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Clinical Practice Guideline Communication

Vitamin D Insufficiency and Epistemic Humility: An Endocrine Society Guideline Communication

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Abstract

A long-held precept is that vitamin D supplementation primarily, if not exclusively, benefits individuals with low circulating 25-hydroxyvitamin D (25[OH]D) concentrations at baseline. However, the most appropriate 25(OH)D threshold to distinguish unacceptably low vs reliably adequate concentrations remains controversial. Such threshold proposals have largely been based on observational studies, which provide less robust evidence compared to randomized clinical trials (RCTs). Since the Endocrine Society's first vitamin D–related guideline was published in 2011, several large vitamin D–related RCTs have been published, and a newly commissioned guideline development panel (GDP) prioritized 4 clinical questions related to the benefits and harms of vitamin D supplementation in generally healthy individuals with 25(OH)D levels below a threshold. The GDP determined that available clinical trial evidence does not permit the establishment of 25(OH)D thresholds that specifically predict meaningful benefit with vitamin D supplementation. The panel noted important limitations in the available evidence, and the panel's overall certainty in the available evidence was very low. Nonetheless, based on the GDP's analyses and judgments, the Endocrine Society no longer endorses its previously proposed definition of vitamin D "sufficiency" (ie, at least 30 ng/mL [75 nmol/L]) or its previously proposed definition of vitamin D "insufficiency" (ie, greater than 20 ng/mL [50 nmol/L] but lower than 30 ng/mL [75 nmol/L]). The Endocrine Society's rationale for such is the subject of this Guideline Communication.

Key Words: Vitamin D, 25-hydroxyvitamin D, vitamin D deficiency, clinical practice guidelines, practice guidelines, systematic reviews

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; CGC, Clinical Guidelines Committee; CPG, clinical practice guideline; DRI, Dietary Reference Intake; GDP, guideline development panel; IOM, Institute of Medicine; PTH, parathyroid hormone; RCT, randomized clinical trial; RDA, Recommended Daily Allowance; RTI, respiratory tract infection; VITAL, VITamin D and OmegA-3 TriaL.

In this issue of the *Journal of Clinical Endocrinology and Metabolism*, the Endocrine Society publishes a clinical practice guideline (CPG) entitled "Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline" (1). Therein, the guideline development panel (GDP)—hereafter referenced as *2024 GDP*—communicates an important conclusion: in generally healthy populations, available clinical trial evidence does not permit the assignment of distinct 25-hydroxyvitamin D (25[OH]D) thresholds that specifically predict net benefit with vitamin D supplementation. In particular, the panel judged that available clinical trial evidence does not clearly indicate net benefit with vitamin D supplementation in those with baseline 25(OH)D concentrations less than 20 to 24 ng/mL (50-60 nmol/L), although certainty in the evidence was very low. Based on the 2024 GDP's analyses and judgments, the Endocrine Society no longer endorses a key component of the Endocrine Society's 2011 vitamin D–related CPG, namely its previously proposed definition of vitamin D "sufficiency" (ie, at least 30 ng/mL [75 nmol/L]) (2). As a corollary, the Endocrine Society no longer endorses vitamin D "insufficiency"—defined by 25(OH)D concentrations above 20 ng/mL (50 nmol/L) but lower than 30 ng/mL (75 nmol/L)—as an actionable designation for generally healthy individuals. In this Guideline Communication, we seek to explain the Endocrine Society's rationale in this regard.

Background

A long-held precept is that vitamin D supplementation will primarily—perhaps even exclusively—benefit individuals with "low" circulating 25(OH)D concentrations at baseline, with 25(OH)D levels currently representing the best indicator of vitamin D status. This concept is implied in the oft-used phrase "vitamin D repletion," and it conforms to numerous physiological observations, including that parathyroid hormone (PTH) suppression is inversely associated with 25(OH)D levels, but only up to a point (3, 4). According to this threshold paradigm (Fig. 1), the 25(OH)D levels above which no maladaptive physiological changes occur may be confidently considered "sufficient." Perhaps more important from a clinical perspective, the concept implies that the risks of undesirable clinical outcomes begin to increase below the

