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Vitamin D supplementation and adverse skeletal and non-skeletal outcomes in individuals at increased cardiovascular risk: Results from the International Polycap Study (TIPS)-3 randomized controlled trial

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KEYWORDS
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Death

Abstract *Background and aims:* Vitamin D has mostly been tested in Western populations. We examined the effect of high dose vitamin D in a population drawn predominantly from outside of Western countries.
Methods and results: This randomized trial tested vitamin D 60,000 IU monthly in 5670 participants without vascular disease but at increased CV risk. The primary outcome was fracture. The secondary outcome was the composite of CV death, myocardial infarction stroke, cancer, fracture or fall. Death was a pre-specified outcome. Mean age was 63.9 years, and 3005 (53.0%) were female. 3034 (53.5%) participants resided in South Asia, 1904 (33.6%) in South East Asia, 480 (8.5%) in South America, and 252 (4.4%) in other regions. Mean follow-up was 4.6 years. A fracture occurred in 20 participants (0.2 per 100 person years) assigned to vitamin D, and 19 (0.1 per 100 person years) assigned to placebo (HR 1.06, 95% CI 0.57–1.99, *p*-value = 0.86). The secondary outcome occurred in 222 participants (1.8 per 100 person years) assigned to vitamin D, and 198 (1.6 per 100 person years) assigned to placebo (HR 1.13, 95% CI 0.93–1.37, $p = 0.22$). 172 (1.3 per 100 person years) participants assigned to vitamin D died, compared with 135 (1.0 per 100 person years) assigned to placebo (HR 1.29, 95% CI 1.03–1.61, $p = 0.03$).

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Conclusion: In a population predominantly from South Asia, South East Asia and South America, high-dose vitamin D did not reduce adverse skeletal or non-skeletal outcomes. Higher mortality was observed in the vitamin D group.
Registration number: NCT01646437.

1. Introduction

Low concentrations of measured 25 hydroxy vitamin D (25(OH)D) are associated with higher risk of adverse skeletal events (e.g. fractures), non-skeletal events (e.g. cardiovascular disease, cancer), and mortality [1–4]. Nutritional supplements are often used to support vitamin D consumption, and can account for between 12 and 40% of daily vitamin D consumption in North America and Europe [5,6]. Randomized controlled trials have shown that vitamin D supplements improve bone mineral density and could reduce fracture risk (when combined with calcium supplementation), but the results of trials on cardiovascular outcomes, cancers, and mortality have not demonstrated beneficial effects [7–13]. Most clinical trials have been conducted in Western populations, with limited data from populations in other regions of the world.

Vitamin D production is impacted by multiple factors, including endogenous production related to skin color, exposure to sunlight, and food fortification policies. Therefore, the impact of routine vitamin D supplementation could vary in different regions of the world, with greater potential benefits in areas where vitamin D deficiency is more common. Vitamin D deficiency is reported to be very common in South Asia, South East Asia, South America, and Africa but studies of vitamin D supplementation are lacking from these regions [1,14,15]. In a large randomized controlled trial of participants at increased cardiovascular disease (CVD) risk focused in regions of the world with limited data on vitamin D supplementation (e.g. South Asia, South East Asia, South America), we evaluated the impact of routine high-dose vitamin D supplementation on skeletal and non-skeletal clinical outcomes. The primary outcome of the study was incident fracture. Additional prespecified outcomes included the composite of CVD, cancer, fractures, or falls; and death from any cause.

2. Methods

2.1. Study design and population

The design and of The International Polycap Study 3 (TIPS-3) has been previously described [16,17]. In summary, it is a 2 × 2 × 2 factorial, double-blind, placebo-controlled randomized controlled trial. The study population consisted of men >50 years of age or women >55 years of age without a history of CVD, but at least at intermediate CVD risk based on an elevated INTERHEART Risk Score [17,18]. Exclusion criteria specific to the vitamin D arm included regular use of vitamin D at doses higher than 400 IU daily, and hypercalcemia, hyperparathyroidism, osteomalacia or other contraindication or indication for vitamin D. Detailed eligibility criteria for the overall trial are summarized in the Supplementary Appendix. The study was approved by local research ethics boards and national regulatory authorities, and participants provided written informed consent.

