Effect of daily 2000 IU versus 800 IU vitamin D on blood pressure among adults age 60 years and older: a randomized clinical trial

Lauren A Abderhalden,[1,2] Sandra Meyer,[1,2] Bess Dawson-Hughes,[3] E John Orav,[4] Ursina Meyer,[1,2] Caroline de Godoi Rezende Costa Molino,[1,2] Robert Theiler,[1,2] Hannes B Stähelin,[5] Frank Ruschitzka,[6] Andreas Egli,[1,2] John P Forman,[7] Walter C Willett,[8] and Heike A Bischoff-Ferrari[1,2]

[1]Department of Geriatrics and Aging Research, University Hospital Zurich and University of Zurich, Zurich, Switzerland; [2]Centre on Aging and Mobility, University Hospital Zurich and Waid City Hospital, Zurich, Switzerland; [3]Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA; [4]Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA; [5]Department of Geriatrics, University of Basel, Basel, Switzerland; [6]Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; [7]Department of Nephrology, Brigham and Women's Hospital, Boston, MA, USA; and [8]Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

ABSTRACT

Background: Observational studies report higher blood pressure (BP) among individuals with lower 25-hydroxyvitamin D concentration. Whether dosage of vitamin D supplementation has a differential effect on BP control remains unclear.

Objective: The study aimed to determine if daily vitamin D supplementation with 2000 IU is more effective than 800 IU for BP control among older adults.

Methods: This randomized, double-blind, ancillary trial of the Zurich Multiple Endpoint Vitamin D Trial in Knee Osteoarthritis enrolled adults aged ≥60 y who underwent elective surgery due to severe knee osteoarthritis. Participants were randomly assigned to receive high dose (2000 IU) or standard dose (800 IU) daily vitamin D_3 for 24 mo. Outcomes included daytime and 24-h mean systolic BP. BP variability and serum 25-hydroxyvitamin D concentration were examined in a post hoc and observational analysis.

Results: Of the 273 participants randomly assigned, 250 participants completed a follow-up 24-h ambulatory BP monitoring (mean age: 70.4 ± 6.4 y; 47.2% men). The difference in daytime mean systolic BP reduction between the 2000 IU (n = 123) and 800 IU (n = 127) groups was not statistically significant (−2.75 mm Hg vs. −3.94 mm Hg; difference: 1.18 mm Hg; 95% CI: −0.68, 3.05; P = 0.21), consistent with 24-h mean systolic BP. However, systolic BP variability was significantly reduced with 2000 IU (average real variability: −0.37 mm Hg) compared to 800 IU vitamin D_3 (0.11 mm Hg; difference: −0.48 mm Hg; 95% CI: −0.94, −0.01; P = 0.045). Independent of group allocation, maximal reductions in mean BP were observed at 28.7 ng/mL of achieved serum 25-hydroxyvitamin D concentrations.

Conclusions: While daily 2000 IU and 800 IU vitamin D_3 reduced mean systolic BP over 2 y to a small and similar extent, 2000 IU reduced mean systolic BP variability significantly more compared with 800 IU. However, without a placebo control group we cannot ascertain whether vitamin D supplementation effectively reduces BP. This trial was registered at www.clinicaltrials.gov as NCT00599807. *Am J Clin Nutr* 2020;112:527–537.

Keywords: vitamin D, blood pressure, blood pressure variability, ARV, older adults, hypertension, 25(OH)D, supplement

Introduction

High blood pressure (BP) is a major risk factor for cardiovascular events (1, 2) and is the biggest single contributor to the global burden of disease and mortality (3). At the same time, it has been suggested that ∼50% of senior adults are vitamin D deficient, and

This project was funded by a Swiss National Science Foundation Professorship (Swiss National Science Foundation's Professorship grant PP00B-114864; to HAB-F), the Velux Stiftung (grant 441; to HAB-F), and the Baugarten Foundation Center Grant to the Centre on Aging and Mobility at the University of Zurich and University Hospital Zurich (to HAB-F). None of the funding agencies had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

LAA and SM contributed equally to this work.

Data described in the manuscript, code book, and analytic code will not be made available to the public because it would require de-identification or full anonymization of the individual participant data underlying the results reported in this article, which would preclude further exploitation for publications or collection of additional data by the investigators. However, the authors will fully cooperate in providing de-identified data used in the manuscript, code book, and analytic code to the editors of *The American Journal of Clinical Nutrition* upon request either before or after publication, for the sole purpose of checking the scientific validity of the results.

Address correspondence to HAB-F (e-mail: heike.bischoff@usz.ch).

Abbreviations used: ARV, average real variability; BP, blood pressure; LOESS, locally estimated scatterplot smoothing; 25(OH)D, 25-hydroxyvitamin D.

Received December 4, 2019. Accepted for publication May 18, 2020.

First published online June 15, 2020; doi: https://doi.org/10.1093/ajcn/nqaa145.

several large cohort studies link vitamin D deficiency to incident hypertension (4–8).

Vitamin D may influence BP through several mechanistic pathways. First, animal studies have shown that vitamin D receptor knock-out mice have 2.5-fold increased angiotensin II, a potent vasoconstrictor, which leads to the development of hypertension in these mice (9). Second, among humans, vitamin D receptors have been found in smooth muscle cells and endothelial cells (10), supported by 1 clinical trial among diabetic patients in which vitamin D supplementation reduced the proliferation of vascular endothelial cells (11). Third, lower 25-hydroxyvitamin D [25(OH)D] status has been associated with higher plasma renin (12), a main driver of hypertension. Finally, vitamin D deficiency has been suggested to have anti-inflammatory and thereby antiatherosclerotic benefits (13).

Despite these data linking vitamin D to several mechanistic pathways of BP regulation and large epidemiological studies in which lower 25(OH)D status was associated with higher systolic BP, incident hypertension, and increased cardiovascular mortality (4, 14), clinical trials on the effect of vitamin D supplementation on BP have shown conflicting results. Some clinical trials have demonstrated vitamin D supplementation to be beneficial for cardiovascular disease risk markers (15) and systolic BP control (16). In contrast, 2 meta-analyses did not support an effect of vitamin D supplementation on systolic BP (17, 18). The null findings may be explained by the fact that the studies included many relatively healthy, younger participants and used office-measured BP (17, 18). Persons with knee osteoarthritis have a 13% higher chance of developing hypertension, possibly due to modifications of extracellular matrix leading to reduced elasticity of blood vessels as well as low physical activity, for which vitamin D on BP might have a different efficacy profile (19). Office-measured BP is vulnerable to white-coat reaction and is often poorly performed in clinical practice (20). Our study is unique in that it used 24-h ambulatory BP monitoring to get a more accurate recording of mean BP and that it contains the added outcome of BP variability. The effect of vitamin D on BP variability has not been explored to the best of our knowledge, offering a unique contribution to nutritional science.

We therefore assessed the efficacy of daily high dose vitamin D_3 supplementation, 2000 IU, compared with the standard of care, 800 IU, for lowering mean systolic BP among adults aged ≥60 y. A post hoc analysis was conducted to explore the effect of vitamin D dose on BP variability. Furthermore, in an observational aim, we examined the relation between serum 25(OH)D and changes in systolic BP.