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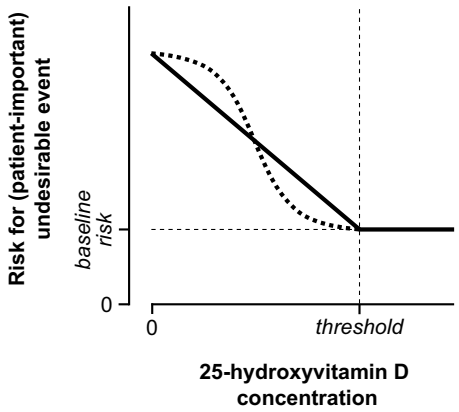

Figure 1. Threshold concept of circulating 25-hydroxyvitamin D concentrations. Under this paradigm, the risk for an undesirable vitamin D–related clinical outcome begins to increase only when 25-hydroxyvitamin D (25[OH]D) levels fall below a specific threshold. In those with 25(OH)D levels below that threshold, the absolute risk reduction expected with vitamin D supplementation may be highly sensitive to numerous factors, including: (1) the threshold 25(OH)D level for that outcome, or the 25(OH)D concentration at which the risk attributable specifically to low vitamin D status falls to zero; (2) the 25(OH)D concentration prior to vitamin D supplementation (baseline concentration); (3) the 25(OH)D concentration achieved with vitamin D supplementation; (4) the nature of the causal 25(OH)D level vs outcome relationship below the threshold (this relationship may be nonlinear); (5) the pre-supplementation event risk; and (6) the baseline event risk (ie, the risk associated with 25[OH]D levels at and above the threshold level). The thick solid line represents a linear cause-effect relationship, while the thick dotted line represents a sigmoid shaped cause-effect relationship. We offer 2 hypothetical scenarios to illustrate the importance of these factors. For those at high baseline risk for the undesirable event, raising 25(OH)D from near-zero levels to above the threshold might produce a marked absolute risk reduction. In contrast, raising 25(OH)D from slightly low levels to above the threshold might produce a trivial absolute risk reduction, especially if the cause-effect relationship is sigmoid shaped and/or if the individual is at relatively low baseline risk for the undesirable event.

threshold, but that raising 25(OH)D levels to the threshold will bring such risks back to baseline. Also of importance, the thresholds at which physiological changes occur (eg, increases in PTH secretion) may or may not conform to the thresholds at which the risks for undesirable clinical outcomes become unacceptable.

In 2011, the Institute of Medicine (IOM; now the National Academy of Medicine) addressed Dietary Reference Intakes (DRIs, including Recommended Daily Allowances [RDAs]) for vitamin D at the population level. The IOM's Committee of scientific experts estimated that 25(OH)D concentrations of 16 ng/mL (40 nmol/L) and 20 ng/mL (50 nmol/L) would meet bone health needs in about 50% and 97.5% of the population, respectively (5-7). Said in another way: the IOM Committee estimated that 97.5% of the population do not need their 25(OH)D levels to be higher than 20 ng/mL to satisfy their bone health needs. (Like with any biological parameter, 25[OH]D levels sufficient for bone health needs are variable among individuals in a population.) In addition, the 2011 IOM committee raised concern that serum 25(OH)D greater than 50 ng/mL (125 nmol/L) may unacceptably increase adverse event risks, and that if RDAs were designed to achieve serum 25(OH)D concentrations of at least 20 ng/mL in 97.5% (ie, nearly all) of the population, some individuals would experience vitamin D–related adverse events (7).

Also in 2011, the Endocrine Society published a guideline titled "Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline" (2). Therein, the GDP—hereafter referenced as *2011 GDP*—advanced the concepts that 25(OH)D levels less than 20 ng/mL (50 nmol/L) represent vitamin D "deficiency," that 25(OH)D levels greater than 20 ng/mL but less than 30 ng/mL (75 nmol/L) represent vitamin D "insufficiency," and that 25(OH)D concentrations of at least 30 ng/mL represent vitamin D "sufficiency."

In keeping with best practices, the Endocrine Society reviews each of its CPGs at least once annually to identify when an update may be needed. In 2019, partly in response to recent and anticipated publication of large new randomized clinical trials (RCTs) of vitamin D, the Clinical Guidelines Committee (CGC) placed its 2011 vitamin D guideline in queue for an update. In essence, on the basis of emerging new evidence, the CGC determined that the 2011 CPG deserved reassessment using a strengthened guideline-development process (8).

