Despite a plethora of observational data supporting a relationship between vitamin D and cardiovascular health via pathways involving BP and large artery stiffness, evidence from our high-quality clinical trial and other existing trials do not support the use of vitamin D supplementation as an intervention to improve these endpoints. Previously documented associations between vitamin D, aPWV, and BP are likely to be epiphenomena rather than causative, and vitamin D supplementation for these aspects of cardiovascular health cannot be recommended.

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Anticoagulant-Related Nephropathy

We congratulate Bohm et al. (1) for their interesting study regarding the effects of warfarin or dabigatran etexilate (DE) on renal function in the patients with atrial fibrillation (AF) receiving oral anticoagulation, showing a decline in renal function that was greater in those taking warfarin compared with DE, which was amplified by diabetes and previous vitamin K antagonist use. The authors propose this adverse renal outcome may be due to inhibition by warfarin of vitamin K-dependent matrix gamma-carboxyglutamic acid (Gla/MPG) and resulting in renal vascular calcification and arterial damage.

Recent data showed that excessive anticoagulation with warfarin can result in acute kidney injury (AKI) by causing glomerular hemorrhage and renal tubular obstruction by red blood cell (RBC) casts in some patients, especially in those with chronic kidney disease (CKD), which was described as warfarin-related nephropathy (WRN) (2). Brodsky et al. (3) was the first to describe this entity through kidney biopsy in a subset of patients with warfarin overdose, hematuria, and AKI, and each biopsy specimen demonstrated evidence of acute tubular injury, glomerular hemorrhage, and renal tubular obstruction by RBC casts. Actually, oxidative stress damage to tubules by an RBC cast, even though the RBC cast did not obstruct the tubule, could lead to WRN. Other important mechanisms, including atheroembolism, interstitial nephritis, apoptosis of glomerular endothelial cells, and direct effects of warfarin on the glomerulus, may also contribute to the development of WRN.

A recent case report (4) also described an anticoagulant-related AKI in a patient who was receiving the thrombin inhibitor dabigatran. Furthermore, Ryan et al. (5) investigate the effects of dabigatran on kidney function in an animal model of CKD, demonstrating that dabigatran resulted in a dose-dependent increase in serum creatinine and hematuria in both control and 5/6 nephrectomy rats. Morphologically, the findings in 5/6 nephrectomy rats treated with dabigatran were similar to those found in animals with WRN, involving RBC tubular casts and acute tubular injury. Unexpectedly, in comparison with WRN, in which kidney injury was seen only in 5/6 nephrectomy rats, the effects of dabigatran were highlighted in control rats as well. These findings suggest that the risk to the kidney by dabigatran may be greater than that by warfarin in patients with normal renal function, which should be taken into account in clinical practice, indicating that regular monitoring of kidney function may be necessary in patients receiving oral anticoagulation therapy including warfarin or dabigatran.