Methods

Participants and study design

The Zurich Multiple Endpoint Vitamin D Trial in Knee Osteoarthritis study was a 24-mo randomized (1:1) double-blind clinical trial testing the impact of daily high dose vitamin D on recovery after unilateral total knee joint replacement (NCT00599807; clinicaltrials.gov) (21). Data were collected from January 2008 to March 2014 at the Centre on Aging and Mobility at the University Hospital Zurich. Eligible participants were adults aged ≥60 y who underwent elective surgery for unilateral knee replacement due to severe knee osteoarthritis, without a planned bilateral knee replacement within the next 2 y. Participants were randomly assigned to either a single capsule of 2000 IU or 800 IU vitamin D_3 supplementation/d. Additionally, all participants received a 500 mg supplement of calcium/d (calcium carbonate). Daily 2000 IU vitamin D did not improve pain and disability following unilateral total knee joint replacement in the main trial (21). The present study reports a predefined secondary endpoint relating to BP change as an ancillary trial of the Zurich Multiple Endpoint Vitamin D Trial in Knee Osteoarthritis study.

Ethics

The study was performed in accordance with the principles outlined in the Declaration of Helsinki, and all participants gave their written informed consent to the study, which was approved by the Cantonal Ethical Commission of Zurich, Switzerland (protocol identifier STZ 20/07).

Outcome variables

24-hour BP.

The primary outcome variables were systolic daytime and 24-h BP. We used home-based 24-h ambulatory BP monitoring according to the most recent guidelines, which recommend the use of 24-h ambulatory or home BP monitoring to confirm hypertension (22–24). In 2011, the guidelines of the method for diagnosing hypertension were refined based on results of a systematic review (22) and a subsequent independent meta-analysis (25) showing that ambulatory or home BP monitoring was better than clinic measures in predicting subsequent risk of cardiovascular events (22, 26).

Systolic and diastolic BP were monitored every 20 min during the day and every hour during individually defined sleep periods by a home-based ambulatory BP monitor (Spacelabs 90217; Spacelabs Healthcare™) for 24 h at 6–8 wk after surgery (baseline), then again at 1 and 2 y. For statistical analysis, we used the mean day, night, and 24-h systolic and diastolic BP as the outcome variables by averaging all BP measurements within the period. Daytime and 24-h systolic BP were the focus of this investigation, as these measures are known to be most responsive to treatments for hypertension.

As a post hoc analysis, short-term BP variability (i.e., within-day BP variance) was assessed using the average real variability (ARV) index, which calculates the average of absolute changes in consecutive BP readings (27), as follows

$$ARV = \frac{1}{N-1}\sum_{k=1}^{N-1}|BP_{k+1} - BP_k| \quad (1)$$

where N represents the total number of BP measurements and BP_k the k^{th} BP recording for a given individual.

Serum 25(OH)D concentration.

In an observational analysis, a secondary outcome variable of achieved 25(OH)D concentration was examined. Fasting blood samples were taken in the morning when the participant arrived at the study center. Serum 25(OH)D concentration was measured

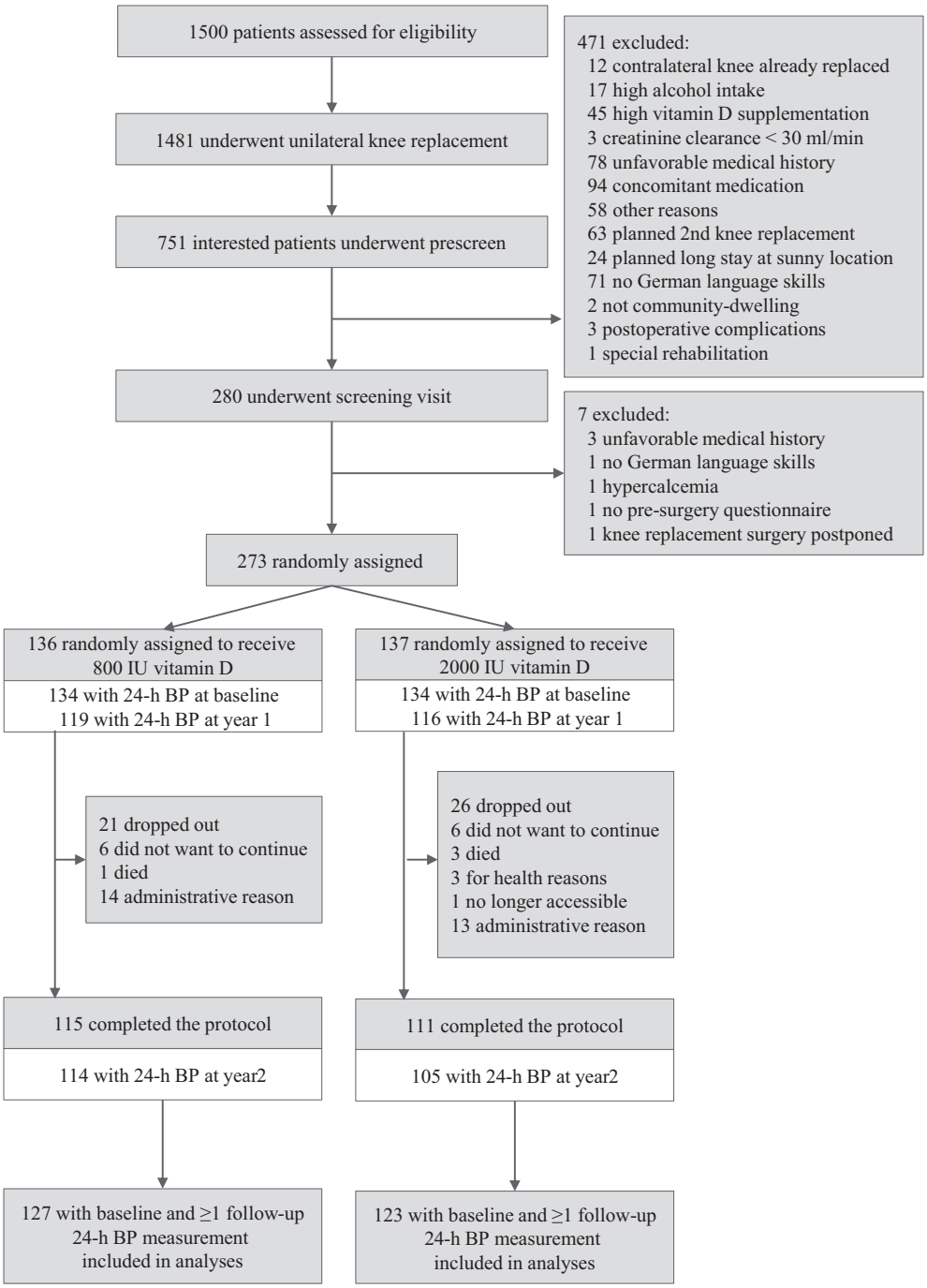

FIGURE 1 Study flow diagram. BP, blood pressure.

at baseline, 1-y, and 2-y visits using the Lumipulse G 25(OH) vitamin D assay on the Lumipulse G 1200 system from Fujirebio. The intra-assay CV% of the Fujirebio 25(OH)D assay for 20 replicates of quality-control samples was 3.4%, 1.6%, and 1.3% for mean 25(OH)D values of 11.0 ng/mL, 31.8 ng/mL, and 71.7 ng/mL, respectively, and 4.6%, 2.6%, and 2.4% after 20 d (28). Furthermore, the Fujirebio assay showed a higher correlation with LC–tandem MS ($R = 0.986$) than assays available from Abbott, Beckman, or Roche.