A Critical Clinical Question: What Is the Most Appropriate *Actionable* 25(OH)D Threshold for Generally Healthy Individuals?

Expert consensus has generally held that 25(OH)D levels below 12 ng/mL (30 nmol/L) will too often be inadequate for optimal skeletal health and, thus, should always be considered deficient, while 25(OH)D concentrations above 30 ng/mL (75 nmol/L) should always be considered adequate (3). For clinicians, this yields a wide zone of uncertainty between 12 and 30 ng/mL, and the most appropriate 25(OH)D threshold to distinguish unacceptably low ("deficient," "insufficient") from adequate ("sufficient") 25(OH)D levels—in particular, *the 25(OH)D level below which clinicians should recommend vitamin D supplementation, or the "actionable" 25(OH)D threshold*—has been highly controversial (3, 9). Such controversy is reflected in 25(OH)D reference ranges offered by different clinical laboratories. For example, as written in the 2024 GDP's Evidence-to-Decision documentation:

> Another potential challenge relates to disagreement and confusion regarding "optimal" vitamin D levels (which in theory could vary by outcome). Most laboratories provide a "normal" reference range for 25(OH)D intended for the general population, and these ranges vary. For example, in one academic center in Boston, the reference range is 20 to 100 ng/mL with a disclaimer that "levels between 20 and 30 ng/mL are borderline and indicate the need for supplementation." In another academic center in Boston, the ranges are: "deficiency" < 20 ng/mL, "insufficiency" 20 to 29 ng/mL, "optimal" ≥ 30 ng/mL. In another US state (Michigan), hospitals have 3 different minimal values: 20, 25, & 30 ng/mL.

Indeed, at the time of this writing, both Quest Diagnostics and Labcorp offer a 30 to 100 ng/mL reference range for 25(OH)D, whether measured by immunoassay or mass spectrometry–based assay (10-13). In contrast, Mayo Clinic Laboratories webpages indicate that less than 10 ng/mL represents severe deficiency ("could be associated with osteomalacia or rickets"), 10 to 19 ng/mL represents mild to moderate deficiency ("may be associated with increased risk of osteoporosis or secondary hyperparathyroidism"), and 20 to 50 ng/mL

represents optimum levels ("optimum levels in the healthy population; patients with bone disease may benefit from higher levels within this range") (14).

Unsurprisingly, such dueling conceptions of acceptable 25(OH)D concentrations have yielded widespread uncertainty regarding which 25(OH)D concentrations justify clinical action—ie, the most appropriate *actionable 25(OH)D threshold*. According to the IOM Committee's 2011 analysis, only a small minority (~2.5%) of the generally healthy population will need 25(OH)D levels higher than 20 ng/mL to meet their bone health needs. In contrast, the 2011 Endocrine Society GDP indicated that 25(OH)D levels less than 30 ng/mL should be considered insufficient. If the IOM committee's analysis was correct, advocating for a 30 ng/mL threshold may promote unnecessary 25(OH)D screening, unnecessary vitamin D supplementation (beyond RDA), and unnecessary 25(OH)D monitoring, in addition to increasing the potential for vitamin D–related adverse events; each of these possibilities would increase health care costs. Conversely, if 30 ng/mL is the most appropriate actionable threshold, relying on vitamin D RDAs alone might leave easy-to-achieve benefits unrealized. The Society recognized that this issue has important implications for individuals, health care systems, and society.

Reassessments in Response to Important New Evidence

As described above, the CGC placed its vitamin D guideline in the queue for update in 2019, partly in response to the emergence of large new clinical trials of vitamin D. The 2024 GDP's scope, which was partly determined by the Society's guideline leadership, included the potential role of 25(OH)D testing for generally healthy populations. Such testing might include both of the following: (1) 25(OH)D testing to identify those with inadequate vitamin D stores (ie, individuals expected to benefit the most from vitamin D supplementation); and (2) 25(OH)D monitoring to confirm achievement of adequate vitamin D stores. Accordingly, the 2024 GDP prioritized four 25(OH)D threshold-related clinical questions with the following basic structure: should vitamin D supplementation vs no vitamin D supplementation be used for [population of interest] *only* when 25(OH)D levels are below a threshold? (Italics ours.) The populations of interest included adults younger than 50 years old, adults aged 50 to 74 years, adults at least 75 years old, and pregnant individuals.