The study was conducted in 86 centers in 9 countries: India, Bangladesh, Philippines, Indonesia, Malaysia, Colombia, Tunisia, Tanzania, and Canada. The Population Health Research Institute (PHRI), Hamilton, Ontario, Canada was the central coordinating center. A steering committee consisting of members of the central coordinating office as well as national leaders from each country oversaw the conduct of the study. An independent data monitoring safety board reviewed efficacy and safety data at regular intervals.

The first factorial randomized participants to a polypill versus matching placebo. The second factorial randomized participants to aspirin versus matching placebo. Results of the polypill and aspirin factorials have been previously published [16]. This analysis focused on the third factorial of the study, which randomized participants to oral high-dose vitamin D_3 60,000 IU given monthly (equivalent to about 2000 IU daily) versus matching placebo. The primary outcome was time to incident fracture during follow-up. The secondary outcome was time to the composite outcome of CVD (defined as CV death, myocardial infarction, or stroke), cancer, fracture, or fall. Time to any death was also a pre-specified outcome for this analysis. Detailed definitions of each outcome are provided in the Supplementary Appendix. All deaths, CVD and cancers reported in the trial underwent central adjudication. Fractures and falls were collected routinely during clinical follow-up on case report forms, but did not undergo central adjudication. The effect of vitamin D on cognitive and functional outcomes were also pre-specified outcomes, but will be reported in a separate analysis.

2.2. Study procedures

Eligible participants entered a 3–4 week run-in phase, during which time they received a low-dose of the polypill and aspirin daily. Participants did not receive vitamin D during the run-in phase. At the randomization visit, those

who successfully completed run-in were randomized to all three factorial arms of the study, including to vitamin D_3 60,000 IU monthly or to matching placebo in a 1:1 ratio. The randomization allocation sequence was generated using a computer-based software system with permuted block randomization occurring at the center level. Participants and study personnel were blinded to the treatment allocation. Follow-up visits were planned for 6 weeks, 3, 6, 9 and 12 months, and then every 6 months until completion of follow-up.

Randomization for the clinical trial occurred between July 30, 2012, and August 12, 2017. End of study visits began in late 2021, with follow-up planned to be completed in 2022. In early 2022, restrictions due to the COVID-19 pandemic presented unique challenges to conducting the final phase of follow-up. In response, intensive efforts were made by the coordinating center, national project offices, and sites to develop strategies to complete the study. This included sites being given the option of dividing data collection at the final visits, with some components conducted by phone (e.g. collecting information on clinical outcomes) and other data (e.g. physical measures, cognitive function) collected at a future date. To account for this protracted final visit schedule, blinded steering committee members prespecified that all clinical outcome data that would be used for primary or secondary outcome analyses would be censored after June 30, 2022, which is the data that our primary publication was based upon. For consistency, this analysis is also based on the same dataset, where all clinical outcome events are reported on until the occurrence of a participant's death, an end of study visit conducted prior to June 30, 2022, or a final date June 30, 2022.

2.3. Sample size and statistical power

The study's sample size was primarily based on the comparison of the polypill versus placebo. For the comparison of vitamin D versus placebo on fractures, we assumed a fracture rate of 1.9% per year based on the observed incidence in prior studies [19]. With a sample size of 5000 and mean follow up of 5 years, the study would have 81% power to detect a 25% relative risk reduction in fractures.