Assessment of covariates

Age, sex, and prevalence of diabetes were assessed at baseline by questionnaires. BMI (in kg/m^2) was calculated at baseline as weight divided by height squared. Prevalent hypertension was assessed using a questionnaire administered by the study physician at the baseline assessment. In addition, use of antihypertensive drugs was extensively assessed at each clinical visit: baseline, 12, and 24 mo. Physical activity during the 24-h BP measurement was assessed by self-reported activity

TABLE 1 Baseline characteristics of treatment groups[1]

Characteristics	Total participants ($n = 250$)	Vitamin D	
		2000 IU ($n = 123$)	800 IU ($n = 127$)
Age, mean ± SD, y	70.4 ± 6.4	70.3 ± 6.8	70.5 ± 5.9
Male, *n* (%)	118 (47.2)	63 (51.2)	55 (43.3)
25(OH)D, mean ± SD, ng/mL	18.3 ± 8.2	18.3 ± 7.9	18.2 ± 8.5
BMI, mean ± SD, kg/m^2	27.2 (3.9)	27.6 (3.6)	26.8 (4.1)
Hypertension,[2] *n* (%)	115 (46.9)	61 (50.8)	54 (43.2)
Diabetes, *n* (%)	15 (6.0)	9 (7.3)	6 (4.8)
Activity,[3] mean ± SD			
Day	2.4 ± 0.2	2.4 ± 0.2)	2.4 ± 0.2
24-h	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2
BP, mean ± SD, mm Hg			
Systolic day	132.9 ± 12.8	131.9 ± 12.4	133.8 ± 13.2
Systolic night	119.1 ± 13.4	119.2 ± 13.3	119.1 ± 13.5
Systolic 24-h	130.5 ± 12.4	129.7 ± 12.1	131.2 ± 12.7
Diastolic day	79.4 ± 8.0	79.1 ± 7.8	79.6 ± 8.1
Diastolic night	67.8 ± 7.9	68.2 ± 8.1	68.2 ± 8.1
Diastolic 24-h	77.3 ± 7.7	77.2 ± 7.6	77.2 ± 7.6
BP ARV, mean ± SD, mm Hg			
Systolic	10.8 ± 2.1	10.9 ± 2.1	10.7 ± 2.1
Diastolic	7.4 ± 1.6	7.4 ± 1.5	7.4 ± 1.6

[1]One participant was missing night systolic and night diastolic BP. Two participants were missing ARV, one in each treatment group, due to insufficient number of valid recordings. ARV, average real variability; BP, blood pressure; 25(OH)D, 25-hydroxyvitamin D.

[2]Assessed by questionnaire at baseline, total $n = 245$.

[3]Self-reported activity at each BP recording: 1 = sleeping, 2 = sitting or lying activity, 3 = light activity (i.e., slow walking), 4 = moderate to vigorous activity (i.e., running, climbing stairs), and 5 = special activity (unusual/strong excitement).

during waking hours. Participants recorded their activity for each BP measurement and rated the activity level in 5 categories: 1 = sleeping, 2 = sitting or lying activity, 3 = light activity (i.e., slow walking), 4 = moderate to vigorous activity (i.e., running, climbing stairs), and 5 = special activity (unusual/strong excitement). Activity recordings were averaged for both daytime and 24-h measurement periods.

Statistical analysis

Changes in day, night, and overall 24-h systolic and diastolic BP and systolic ARV from baseline were evaluated in a linear mixed model with random intercepts for each subject to allow for serial correlation of BP recordings at 1 and 2 y. All models were adjusted for age, sex, BMI, diabetes, hypertension, activity (for daytime and 24-h models), and baseline BP. To examine the prospective improvements among treatment groups, indicators for time, treatment group, and the interaction between time and treatment group were included. Two versions of BP variability models were examined: the first unadjusted for mean systolic BP and the second adjusted for mean systolic BP to determine if any potential changes in BP variability were dependent on mean BP. Sensitivity analyses were conducted for all models whereby we further adjusted for a time-dependent indicator variable for the use of any antihypertensive medication. An observational analysis was conducted to investigate the relation of achieved 25(OH)D serum concentration and daytime systolic BP 1-y change from baseline. A nonparametric LOESS (locally estimated scatterplot smoothing) curve with 75% smoothing and 95% CI bands was plotted. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc.) and R version 3.5.0 (R Core Team) with a 2-sided P-value <0.05 considered statistically significant.

Results

Participants

The trial enrolled 273 participants, of whom 254 (93.0%) completed the 12-mo visit and 226 (82.8%) completed the 24-mo visit (21). Of those participants completing visits, noncompliance by refusing to wear the 24-h BP-monitoring device occurred in 5 participants at baseline (1.8%), 19 participants at 12 mo (7.5%), and 7 participants at 24 mo (3.1%) (**Figure 1**). Of the 250 participants with baseline and ≥1 follow-up BP recording, 127 (50.8%) received the 800 IU standard dose and 123 (49.2%) received the 2000 IU high dose. Covariate information was missing for 6 participants (2.4%).

Baseline characteristics of the 250 participants included in the analysis (mean ± SD age: 70.4 ± 6.4 y; 47.2% males) are presented overall and by treatment group in **Table 1**. The mean ± SD 25(OH)D concentration was 18.3 ± 8.2 ng/mL and 56.8% of the participants were vitamin D deficient [25(OH)D <20 ng/mL] at baseline. Half of the participants (46.9%) were hypertensive at baseline. Mean ± SD daytime systolic BP was 132.9 ± 12.8 (24-h ARV: 10.8 ± 2.1) mm Hg and diastolic BP was 79.4 ± 8.0 (24-h ARV: 7.4 ± 1.6) mm Hg. One participant was missing night systolic and diastolic BP. On average, 41.9 ± 7.6 daytime, 8.6 ± 2.5 nighttime, and 50.5 ± 7.8 24-h BP recordings were obtained for each participant. There were no statistically significant differences in the number of people taking antihypertensive drugs, the mean number of antihypertensive drug classes, or the number of people taking any particular class of antihypertensive

TABLE 2 Antihypertensive drug use[1]

	Overall	Vitamin D		P[2]
		2000 IU	800 IU	
Baseline				
n	268	134	134	
Taking any antihypertensive drug, *n* (%)	128 (47.8)	67 (50.0)	61 (45.5)	0.46
Number of antihypertensive drug classes,[3] mean ± SD	1.9 ± 0.9	1.9 ± 0.9	1.9 ± 0.9	0.96
Class of antihypertensive drug, *n* (%)				
Diuretics	67 (25.0)	32 (23.9)	35 (26.1)	0.67
ARBs	58 (21.6)	29 (21.6)	29 (21.6)	0.99
B-Blockers	56 (20.9)	29 (21.6)	27 (20.2)	0.76
ACE inhibitors	32 (11.9)	19 (14.2)	13 (9.7)	0.26
Calcium channel blockers	30 (11.2)	16 (11.9)	14 (10.5)	0.70
Vasodilator	3 (1.1)	3 (2.2)	0 (0.0)	0.25
Renin inhibitors	1 (0.4)	1 (0.8)	0 (0.0)	0.99
Year 1				
n	236	116	119	
Taking any antihypertensive drug, *n* (%)	120 (50.9)	61 (52.6)	59 (49.6)	0.56
Number of antihypertensive drug classes,[3] mean ± SD	2.0 ± 0.9	2.0 ± 0.9	1.9 ± 1.0	0.40
Class of antihypertensive drug, *n* (%)				
Diuretics	68 (28.8)	35 (30.2)	33 (27.7)	0.68
ARBs	52 (22.0)	26 (22.4)	26 (21.9)	0.92
B-Blockers	50 (21.2)	28 (24.1)	22 (18.5)	0.29
ACE inhibitors	32 (13.6)	17 (14.7)	15 (12.6)	0.65
Calcium channel blockers	30 (12.7)	14 (12.1)	16 (13.5)	0.75
Vasodilator	2 (0.9)	2 (1.7)	0 (0.0)	0.15
Renin inhibitors	2 (0.9)	1 (0.9)	1 (0.8)	0.99
Year 2				
n	219	105	114	
Taking any antihypertensive drug, *n* (%)	118 (53.9)	59 (56.2)	59 (51.8)	0.51
Number of antihypertensive drug classes,[3] mean ± SD	1.9 ± 0.9	2.0 ± 0.9	1.9 ± 1.0	0.76
Class of antihypertensive drug, *n* (%)				
Diuretics	57 (26.0)	28 (26.7)	29 (25.4)	0.84
ARBs	53 (24.2)	27 (25.7)	26 (22.8)	0.62
B-Blockers	46 (21.0)	24 (22.9)	22 (19.3)	0.52
ACE inhibitors	28 (12.8)	13 (12.4)	15 (13.2)	0.86
Calcium channel blockers	36 (16.4)	18 (17.1)	18 (15.8)	0.79
Vasodilator	4 (1.8)	4 (3.8)	0 (0.0)	0.05
Renin inhibitors	3 (1.4)	1 (1.0)	2 (1.8)	0.99