How Should Actionable 25(OH)D Thresholds Be Derived?

The 2011 IOM Committee considered numerous potential health indicators (outcomes) that might inform their vitamin D DRIs. After consideration of several systematic evidence reviews, in addition to more recent evidence, the 2011 IOM Committee concluded that the then-available evidence for most of the potential indicators they considered—including those related to cancer, cardiovascular disease, falls, and infections—was not sufficient for DRI development. Thus, the IOM Committee relied on bone health indicators, including fractional intestinal calcium absorption, bone mineral content and bone mineral density (BMD), histopathological assessments of osteomalacia, risk of nutritional rickets, and fracture risk. The IOM Committee's conclusions included the following: fractional calcium absorption likely plateaus at a 25(OH)D level of 20 ng/mL; the risk for nutritional rickets is minimal at 25(OH)D levels between 12 and 20 ng/mL (assuming adequate calcium intake); and histopathologic evidence of osteomalacia appears to be rare with 25(OH)D levels greater than 20 ng/mL (5). In light of these and other findings, the IOM Committee determined that a 20 ng/mL 25(OH)D concentration is adequate for most individuals' bone health needs.

The 2011 Endocrine Society GDP described some of the data that informed its proposed definition of vitamin D sufficiency (2). The 2011 GDP highlighted a study in postmenopausal women suggesting a possible 45% to 65% increase in intestinal calcium absorption when 25(OH)D levels were raised from an average of 20 to 32 ng/mL (15). An inverse association between 25(OH)D and PTH concentrations is well known, and the 2011 GDP cited that some but not all studies suggest that PTH plateaus at 25(OH)D levels between 30 and 40 ng/mL (5, 16-18). The panel cited an assessment of National Health and Nutrition Examination Survey (NHANES) data indicating a correlation between higher serum 25(OH)D concentrations (roughly spanning 9 to 38 ng/mL) and higher BMD (19). They highlighted that, in one postmortem study, no pathological accumulation of osteoid was observed in those with 25(OH)D levels above 30 ng/mL (20). In addition, the 2011 GDP highlighted RCT meta-regression analyses suggesting that hip and nonvertebral antifracture efficacy is predicted by higher achieved 25(OH)D concentrations, and that antifracture effects may not be evident at achieved 25(OH)D levels less than 30 ng/mL (21, 22). The 2011 GDP judged that, in the absence of higher-quality evidence related to patient-important outcomes, these data, including the 25(OH)D levels at which PTH is normalized, could indirectly inform treatment decisions (2).

Importantly, many of the studies cited in support of specific 25(OH)D thresholds involved surrogate outcomes, such as apparent intestinal calcium absorption, PTH concentrations, and histopathologic evidence of bone mineralization defects. (As discussed further below, the use of surrogate outcomes rather than patient-important outcomes reduces certainty in the evidence.) In addition, many were observational studies that cannot establish causality. For example, in the Priemel study (20) cited by both the IOM Committee and the 2011 GDP, it is possible that factors other than 25(OH)D status (eg, calcium intake, general nutrition status) explained why mineralization defects were not observed in those with a 25(OH)D greater than 30 ng/mL. Moreover, the RCT meta-regression analyses cited by the 2011 CPG (21, 22) are subject to ecological fallacy, whereby inferences about 25(OH)D levels in individual study participants are made on the basis of group averages, and this can lead to misclassification bias. Moreover, it remains possible that variable study-design elements or different study-participant characteristics (other than achieved 25[OH]D levels) explained the apparent inter-trial variability in vitamin D efficacy.

As indicated by the 2011 GDP (2), a better way to establish an actionable 25(OH)D threshold is to confirm in clinical trials a putative threshold's ability to uniquely predict improvement in patient-important outcomes with vitamin D supplementation. Given the availability of new evidence, the 2024 GDP aspired to do just that.

Foundational Decisions Guiding the 2024 Guideline Development Panel's Approach

With the availability of new clinical trials, some of which reported outcomes in subgroups with 25(OH)D levels below a

threshold, the 2024 GDP sought to assess whether a 25(OH)D threshold would specifically predict clinically meaningful net benefits with vitamin D supplementation. Given that observational studies are susceptible to various forms of bias and confounding, the 2024 GDP made an a priori decision to focus primarily, if not exclusively, on RCTs. Moreover, the 2024 GDP determined that, whenever possible, it would restrict its outcome analyses to patient-important outcomes, and this decision deserves clarification.