2.4. Statistical analysis

Primary analyses were based on intention to treat principal, with all randomized participants included based on their allocated treatment group. Kaplan-Meier survival curves were generated for each pre-specified outcome. Proportional hazard assumptions were not violated for the primary outcome, secondary outcome and for deaths (see Supplementary Table 1). We used Cox-proportional hazard models to estimate the hazard ratio for vitamin D versus placebo for each clinical outcome of interest. Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Differences in treatment effects were assessed in pre-specified subgroups, with testing for interactions in categorical groups, and for trend in ordinal groups. Due to higher than expected rates of drug discontinuation for non-medical reasons in the trial, additional sensitivity analyses were performed on pre-specified outcomes limiting events to those occurring within 30 days of study-drug discontinuation for non-medical reasons. A p-value <0.05 was considered statistically significant. Analyses were conducted using SAS. The trial was registered with ClinicalTrials.Gov, registration: NCT01646437.

Role of the funding source

Funders had no role in the design of the study, analysis of the data, interpretation of the results, or writing of the report.

3. Results

A total of 7793 individuals were screened for the trial, and of these 7534 entered the run-in phase. 5713 participants completed run-in and proceeded to randomization. Of these, 43 participants did not undergo randomization to the vitamin D arm of the study, resulting in 5670 participants randomized to either vitamin D 60,000 IU monthly or matching placebo (Supplementary Figure 1). Randomization of participants to the vitamin D arm occurred between July 30, 2012 and August 12, 2017.

3.1. Baseline characteristics

Mean age of the study population was 63.9 years, and 3005 (53.0%) were female. 3034 (53.5%) participants resided in South Asia, 1904 (33/6%) in South East Asia, 480 (8.5%) in South America, and 252 (4.4%) in other regions. 4758 (83.9%) had hypertension, and 2089 (36.8%) had diabetes. Mean BMI was 25.8 (SD 4.7). INTERHEART risk score was 17.9 (SD 4.8), which was consistent with an intermediate risk primary CVD prevention population. Baseline characteristics were similar between those randomized to vitamin D or to placebo (Table 1).

3.2. Follow-up and adherence

During follow-up, 57 participants randomized to the vitamin D or matching placebo arm were withdrawn early due to site closures, but clinical outcome data from patients at these centers are included prior to their withdrawal. For the remaining participants, follow up for clinical events occurred until their final study visit or June 30, 2020. Clinical event data were available in 98.9% of participants upon completion of the study. Mean follow up of the study population was 4.6 years.

At 24 months, 18.1% of participants had stopped vitamin D or matching placebo (18.6% in the active group and 17.5% in the placebo group). At 48 months, 25.7% had stopped vitamin D or matching placebo (24.8% in the active group and 26.6% in the placebo group). At the final study visit,

Table 1 Baseline characteristics of the study population.

	Vitamin D active	Placebo
Randomized	(N = 2835)	(N = 2835)
Age - mean (SD)	64.0 (6.6)	63.8 (6.5)
Female - n (%)	1504 (53.1)	1501 (52.9)
Region – n (%)		
India or Bangladesh	1518 (53.5)	1516 (53.5)
Philippines, Malaysia, or Indonesia	951 (33.5)	953 (33.6)
Colombia	241 (8.5)	239 (8.4)
Canada	54 (1.9)	52 (1.8)
Tanzania	19 (0.7)	20 (0.7)
Tunisia	52 (1.8)	55 (1.9)
Hypertension or SBP >140 mm Hg	2374 (83.7)	2384 (84.1)
Blood pressure, mmHg – mean (SD)		
SBP	144.3 (16.8)	144.7 (16.9)
DBP	83.7 (9.3)	84.0 (10.1)
Diabetes or FPG >126 mg/dl - n (%)	1024 (36.1)	1065 (37.6)
Fasting plasma glucose, mg/dl – mean (SD)	113.4 (43.8)	115.3 (46.3)
Current smoking – n (%)	257 (9.1)	251 (8.9)
Cholesterol, mg/dl – mean (SD)		
Total Cholesterol	196.1 (45.7)	195.9 (45.6)
LDL	120.8 (40.7)	120.4 (40.9)
HDL	47.8 (13.2)	47.5 (12.7)
Triglycerides	145.1 (70.2)	146.5 (78.3)
Body-mass index, kg/m^2 – mean (SD)	25.7 (4.8)	25.9 (4.6)
Waist-to-hip ratio – mean (SD)		
Women	0.91 (0.07)	0.91 (0.07)
Men	0.96 (0.06)	0.96 (0.07)
Creatinine, mg/dl – mean (SD)	0.9 (0.3)	0.9 (0.3)
INTERHEART risk score - mean (SD)	18.0 (4.8)	17.9 (4.8)