[1]The table displays antihypertensive drug data among participants with measured 24-h blood pressure. Medications taken as needed were excluded. All medications were coded according to the following Anatomical Therapeutic Chemical Classification (ATC) codes: C01D (vasodilators), C02 (antihypertensives), C03 (diuretics), C04 (peripheral vasodilators), C07 (B-blockers), C08 (calcium channel blockers), C09A (ACE inhibitors), C09C (angiotensin II receptor blockers), and C09X (renin inhibitors) (29). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; B-Blockers, beta blockers.

[2]*P* values were obtained using Fisher's exact test for the antihypertensive drug classes vasodilator and renin inhibitors at all 3 time points.

[3]Average number of antihypertensive drug classes taken among participants taking ≥1 antihypertensive drug.

drugs between treatment groups, at any of the 3 time points (**Table 2**). The most frequently used antihypertensive drugs were diuretics (25.0%), angiotensin II receptor blockers (21.6%), and B-blockers (20.9%). Twenty participants, 10 in each treatment group, initiated antihypertensive drugs during the course of the study ($P = 0.94$ between treatment groups). Adherence, as defined by ≥80% adherent to the vitamin D study medication, was achieved by 93% of participants in the 800 IU group and 92% in the 2000 IU group.

Primary endpoint of BP by treatment group

Absolute average yearly changes in BP by treatment group are presented in **Figure 2**. Adjusted changes in BP by treatment group at years 1 and 2 are displayed in **Table 3**. Treatment with 2000 IU/d produced a 2.75-mm Hg reduction (95% CI: −4.07, −1.43), while treatment with 800 IU/d produced a 3.94-mm Hg reduction (95% CI: −5.23, −2.64) in daytime systolic BP throughout the entire 2-y follow-up. However, the difference of reductions in daytime systolic BP was not statistically significant between treatment groups (difference: 1.18 mm Hg; 95% CI: −0.68, 3.05; $P = 0.22$). There were modest reductions in daytime diastolic BP for both treatment groups (2000 IU: −1.53 mm Hg; 95% CI: −2.28, −0.78; 800 IU: −2.51 mm Hg; 95% CI: −3.25, −1.78), although similarly, these reductions in daytime diastolic BP were not statistically significant between treatment groups (difference: 0.98 mm Hg; 95% CI: −0.07, 2.04; $P = 0.06$). Analyses including the time-dependent variable

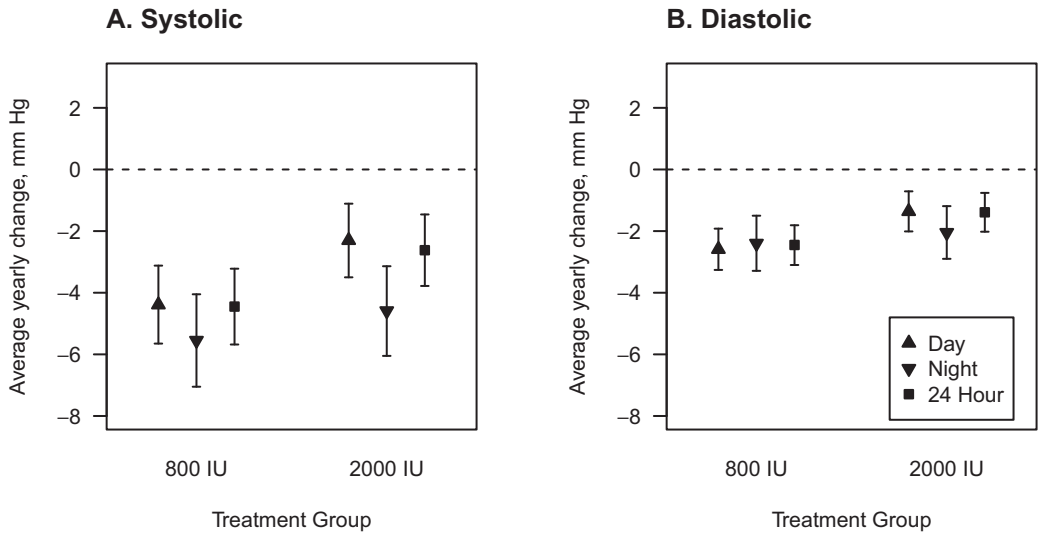

FIGURE 2 (A, B) Absolute changes in blood pressure with 800 IU and 2000 IU daily vitamin D supplementation. Absolute average yearly changes in systolic and diastolic blood pressure by treatment group are shown. Sample sizes for panel A (systolic): day (800 IU: $n = 127$; 2000 IU: $n = 123$), night (800 IU: $n = 125$; 2000 IU: $n = 123$), and 24 h (800 IU: $n = 127$; 2000 IU: $n = 123$); panel B (diastolic): day (800 IU: $n = 127$; 2000 IU: $n = 123$), night (800 IU: $n = 125$; 2000 IU: $n = 123$), and 24 h (800 IU: $n = 127$; 2000 IU: $n = 123$). Error bars represent 95% confidence limits around the mean.

for antihypertensive drug usage resulted in an attenuation of the reduction in mean systolic daytime BP (2000 IU: −2.61 mm Hg; 95% CI: −3.91, −1.30; 800 IU: −3.75 mm Hg; 95% CI: −5.03, −2.46); however this did not principally change the final result (difference: 1.14 mm Hg; 95% CI: −0.70, 2.98; $P = 0.22$). A similar result followed for 24-h mean systolic BP. We also analyzed the effects of 2000 and 800 IU/d of vitamin D on BP among the 56.8% of participants who were vitamin D deficient at baseline and separately among hypertensive and normotensive participants. There were no statistically significant differences between treatment effects in these subgroups (vitamin D deficient: 0.72 mm Hg; 95% CI: −1.75, 3.19; $P = 0.57$; hypertensive: 1.70 mm Hg; 95% CI: −1.43, 4.83; $P = 0.29$; normotensive: 0.40 mm Hg; 95% CI: −1.88, 2.68; $P = 0.73$).

BP variability by treatment group

Systolic BP variability was significantly reduced in the 2000 IU group (mean yearly change from baseline: −0.37 mm Hg; 95% CI: −0.70, −0.04) compared with the 800 IU group (0.11 mm Hg; 95% CI: −0.21, 0.43; difference: −0.48 mm Hg; 95% CI: −0.94, −0.01; $P = 0.04$) (**Figure 3**). Including mean 24-h systolic BP in BP variability models did not change the results, indicating the reduction in systolic BP variability attributed to the 2000 IU vitamin D group was independent of BP. Adjusting for time dependent antihypertensive drug usage did not change the results (e.g., systolic ARV: −0.48 mm Hg; 95% CI: −0.94, −0.01; $P = 0.05$).