Unless conditioned to do so, patients will not generally assign much if any importance to the avoidance of reduced intestinal calcium absorption or high PTH levels, as these phenomena by themselves do not materially impact individuals' day-to-day experiences. Similarly, unless conditioned to do so, patients will not assign much if any importance to the avoidance of low BMD, as low BMD per se does not cause symptoms. In contrast, patients and clinicians alike assign substantial importance to the avoidance of fragility fractures, which may result in pain, disability, medical expenses, etc. In this context, fragility fracture is a prime example of a patient-important outcome, and intestinal calcium absorption, PTH, and BMD are examples of surrogate outcomes. A panel's certainty in the evidence decreases when it relies on a surrogate outcome instead of a patient-important outcome, and said uncertainty typically varies as a function of the distance between the two along a (putative) causal chain (23).

Systematic Review Results and Panel Judgments

The 2024 GDP and its partners at the Mayo Clinic Evidence-Based Practice Center identified numerous RCTs of vitamin D that reported on patient-important outcomes (1, 24). As described in the 2024 guideline's Evidence-to-Decision documentation, the panel initially performed study subgroup analyses according to the average baseline 25(OH)D level in each trial: in no case was study-specific average baseline 25(OH)D a significant predictor of vitamin D's apparent impact on outcomes. However, since such analyses are subject to ecological fallacy, these initial study subgroup analyses were not included in the final systematic review report or in the guideline manuscript. Instead, to address these threshold-related questions, the panel limited its final assessment to available data in study subgroups with baseline 25(OH)D concentrations less than 20 to 24 ng/mL.

As described in the guideline and systematic review (1, 24), clinical trials with participants approximating 50 to 74 years did not disclose clear net benefit of vitamin D supplementation, including in subgroups with 25(OH)D levels below 20 to 24 ng/mL (Fig. 2). Accordingly, the GDP suggested against empiric vitamin D supplementation (beyond RDA) in the general population aged 50 to 74 years. The GDP also suggested against routine 25(OH)D testing in this group, in part because an appropriate actionable 25(OH)D level—ie, the 25(OH)D level below which vitamin D supplementation is expected to provide important net benefit—remains unknown.

Studies for which a majority of participants exceeded 75 years of age suggested a small but important mortality benefit, and risk reduction point estimates were not materially different in subgroups with 25(OH)D levels below 20 ng/mL (1, 24) (Fig. 2). Thus, it wasn't clear to the panel that the likely mortality benefit is restricted to those with 25(OH)D levels below a specific threshold. While one could speculate on the basis of Fig. 2 that fall risk reduction might possibly be greater in those with 25(OH)D less than 20 ng/mL (very imprecise estimate), and while it remains possible that vitamin D may reduce the risks of fracture and respiratory tract infection (RTI) in those with 25(OH)D less than 20 ng/mL (no data was available), such hypothetical scenarios would merely support the panel's suggestion for empiric vitamin D supplementation (beyond RDA) in this group. Thus, the panel suggested against routine 25(OH)D testing in the general population aged 75 years and older, largely because it was not clear that clinical action should be contingent on pre-supplementation 25(OH)D levels.

The 2024 GDP did not identify sufficient evidence to inform 25(OH)D threshold decisions in some groups of interest, including adults younger than 50 years and pregnant individuals. Available clinical trial evidence did not clearly support routine vitamin D supplementation (beyond RDA) for adults younger than age 50 years, regardless of baseline 25(OH)D levels. One small (n = 34) pilot study of generally healthy participants aged 18 to 52 years suggested a statistically significant beneficial impact of vitamin D on infections—mostly RTIs—in the exceptionally small (n = 4) subgroup with baseline 25(OH)D less than 16 ng/mL, but not in the larger-but-still-small subgroups defined by baseline 25(OH)D less than 20 ng/mL (n = 8), less than 24 ng/mL (n = 10), or less than 28 ng/mL (n = 17) (25). In contrast, a larger RCT (n = 322) did not indicate a beneficial impact of vitamin D on upper RTI, including in the subgroup of participants with baseline 25(OH)D levels less than 20 ng/mL (26). Relevant evidence was not available for the other outcomes of interest in this age group.