39.1% of participants had permanently stopped vitamin D or matching placebo (38.9% in the active group, and 39.3% in the placebo group). 0.9% of discontinuations were due to side effects, 15.6% were due to refusal unrelated to side effects, and 17.3% were due to delays in drug re-supply (including inability to resupply at sites due to the COVID 19 pandemic, Supplementary Table 2).

3.3. Efficacy

No interactions occurred between the different randomized study treatments. The primary efficacy outcome of a fracture occurred in 20 participants (0.2 per 100 person years) assigned to vitamin D compared with 19 (0.1 per 100 person years) participants assigned to placebo (HR 1.06, 95% CI 0.57–1.99, p-value = 0.86) (Table 2, Fig. 1a). The secondary outcome of CV death, MI, stroke, cancer, fracture or fall occurred in 222 participants (1.8 per 100 person years) assigned to vitamin D compared with 198 (1.6 per 100 person years) assigned to placebo (HR 1.13, 95% CI 0.93–1.37, p = 0.22, Table 2, Fig. 1b). 172 (1.3 per 100 person years) participants assigned to vitamin D died during follow-up compared with 135 (1.0 per 100 person years) participants assigned to placebo (HR 1.29, 95% CI 1.03–1.61, p = 0.03, Table 2, Fig. 1c). Both CV deaths and non-CV deaths showed an excess with vitamin D compared to placebo (Table 2). When comparing individual categories of death, the largest numerical differences between vitamin D and placebo occurred for presumed cardiovascular deaths (33 versus 16), and deaths due to an unknown cause (and presumed cardiovascular) as per the pre-specified definitions (32 versus 16, Supplementary Table 3). The effect of vitamin D on the primary outcome, secondary outcome, and deaths were consistent across pre-specified subgroups stratified by age, sex, geographical location, and cardiometabolic risk factor levels (Supplementary Figures 2–4). A post hoc analysis of the composite CVD outcome of CV death, MI or stroke showed this outcome occurred in 139 participants (1.1 per 100 person years) assigned to vitamin D, and in 107 (0.8 per 100 person years) assigned to placebo (HR 1.31 (95% CI 1.02–1.69, p = 0.03).

3.4. Sensitivity analysis

In prespecified analyses excluding outcome events occurring after 30 days of drug discontinuation for non-medical reasons, there were no significant differences in risks of the primary outcome, secondary outcome, or deaths between the vitamin D group and the placebo group (Supplementary Table 4). In post hoc analyses excluding

Table 2 Efficacy of vitamin D on clinical outcomes.

	Vitamin D Placebo		Vitamin D Active		Vitamin D vs Placebo	
	N	Rate/100 Pt Years	N	Rate/100 Pt Years	HR (95% CI)	p-value
Primary outcome						
Fracture	19	0.1	20	0.2	1.06 (0.57–1.99)	0.86
Secondary outcome						
Fracture/Fracture/Fall/CV Death/MI/Stroke/Cancer/	198	1.6	222	1.8	1.13 (0.93–1.37)	0.22
Fall	57	0.4	42	0.3	0.74 (0.49–1.10)	0.13
CV Death	78	0.6	106	0.8	1.37 (1.02–1.84)	0.03
MI	19	0.1	21	0.2	1.11 (0.60–2.07)	0.73
Stroke	32	0.2	30	0.2	0.94 (0.57–1.55)	0.82
Cancer	36	0.3	40	0.3	1.12 (0.71–1.75)	0.63
All Cause Death	135	1.0	172	1.3	1.29 (1.03–1.61)	0.03
Non-CV Death	57	0.4	66	0.5	1.17 (0.82–1.66)	0.39