BP reduction by achieved 25(OH)D concentration

Daytime systolic BP change plotted by serum 25(OH)D concentration using LOESS smoothing is displayed in **Figure 4**. The shaded region represents the 95% CI bands. Greater BP reductions were observed when moving from deplete 25(OH)D concentrations to a maximal reduction at 28.7 ng/mL. At 25(OH)D concentrations > 28.7 ng/mL, the observed reductions in BP are lost. This clear dip in both changes to daytime and 24-h systolic BP at ∼28.7 ng/mL serum 25(OH)D represents the lowest BP reductions observed, with possible bias due to confounding of this particular study sample. An achieved concentration of 28.7 ng/mL 25(OH)D was associated with a −6.01 mm Hg (95% CI: −8.20, −3.82) decrease in daytime systolic BP and a −5.93 mm Hg (95% CI: −8.05, −3.80) decrease in 24-h systolic BP compared with the individual's baseline BP. The percentage of participants in each treatment group by quartile of achieved 25(OH)D is presented in **Figure 5** to support the interpretation of all results.

Discussion

In this trial, a 2-y course of 2000 IU vitamin D/d did not show a greater benefit or harm in terms of BP reduction compared with a standard dose of 800 IU vitamin D/d among adults aged ≥60 y following total unilateral knee replacement. Notably, both treatment groups experienced a significant and similar reduction in day, night, and 24-h systolic and diastolic BP. Only in a post hoc analysis, 2000 IU compared with 800 IU appeared to be significantly more effective in decreasing systolic BP variability by nearly 0.5 mm Hg, consistent with a 4.4% decrease. In order to further explore BP control with regard to achieved 25(OH)D status, our observational study suggested that a target concentration of 28.7 ng/mL may be associated with maximal BP reduction, independent of treatment dose.

High short-term BP variability is associated with subclinical damage to organs including the heart, kidney, and vessels independent of mean BP levels (30–32). Further, high ARV is associated with greater prevalence of cerebral small vessel disease, a relevant contributor to stroke and cognitive decline in older adults (OR: 1.27; 95% CI: 1.14, 1.42) as well as all-cause

TABLE 3 Effect of 800 IU and 2000 IU daily vitamin D supplementation on blood pressure[1]

	Vitamin D			
Blood pressure, mm Hg	2000 IU ($n = 123$)	800 IU ($n = 127$)	Difference (95% CI)[2]	*P*
Systolic day				
Baseline unadjusted, mean ± SD	131.86 ± 12.37	133.85 ± 13.17	−1.99 (−5.17, 1.20)	0.22
Adjusted 1-y change	−2.89 (−4.40, −1.37)	−4.22 (−5.72, −2.72)	1.33 (−0.81, 3.48)	0.22
Adjusted 2-y change	−2.62 (−4.20, −1.03)	−3.65 (−5.19, −2.11)	1.04 (−1.19, 3.26)	0.36
Across 2 y	−2.75 (−4.07, −1.43)	−3.94 (−5.23, −2.64)	1.18 (−0.68, 3.05)	0.21
Systolic night				
Baseline unadjusted, mean ± SD	119.16 ± 13.26	119.12 ± 13.51	0.04 (−3.31, 3.38)	0.98
Adjusted 1-y change	−4.93 (−6.64, −3.22)	−6.25 (−7.96, −4.55)	1.32 (−1.10, 3.74)	0.28
Adjusted 2-y change	−4.73 (−6.53, −2.94)	−4.32 (−6.07, −2.58)	−0.41 (−2.92, 2.10)	0.75
Across 2 y	−4.83 (−6.34, −3.33)	−5.29 (−6.77, −3.80)	0.46 (−1.67, 2.58)	0.67
Systolic 24 h				
Baseline unadjusted, mean ± SD	129.75 ± 12.10	131.23 ± 12.70	−1.49 (−4.58, 1.60)	0.34
Adjusted 1-y change	−3.24 (−4.68, −1.79)	−4.37 (−5.80, −2.93)	1.13 (−0.91, 3.17)	0.28
Adjusted 2-y change	−2.88 (−4.39, −1.38)	−3.53 (−5.00, −2.06)	0.64 (−1.47, 2.76)	0.55
Across 2 y	−3.06 (−4.32, −1.80)	−3.95 (−5.18, −2.71)	0.88 (−0.89, −2.66)	0.33
Diastolic day				
Baseline unadjusted, mean ± SD	79.10 ± 7.79	79.64 ± 8.13	−0.54 (−2.52, 1.45)	0.59
Adjusted 1-y change	−1.34 (−2.19, −0.50)	−2.32 (−3.16, −1.48)	0.98 (−0.22, 2.18)	0.11
Adjusted 2-y change	−1.72 (−2.60, −0.83)	−2.70 (−3.56, −1.84)	0.99 (−0.25, 2.23)	0.12
Across 2 y	−1.53 (−2.28, 0.78)	−2.51 (−3.25, −1.78)	0.98 (−0.07, 2.04)	0.07
Diastolic night				
Baseline unadjusted, mean ± SD	68.21 ± 8.10	67.37 ± 7.61	0.84 (−1.12, 2.81)	0.40
Adjusted 1-y change	−2.00 (−3.09, −0.91)	−2.35 (−3.44, −1.26)	0.35 (−1.19, 1.90)	0.65
Adjusted 2-y change	−2.16 (−3.31, −1.01)	−2.45 (−3.56, −1.33)	0.29 (−1.32, 1.89)	0.73
Across 2 y	−2.08 (−3.03, −1.13)	−2.40 (−3.34, −1.46)	0.32 (−1.02, 1.66)	0.64
Diastolic 24 h				
Baseline unadjusted, mean ± SD	77.20 ± 7.59	77.46 ± 7.80	−0.26 (−2.17, 1.66)	0.79
Adjusted 1-y change	−1.43 (−2.24, −0.62)	−2.17 (−2.98, −1.37)	0.74 (−0.41, 1.89)	0.20
Adjusted 2-y change	−1.67 (−2.52, −0.83)	−2.49 (−3.31, −1.66)	0.82 (−0.37, 2.00)	0.18
Across 2 y	−1.55 (−2.27, −0.83)	−2.33 (−3.04, −1.62)	0.78 (−0.23, 1.79)	0.13

[1]The table displays changes in day, night, and 24-h systolic and diastolic blood pressure from baseline evaluated in linear mixed models with random intercepts for each subject to allow for serial correlation of blood pressure recordings at 1 and 2 y. All models were adjusted for age, sex, BMI, diabetes, hypertension, activity (for daytime and 24-h models), and baseline blood pressure, and included an interaction between treatment group and time. Changes by year are changes from baseline to the end of that year. Changes across the 2 y are the average of both annual changes from baseline. All values are means (95% CIs) unless otherwise noted.

[2]The difference is the change from baseline, or at baseline for baseline unadjusted means, between the 2000 IU and 800 IU treatment groups.

mortality (HR: 1.10; 95% CI: 1.04, 1.16), both independently of mean BP (33, 34). Therefore, BP variability is being established as a new therapeutic target. Most antihypertensive drug classes have been shown to reduce short-term BP variability, with long-acting calcium channel blockers being the most effective (35). However, these drugs come with side effects and opportunity for harmful drug interactions and adverse drug reactions. In this study, daily high dose (2000 IU) vitamin D supplementation was found to effectively reduce BP variability compared with the standard dose. While more research is needed, this study offers promising results on a low-cost and safe nutritional supplement as a possible therapy to reduce BP variability.