The panel did not identify clinical trials that reported on outcomes of interest in pregnant individuals with 25(OH)D levels below a threshold. Thus, it was unclear whether (likely) benefit during pregnancy was restricted to those with low 25(OH)D. Since it is possible that net benefit was also realized among study participants with higher baseline 25(OH)D levels, the panel reasoned that empiric vitamin D supplementation should generally proceed without regard to baseline 25(OH)D levels; such an approach accords with study procedures in the clinical trials the panel assessed.

To summarize, the 2024 GDP judged that available clinical trial evidence did not support the establishment of distinct 25(OH)D thresholds tied to outcome-specific benefits in the populations it examined. The panel was careful to avoid implying a denial of such thresholds; the panel merely expressed uncertainty regarding the most appropriate actionable 25(OH)D thresholds for clinical use.

An Illustrative Example: The VITamin D and OmegA-3 TriaL

Available clinical trial evidence was insufficient to satisfactorily address other potential 25(OH)D thresholds, including 30 ng/mL. However, the fracture-related analyses from the VITamin D and OmegA-3 TriaL (VITAL) are of potential interest in this regard (27). (If differential benefit on the basis of low baseline 25[OH]D is demonstrable for any patient-important outcome, one might hold greatest optimism for fractures.) VITAL was an RCT designed to assess the impact of vitamin D, n-3 fatty acids, or both on cardiovascular and cancer outcomes, and participants randomized to vitamin D