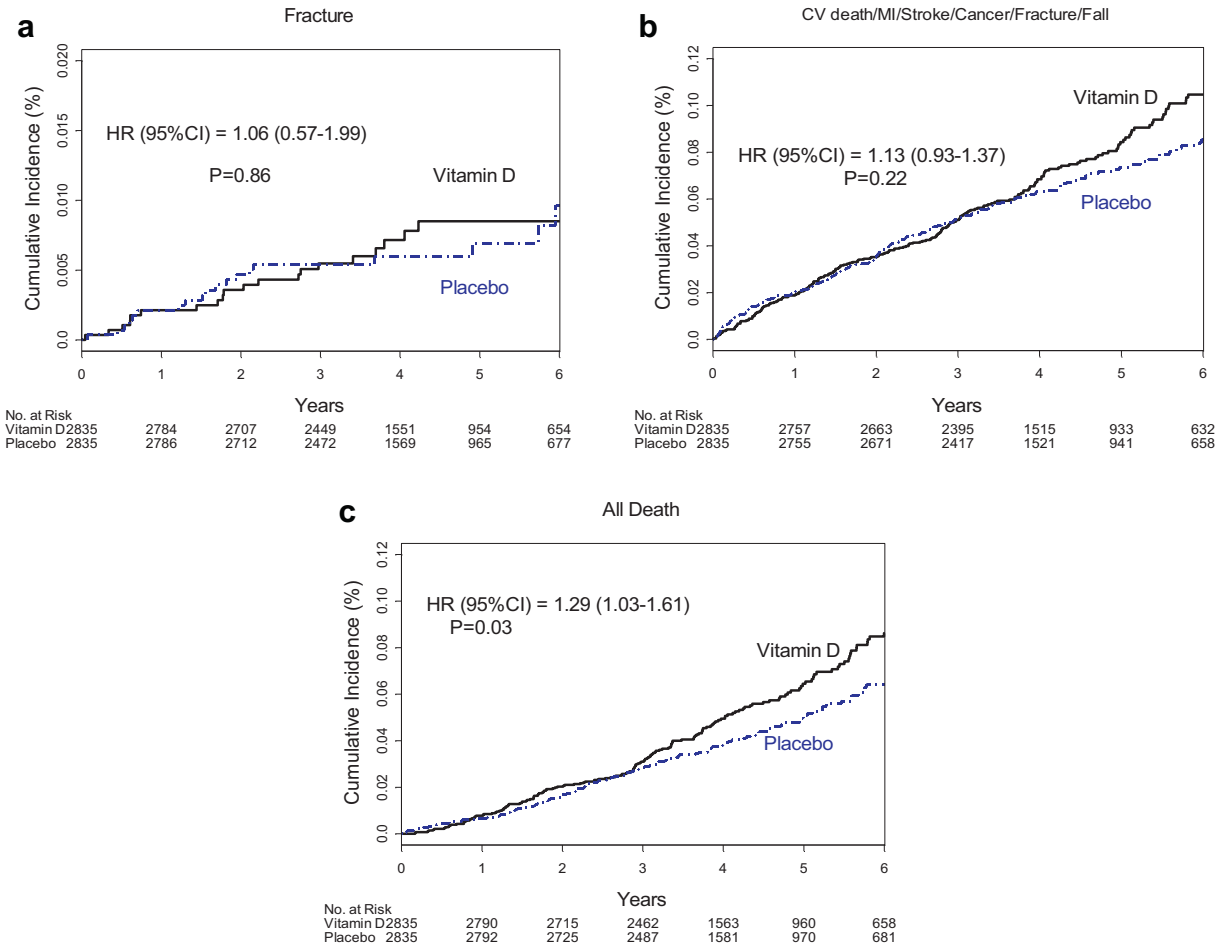

Figure 1 Kaplan meier curves for vitamin D versus placebo and the outcomes of a) Fracture, b) Composite of CVD, cancer, fracture or fall, and c) Death.

events occurring prior to the first year of follow up, and prior to the second year of follow up, the proportional risks associated with vitamin D were similar to the main analyses that included all events (Supplementary Table 5).