At 25(OH)D concentrations < and >28.7 ng/mL, an increasing loss of benefit was observed; however, this finding is observational in nature and consequently needs to be interpreted with caution. In this study, an achieved concentration of 28.7 ng/mL of 25(OH)D was associated with a 6.01 mm Hg (95% CI: −8.20, −3.82) reduction in daytime systolic BP, while concentrations of 20, 35, and 40 ng/mL were associated with reductions of 2.59 (95% CI: −5.73, 0.56), 2.78 (95% CI: −5.05, −0.51), and 1.92 (95% CI: −4.45, 0.62) mm Hg, respectively. Researchers have long been trying to determine if there exists an optimum concentration of circulating 25(OH)D. A recent meta-analysis found a dose–response relationship between 25(OH)D concentration and hypertension risk, in which the risk of hypertension substantially increased at <75 nmol/L (28.4 ng/mL), then flattened but remained significant beyond this point (18). Our study is in line with these findings as well as extensive reviews by the Institute of Medicine and the Endocrine Society, which concluded a desirable serum 25(OH)D concentration of 20 ng/mL and a recommended dose of 600 to 800 IU and a serum 25(OH)D concentration of 30 ng/mL and a recommended dose of 600 to 2000 IU, respectively (36, 37). Greater adiposity, more so than body weight, is associated with lower 25(OH)D concentrations with the hypothesis that adipose tissue serves as a reservoir for vitamin D (38, 39). The association of 25(OH)D concentration and BP reduction found in this study could be confounded by adiposity, for which adjustment by BMI did not fully capture. Our findings from both the trial and the observational portion of the study may help elucidate the

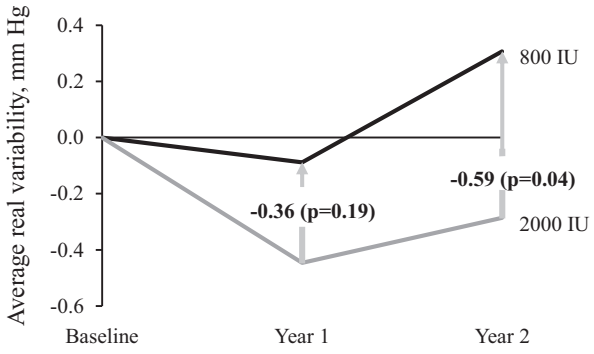

FIGURE 3 Changes in blood pressure variability by treatment group. The figure shows changes in systolic blood pressue average real variability evaluated by a linear mixed model with random intercepts for each subject to allow for serial correlation of average real variability measurements at 1 and 2 y. The model was adjusted for age, sex, BMI, diabetes, hypertension, activity, and baseline average real variability, and included an interaction between treatment group and time. The estimates represent the change in average real variability from baseline, by year. The differences in the changes between both treatment groups at year 1 and year 2 are displayed with its accompanying *P* value. Total sample size for year 1 is $n = 233$ (800 IU: $n = 117$; 2000 IU: $n = 116$) and year 2 is $n = 217$ (800 IU: $n = 112$; 2000 IU: $n = 105$).

possibility that the concentration of achieved 25(OH)D status, rather than vitamin D dose, is important for effective BP control. These findings provide motivation towards an individualized concept of vitamin D for BP control.

This study corroborates a plethora of cross-sectional and cohort analyses demonstrating low 25(OH)D status to be associated with elevated systolic BP and hypertension (40, 41). However, whether low 25(OH)D concentration contributes to the risk of hypertension remains unclear. While prospective studies have demonstrated poor 25(OH)D status to be associated with high systolic BP (42), incident hypertension (4, 43), and adverse cardiovascular events (44), there is an ongoing debate as to whether low 25(OH)D concentrations cause incident hypertension or whether vitamin D supplementation can help in the treatment of hypertension (45). In fact, several trials have concluded that vitamin D supplementation is ineffective for BP reduction in hypertensive individuals (42, 46–50).

Several trials using a high, intermittent dose of vitamin D supplementation did not find an effect of vitamin D supplementation on BP (47, 48). This could be due to the inability of such a dosing strategy to effectively restore 25(OH)D status to a moderate concentration (45). Our study further suggests that, rather than the dosage of vitamin D supplementation, maintaining a moderate concentration of serum 25(OH)D might be most important.

Our study had strengths and limitations. A strength of this study includes the use of 24-h BP monitoring compared with in-office recording. Mean daytime, nighttime, and 24-h ambulatory BP monitoring has been shown to be consistent under common pitfalls including white-coat and masked hypertension, dipping status, and BP variability from in-office recordings. A limitation of our study is the absence of a placebo control group, which does not allow us to claim a BP-reducing benefit from vitamin D supplementation. At the time of this study, the ethical commission

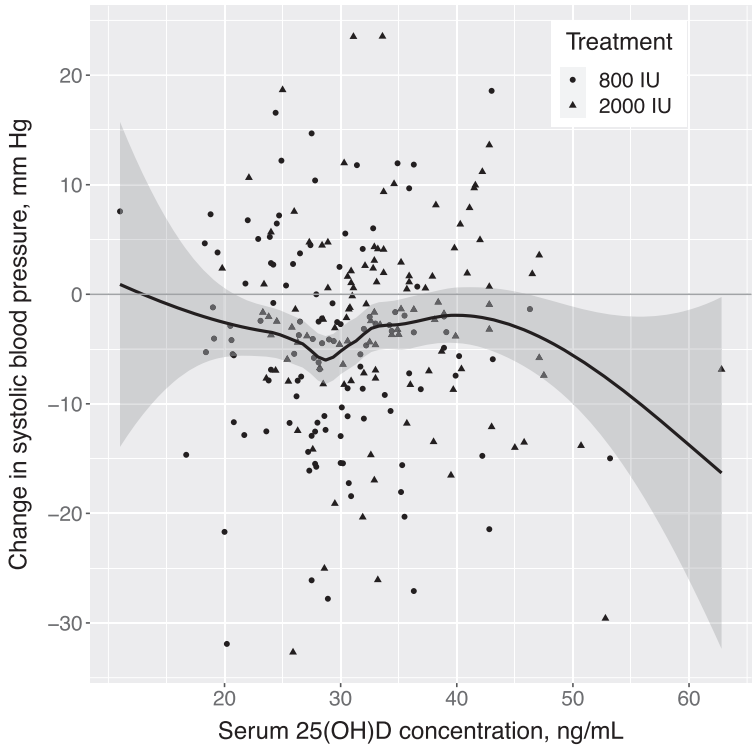

FIGURE 4 Change in daytime systolic blood pressure by serum 25(OH)D concentration. The LOESS curve shows the change in daytime systolic blood pressure at 1 y from baseline as a function of achieved 25(OH)D. The shaded area represents the 95% CI bands. The total sample size is $n = 233$ (800 IU: $n = 117$; 2000 IU: $n = 116$). LOESS, locally estimated scatterplot smoothing; 25(OH)D, 25-hydroxyvitamin D.