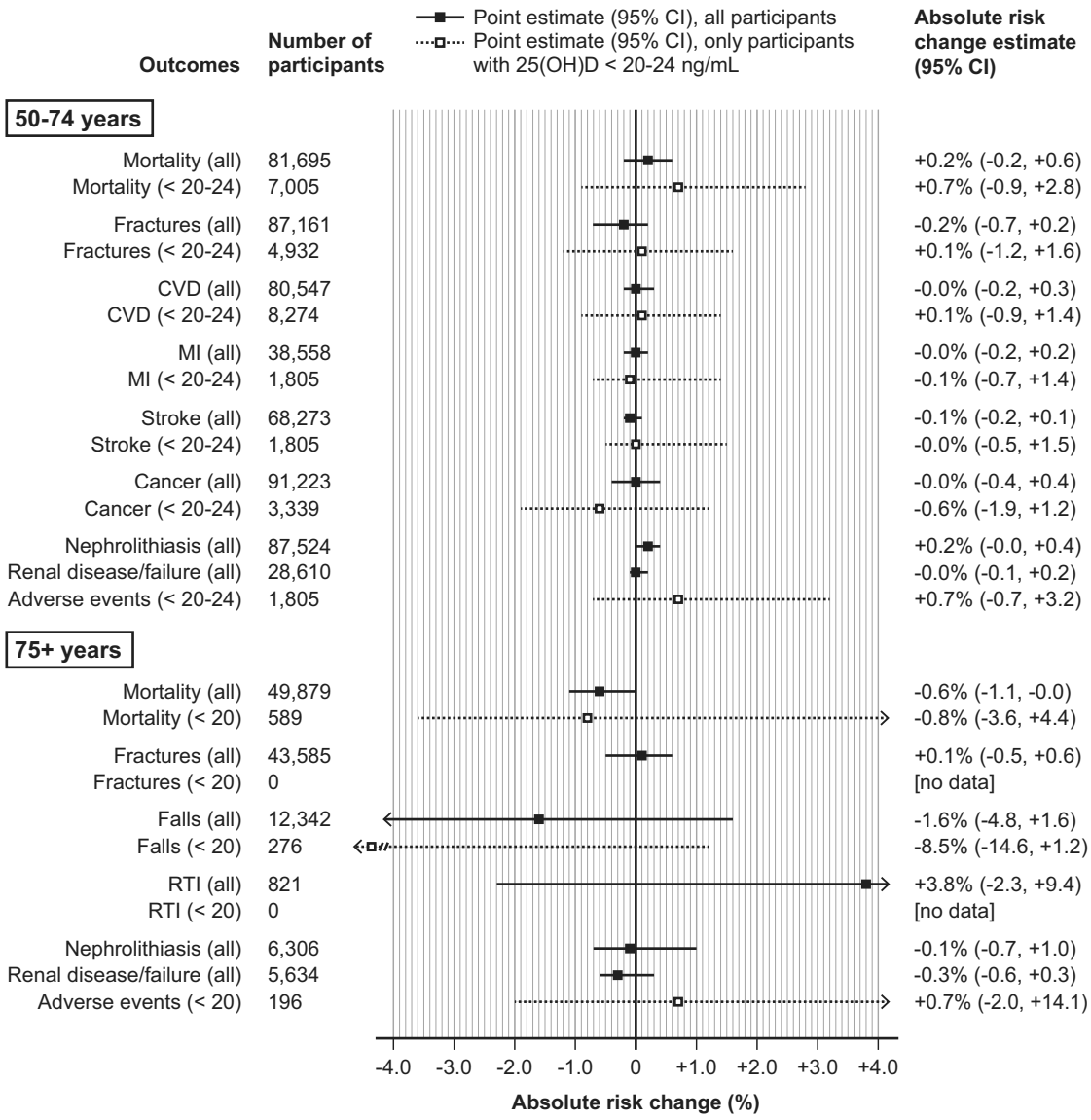

Figure 2. Estimated absolute risk changes attributable to vitamin D supplementation: all study participants vs study participants with baseline 25-hydroxyvitamin D concentrations below 20 to 24 ng/mL (50-60 nmol/L). These data are taken from the commissioned systematic reviews conducted by the Mayo Clinic Evidence-Based Practice Center (24). Abbreviations: 25(OH)D, 25-hydroxyvitamin D; RTI, respiratory tract infections.

received 2000 IU daily vitamin D3—expected to raise mean 25(OH)D to approximately 40 ng/mL (100 nmol/L)—for a median of 5.3 years. Exploratory analyses of the total fracture outcome (ie, incident fragility or non-fragility fracture regardless of location) did not imply differential benefits in subgroups defined by baseline 25(OH)D thresholds of 31, 24, or 12 ng/mL (Table 1).

This ancillary VITAL study illustrates some of the 2024 GDP's uncertainties in the evidence regarding 25(OH)D thresholds. The VITAL study was not specifically designed to evaluate fracture outcomes in those with low 25(OH)D at baseline, and median baseline 25(OH)D level was 31 ng/mL in the overall study population. Similarly, VITAL was not specifically powered to support the aforementioned subgroup analyses on the basis of baseline 25(OH)D concentration: the VITAL subgroup with 25(OH)D less than or equal to 24 ng/mL was relatively small (n = 4270), and the subgroup with 25(OH)D less than 12 ng/mL was especially small (n = 401). Although approximately 5% of all VITAL participants were taking osteoporosis medications at baseline, and around 10% had a history of fragility fracture, the overall study population was at low risk for incident fractures, and the baseline risks for fracture in the subgroups with low 25(OH)D is unclear. The duration of treatment (median 5.2 years for the overall cohort) may not have been long enough to identify important long-term differences. While calcium supplementation up to 1200 mg per day was permitted (and taken by approximately 20% of study participants), it was neither required nor standardized; this may be relevant given that the skeletal effects of vitamin D appear to be contingent on adequate calcium intake. It is also important to note that all VITAL participants—including those in the placebo group—were allowed to take up to 800 IU of vitamin D daily (at baseline approximately 43% of study participants were taking vitamin D). In this regard, however, the resulting comparisons in VITAL are not inconsistent with the 2024 GDP's assumption that all individuals should take the RDA for vitamin D

Table 1. Total fracture outcome estimates partitioned by baseline total 25-hydroxyvitamin D concentration

Group analyzed	Number of participants	Hazard ratio (95% CI), vitamin D vs placebo
All participants in the ancillary study of VITAL	25 871	0.98 (0.89-1.08)
Subgroup with 25(OH)D < 31 ng/mL (median)	**8430**	**1.02 (0.85-1.22)**
Subgroup with 25(OH)D ≥ 31 ng/mL (median)	8327	0.93 (0.80-1.08)
Subgroup with 25(OH)D ≤ 24 ng/mL (quartile 1)	**4270**	**1.04 (0.80-1.36)**
Subgroup with 25(OH)D 24.1 to 30.0 ng/mL (quartile 2)	**4104**	**0.98 (0.77-1.26)**
Subgroup with 25(OH)D 30.1 to 36.9 ng/mL (quartile 3)	4097	0.98 (0.78-1.23)
Subgroup with 25(OH)D ≥ 37.0 ng/mL (quartile 4)	4286	0.89 (0.73-1.10)
Subgroup with 25(OH)D < 12.0 ng/mL	**401**	**1.03 (0.36-2.95)**
Subgroup with 25(OH)D ≥ 12.0 ng/mL	16 356	0.97 (0.86-1.09)