3.5. Adverse events

Serious adverse events occurred in 29 (1.0%) participants assigned to vitamin D, and 26 (0.9%) participants assigned to placebo (Supplementary Table 6). Hospitalizations rates were similar in both groups (Supplementary Table 7).

4. Discussion

Among individuals without a history of CVD but at increased CVD risk, treatment with vitamin D at a dose of 60,000 IU monthly did not result in a lower risk of fractures, although fracture rates were substantially lower than predicted. Further, the combined clinical endpoint of adverse CVD events, cancers, fractures or falls was not significantly different between randomized groups. Vitamin D was associated with a higher risk of death during the period of follow-up.

Our cohort was predominantly comprised of middle-aged and elderly community-dwelling participants, and the overall incidence of fractures was low during follow-up. While this would limit the power to detect a difference in fracture risk between vitamin D and placebo, our findings remain largely consistent with prior data evaluating the impact of vitamin D supplementation alone on fracture risk. A 2019 meta-analysis of 11 large randomized controlled trials predominantly conducted in western populations observed that treatment with vitamin D without parallel use of calcium did not reduce fracture risk [10]. In this context, our findings suggest that the neutral effects of vitamin D supplementation alone for preventing fractures in community dwelling individuals likely extend to populations outside of North America and Europe.

Given prior observations that 25(OH)D levels were associated with both CVD and cancers, there has been considerable interest in determining whether vitamin D supplementation could provide broader benefits for reducing adverse non-skeletal outcomes as well as skeletal outcomes. Despite using a high daily equivalent dose of vitamin D, and a high event rate for our composite outcome, we did not observe a benefit with vitamin D. This indicates a lack of benefit for preventing skeletal and non-

skeletal adverse outcomes with monthly high dose vitamin D in our study population. These findings are consistent with prior randomized controlled trials conducted in Western populations. Cumulative data from clinical trials have not demonstrated that routine supplementation of vitamin D alone reduces the risk of fractures [11]. The D-health trial reported no significant effect on the risk of falls with 60,000 IU supplementation of vitamin D monthly [20]. In The Vitamin D and Omega-3 Trial (VITAL) of 25,871 participants from the United States followed for a median of 5.3 years, there was no benefit observed with Vitamin D_3 at a daily dose of 2000 IU on incident CVD or cancer [8]. Similarly, neutral effects on CVD and cancer outcomes were observed in The Vitamin D Assessment Study (ViDA) of 5110 participants from New Zealand who were treated with 100,000 IU of vitamin D supplementation monthly or matching placebo [21,22]. In a post hoc analysis examining the effect of our monthly vitamin D regimen on the combined endpoint of CV death, MI and stroke, we observed a higher risk of this composite CV outcome associated with vitamin D. However, this finding should be interpreted in the context of being a post hoc analysis that was of marginal statistical significance, and driven largely by CV death without a consistent effect on MI or stroke. Additional data would be needed to confirm whether high dose monthly vitamin D supplementation in fact increases CV risk in similar populations to ours outside of North America and Europe. The overall findings of these large clinical trials along with our present study indicate that routine administration of high dose vitamin D is ineffective at preventing CVD, incident cancer, falls or fractures.