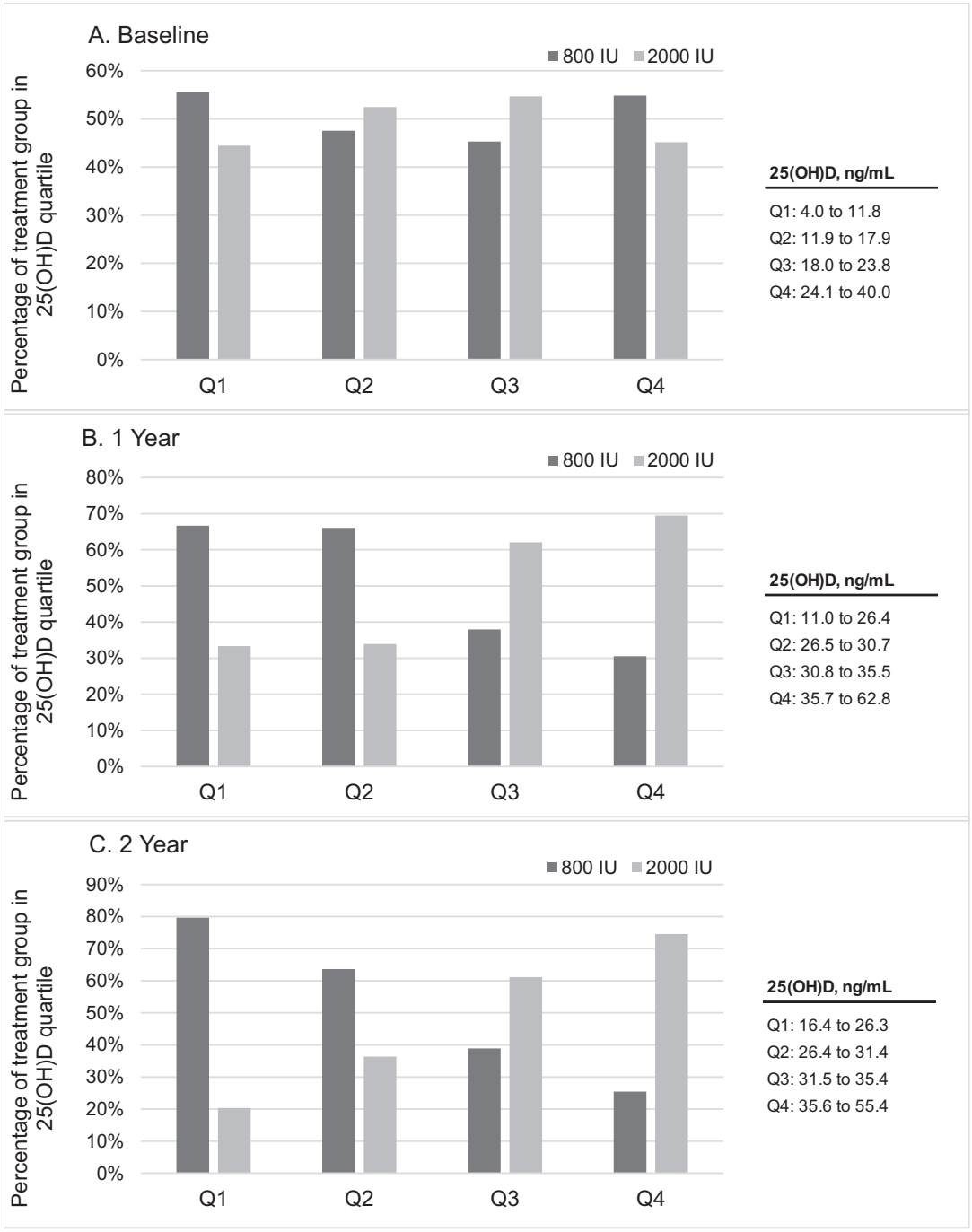

FIGURE 5 (A–C) Achieved 25(OH)D serum concentrations by treatment group. The percentage of each treatment group comprising achieved 25(OH)D concentration quartiles at baseline (A) (800 IU: $n = 127$; 2000 IU: $n = 123$), 1 y (B) (800 IU: $n = 117$; 2000 IU: $n = 116$), and 2 y (C) (800 IU: $n = 113$; 2000 IU: $n = 105$). Q, quartile; 25(OH)D, 25-hydroxyvitamin D.

requested that the comparison group be the standard 800 IU dose to be consistent with current recommendations given the high risk of falls and hip fractures among older adults with knee osteoarthritis. Further, 24-h BP was a secondary endpoint in the original trial; as such, the present study may be underpowered and results should be considered hypothesis generating. Additionally, dosage of vitamin D supplementation to reach a set threshold can depend on many factors including race, calcium intake, renal function, adiposity, BMI, and polymorphisms in key proteins/enzymes involved in the vitamin D metabolism and action (38, 51). Finally, our conclusions may not be generalizable to younger adults.

Our findings indicate a daily dose of 2000 IU is no more beneficial or harmful than a standard dose of 800 IU to realize vitamin D's potential BP-reducing benefits. Despite significant reductions in systolic and diastolic BP among both treatment

groups, without a placebo control group we cannot definitively conclude a BP-reducing benefit attributed to vitamin D supplementation. In a post hoc analysis, daily high dose vitamin D supplementation was found to reduce BP variability compared with the standard dose. The observational aim exploring vitamin D serum status revealed moderate concentrations of 25(OH)D at 28.7 ng/mL to be associated with the greatest reduction in mean BP in this particular sample of older adults recovering from unilateral knee replacement. Additional studies are needed to determine if vitamin D supplementation can effectively reduce BP and BP variability, and lower the risk of incident hypertension.

In conclusion, the results of this study show no added benefit of daily 2000 IU vitamin D supplementation compared with 800 IU for reducing BP. BP variability was significantly reduced in the 2000 IU compared with the 800 IU vitamin D group. Observed 25(OH)D concentrations at 28.7 ng/mL (71.75 nmol/L) were associated with the greatest reductions in BP.

The authors' responsibilities were as follows—LAA, SM, and HAB-F: contributed equally to the study and drafted the manuscript with input from all co-authors; LAA: conducted statistical analyses with input from EJO and HAB-F, which were reviewed by all authors; LAA, UM, EJO, CGRCM, and HAB-F: had full access to the data; SM, AE, UM, and HAB-F: conducted the trial implementation and data collection according to Good Clinical Practice; HAB-F: is the principal investigator responsible for the design of the original trial, this ancillary BP trial, and the observational study; BD-H, HBS, FR, RT, JPF, and WCW: contributed to the design of the original trial including the BP endpoint; and all authors: reviewed the results of the analyses, contributed to the final draft of the manuscript, and read and approved the final manuscript. HAB-F reports 1 grant from DSM Nutritional Products on the effects of vitamin D on muscle health and investigator-initiated grants from Pfizer and Wild, as well as speaker's fees from Roche-Diagnostics, MedaPharma, and Wild outside the submitted work. BD-H reports grants from DSM Nutritional Products and Pfizer, outside the submitted work. The other authors report no conflicts of interest.