Abbreviation: 25(OH)D, 25-hydroxyvitamin D. These results are from an ancillary study of the VITamin D and OmegA-3 TriaL (VITAL); adapted from LeBoff MS et al. *N Engl J Med*. 2022;387(4):299-309. © Massachusetts Medical Society (27). In approximately 65% of study participants, baseline total 25(OH)D level was assessed using a liquid chromatography–tandem mass spectrometry assay calibrated to Centers for Disease Control and Prevention (CDC) standards. The subgroups likely to be of greatest interest are shown in bold text. To convert ng/mL to nmol/L, multiply by 2.496.

(ie, 600 IU/day for those aged 50 to 70 years, 800 IU/day for those older than 70 years).

Regarding 25(OH)D Screening and Monitoring in Generally Healthy Persons

The panel reasoned that if clinical trials supported the intuition that net benefit with vitamin D *specifically* accrues to those with 25(OH)D concentrations below a threshold, then it would potentially (but not necessarily) be important to perform 25(OH)D testing to identify those individuals. In contrast, if no net benefit is apparent with vitamin D regardless of baseline 25(OH)D concentrations, or if material net benefit does not appear to be *restricted* to those with low baseline 25(OH)D concentrations (ie, if important net benefit could also be realized by those with higher baseline 25[OH]D levels), then baseline 25(OH)D screening and 25(OH)D monitoring might be unnecessary. The panel recognized that putative thresholds could vary according to the outcomes of interest, and the panel remained open to the idea that some outcomes may not demonstrate the same kinds of ceiling effects presumed to occur with calcium homeostasis and skeletal outcomes. That is, for some outcomes, exogenous vitamin D could represent a form of pharmacologic treatment rather than simply vitamin D "repletion." As described in the preceding section, available clinical trial evidence did not clearly indicate 25(OH)D thresholds that specifically predict net benefit with vitamin D supplementation beyond the IOM-determined RDAs, and this informed the 2024 GDP's suggestions against routine 25(OH)D measurement in the populations they assessed.

Endocrine Society's Response to the 2024 Vitamin D Guideline

Informed by the 2024 GDP's analyses and judgments, *the Endocrine Society no longer endorses its previously proposed definitions of vitamin D "sufficiency" (25[OH]D at least 30 ng/mL) and vitamin D "insufficiency" (25[OH]D greater than 20 ng/mL but lower than 30 ng/mL)*. This is primarily because available clinical trial evidence does not clearly indicate that, in generally health persons, net benefit with vitamin D is specifically predicted by 25(OH)D concentrations below 20 to 24 ng/mL. With these findings in mind, and in light of the prevailing threshold concept of vitamin D requirements, it seems difficult to strongly defend the notion that a 25(OH)D threshold higher than 20 to 24 ng/mL (eg, 30 ng/mL) will better predict net benefit with vitamin D supplementation in generally healthy individuals. However, we fully agree with the 2024 GDP that available evidence is incomplete, and many unknowns remain.

As implied by the title of this Guideline Communication, the Endocrine Society's updated position regarding the clinical utility of 25(OH)D thresholds in healthy persons is one of epistemic humility, mirroring that of the 2024 GDP. The Society's withdrawal of 2 prior endorsements—namely, of the vitamin D "sufficiency" and "insufficiency" definitions advanced in the 2011 guideline—reflects its desire to follow the best available scientific evidence, even when it means reversing long-held positions. Like the 2024 GDP, we advocate for additional research to assess whether discrete 25(OH)D thresholds will specifically predict important net benefit with vitamin D supplementation.

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Disclosures

C.R.M. and M.E.M. are member leaders in the Endocrine Society, and M.D.C. and R.W.L. are employed by the Endocrine Society. The authors have no other potential dualities of interest to declare.

Data Availability

Data sharing is not applicable to this article as no datasets were generated for the current manuscript.

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