We observed a higher risk of death associated with vitamin D. A 2019 meta-analysis of 52 randomized controlled trials reported a neutral effect of vitamin D supplementation and all-cause mortality, and so the findings of our study need to be placed in this context [12]. Death was not a primary or secondary outcome of our study, and it is possible that the excess deaths observed in the vitamin D arm of our study may be due to chance. Our sensitivity analysis excluding events occurring after 30-days of study drug discontinuation for non-medical reasons did not show a higher risk of death with vitamin D. However, other possible reasons for the discordant results between our trial and prior data also need to be considered. In an exploratory analysis of the D-Health study, high dose vitamin D given monthly was associated with a higher risk of delayed cancer related mortality [9]. Moreover, some observational data suggest a 'reverse J-shape' relationship between serum vitamin D level and mortality. Both the Copenhagen vitamin D (CopD) study and the National Health and Nutrition Examination Survey (NHANES) have observed a higher risk of death with serum 25(OH)D levels below 50 nmol/L, but also with levels above 100 nmol/L. Further, the proportion of total serum 25(OH)D that exists in its biologically active free form is related to polymorphisms of vitamin D binding protein (DBP), which are known to vary between ethnic groups, and could influence response to vitamin D supplementation. In a small experimental study (N = 60) of Asian and Caucasian men receiving a single dose 150,000 IU of vitamin D3, Asians had a greater increase in free 25(OH)D compared to Caucasians despite similar levels of total serum hydroxyvitamin D, and this difference was potentially mediated by varying effects of DBP between groups [17]. It is possible that high doses of supplementary vitamin D resulted in excess free 25(OH)D in our population. This could not be proven in our study as 25(OH)D levels were not measured at baseline or during follow-up. However, our findings highlight the need to better understand how the metabolism of vitamin D supplementation differs between ethnic groups, and how this may impact their use in different parts of the world.

Some potential limitations of our study warrant consideration as to the generalizability of our findings. We used a monthly dosing regimen of vitamin D. Some data suggest that interval vitamin D dosing can result in more variability in 25(OH)D levels compared with daily dosing, although the mean achieved 25(OH)D level appears to be similar with both types of regimens [23–25]. Further, our treatment regimen did not include calcium supplementation, and prior studies suggest that the combination of vitamin D with calcium is necessary to prevent the risk of fractures [11]. Since serum 25(OH)D levels were not measured, we could not determine the proportion of participants that had evidence of vitamin D deficiency at baseline. Finally, our study population had a low incidence of fractures. Given many participants were from middle- or low-income countries, it is possible that in countries with less access to health resources, fractures were diagnosed less often. However, this would not introduce bias into our estimates of the treatment effect. It is also possible that the treatment might demonstrate a benefit if tested in populations at higher risk (e.g. only elderly, at increased risk of falls, or with established vitamin D deficiency). Ultimately, more clinical trials in regions outside of North America or Europe are needed to determine whether specific populations derive benefit from vitamin D (with or without calcium) for skeletal outcomes, as well as the optimal dosing strategy that is both safe and effective. However, our data do not support the recommendations that South Asians and other non-white populations should routinely consume supplementary vitamin D.

In conclusion, in a multi-national population of middle-age to elderly individuals without vascular disease but at increased CVD risk, the routine use of monthly high dose vitamin D did not reduce skeletal or non-skeletal adverse outcomes. There was unexpectedly, a higher mortality with vitamin D compared to placebo in this population. Monthly high dose vitamin D should not be used for the prevention of skeletal and non-skeletal adverse outcomes in similar populations.

Author contributions

SY and PP are the principal investigators for the trial, designed the study and obtained funding for the study. PJ and SY drafted the manuscript. PG led the statistical

analysis. All other authors participated in coordination of the study, and provided critical review of the manuscript. All authors approved the final manuscript, with the exception of KY who passed away during the development of the manuscript. PG, SY and PG have verified the validity of the underlying data.

Data sharing

We do not plan to make datasets available to others. Summary data can be made available upon request for the purposes of meta-analyses after approval from the steering committee.

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Declaration of competing interest

Dr. Yusuf reports receiving lecture fees and support for travel from AstraZeneca and grant support, lecture fees, and support for travel from Bayer. Dr. D. Xavier reports receiving grant support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Coca-Cola India, and Pfizer and lecture fees from Eli Lilly and Sanofi. Dr. Dagenais reports receiving lecture fees from Bayer. Dr. Bosch reports receiving advisory board fees and adjudication fees from Bayer. Other authors do not report any relevant conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2022.11.001.

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