References

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab 2012;97(4):1153–8.
2. Pilz S, Gaksch M, O'Hartaigh B, Tomaschitz A, Marz W. The role of vitamin D deficiency in cardiovascular disease: where do we stand in 2013? Arch Toxicol 2013;87(12):2083–103.
3. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet North Am Ed 2012;380(9859):2224–60.
4. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension 2007;49(5):1063–9.
5. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117(4):503–11.
6. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. Am J Hypertens 2007;20(7):713–19.
7. Maier S, Sidelnikov E, Dawson-Hughes B, Egli A, Theiler R, Platz A, Staehelin HB, Simmen HP, Meier C, Dick W, et al. Before and after hip fracture, vitamin D deficiency may not be treated sufficiently. Osteoporos Int 2013;24(11):2765–73.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003; 42(6):1206–52.
9. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110(2):229–38.
10. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, Lieben L, Mathieu C, Demay M. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev 2008;29(6):726–76.
11. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with type 2 diabetes mellitus and low vitamin D levels. Diabet Med 2008;25(3):320–5.
12. Forman JP, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertension 2010;55(5):1283–8.
13. Geleijnse JM. Vitamin D and the prevention of hypertension and cardiovascular diseases: a review of the current evidence. Am J Hypertens 2011;24(3):253–62.
14. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med 2008;168(12):1340–9.
15. Zittermann A, Frisch S, Berthold HK, Gotting C, Kuhn J, Kleesiek K, Stehle P, Koertke H, Koerfer R. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. Am J Clin Nutr 2009;89(5):1321–7.
16. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab 2001;86(4):1633–7.
17. Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM, Alvarez JA, Boxer RS, Dalbeni A, Gepner AD, et al. Effect of vitamin D supplementation on blood pressure: A systematic review and meta-analysis incorporating individual patient data. JAMA Intern Med 2015;175(5):745–54.
18. Zhang D, Cheng C, Wang Y, Sun H, Yu S, Xue Y, Liu Y, Li W, Li X. Effect of vitamin D on blood pressure and hypertension in the general population: An update meta-analysis of cohort studies and randomized controlled trials. Prev Chronic Dis 2020;17:E03.
19. Veronese N, Stubbs B, Solmi M, Smith TO, Noale M, Schofield P, Maggi S. Knee osteoarthritis and risk of hypertension: a longitudinal cohort study. Rejuvenation Res 2018;21(1):15–21.
20. Stergiou GS, Parati G, Vlachopoulos C, Achimastos A, Andreadis E, Asmar R, Avolio A, Benetos A, Bilo G, Boubouchairopoulou N, et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: current status and future directions—position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. J Hypertens 2016;34(9):1665–77.
21. Bischoff-Ferrari HA, Orav EJ, Egli A, Dawson-Hughes B, Fischer K, Staehelin HB, Rizzoli R, Hodler J, von Eckardstein A, Freystaetter G, et al. Recovery after unilateral knee replacement due to severe osteoarthritis and progression in the contralateral knee: a randomised clinical trial comparing daily 2000 IU versus 800 IU vitamin D. RMD Open 2018;4(2):e000678.
22. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; Guideline Development Group. Management of hypertension: summary of NICE guidance. BMJ 2011;343:d4891.
23. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31(7):1281–357.
24. Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, Gelfer M, Lamarre-Cliche M, Milot A, Bolli P, et al. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2015;31(5):549–68.
25. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. J Hypertens 2007;25(11):2193–8.

26. McManus RJ, Caulfield M, Williams B; National Institute for Health and Clinical Exellence. NICE hypertension guideline 2011: evidence based evolution. BMJ (Clin Res Ed) 2012;344:e181.
27. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G, Sulbaran T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens 2005;23(3):505–11.
28. Saleh L, Mueller D, von Eckardstein A. Analytical and clinical performance of the new Fujirebio 25-OH vitamin D assay, a comparison with liquid chromatography-tandem mass spectrometry (LC-MS/MS) and three other automated assays. Clin Chem Lab Med 2016;54(4):617–25. doi: 10.1515/cclm-2015-0427.
29. WHO Collaborating Centre for Drug Statistics Methodology. International language for drug utilization research. [Internet] [accessed February 2018]. Available from: https://www.whocc.no/.
30. Tatasciore A, Renda G, Zimarino M, Soccio M, Bilo G, Parati G, Schillaci G, De Caterina R. Awake systolic blood pressure variability correlates with target-organ damage in hypertensive subjects. Hypertension 2007;50(2):325–32.
31. Shintani Y, Kikuya M, Hara A, Ohkubo T, Metoki H, Asayama K, Inoue R, Obara T, Aono Y, Hashimoto T, et al. Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study. J Hypertens 2007;25(8):1704–10.
32. Leoncini G, Viazzi F, Storace G, Deferrari G, Pontremoli R. Blood pressure variability and multiple organ damage in primary hypertension. J Hum Hypertens 2013;27(11):663–70.
33. Tully PJ, Yano Y, Launer LJ, Kario K, Nagai M, Mooijaart SP, Claassen J, Lattanzi S, Vincent AD, Tzourio C. Association between blood pressure variability and cerebral small-vessel disease: a systematic review and meta-analysis. JAHA 2020;9(1):e013841.
34. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, McManus RJ. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ (Clin Res Ed) 2016;354:i4098.
35. Nardin C, Rattazzi M, Pauletto P. Blood pressure variability and therapeutic implications in hypertension and cardiovascular diseases. High Blood Pressure Cardiovasc Prev 2019;26(5):353–9.
36. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, et al. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96(1):53–8.
37. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96(7):1911–30.
38. Yeum KJ, Dawson-Hughes B, Joo NS. Fat mass is associated with serum 25-hydroxyvitamin D concentration regardless of body size in men. Nutrients 2018;10(7);850.
39. Carrelli A, Bucovsky M, Horst R, Cremers S, Zhang C, Bessler M, Schrope B, Evanko J, Blanco J, Silverberg SJ, et al. Vitamin D storage in adipose tissue of obese and normal weight women. J Bone Miner Res 2017;32(2):237–42.
40. Burgaz A, Orsini N, Larsson SC, Wolk A. Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis. J Hypertens 2011;29(4):636–45.
41. Judd SE, Nanes MS, Ziegler TR, Wilson PW, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. Am J Clin Nutr 2008;87(1):136–41.
42. Larsen T, Mose FH, Bech JN, Hansen AB, Pedersen EB. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. Am J Hypertens 2012;25(11):1215–22.
43. Forman JP, Bischoff-Ferrari HA, Willett WC, Stampfer MJ, Curhan GC. Vitamin D intake and risk of incident hypertension: results from three large prospective cohort studies. Hypertension 2005;46(4):676–82.
44. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168(11):1174–80.
45. Legarth C, Grimm D, Wehland M, Bauer J, Kruger M. The impact of vitamin D in the treatment of essential hypertension. Int J Mol Sci 2018;19(2):455.
46. Arora P, Song Y, Dusek J, Plotnikoff G, Sabatine MS, Cheng S, Valcour A, Swales H, Taylor B, Carney E, et al. Vitamin D therapy in individuals with prehypertension or hypertension: the DAYLIGHT trial. Circulation 2015;131(3):254–62.
47. Witham MD, Price RJ, Struthers AD, Donnan PT, Messow CM, Ford I, McMurdo ME. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. JAMA Intern Med 2013;173(18):1672–9.
48. Witham MD, Ireland S, Houston JG, Gandy SJ, Waugh S, Macdonald TM, Mackenzie IS, Struthers AD. Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. Hypertension 2014;63(4):706–12.
49. Chen WR, Liu ZY, Shi Y, Yin DW, Wang H, Sha Y, Chen YD. Vitamin D and nifedipine in the treatment of Chinese patients with grades I-II essential hypertension: a randomized placebo-controlled trial. Atherosclerosis 2014;235(1):102–9.
50. Mozaffari-Khosravi H, Loloei S, Mirjalili MR, Barzegar K. The effect of vitamin D supplementation on blood pressure in patients with elevated blood pressure and vitamin D deficiency: a randomized, double-blind, placebo-controlled trial. Blood Press Monit 2015;20(2):83–91.
51. Fuleihan Gel H, Bouillon R, Clarke B, Chakhtoura M, Cooper C, McClung M, Singh RJ. Serum 25-hydroxyvitamin D levels: variability, knowledge gaps, and the concept of a desirable range. J Bone Miner Res 2015;30(7):1119–33.