Original Article

Prevalence of Inadequate Vitamin D Status in Ambulatory Thai Patients with Cardiometabolic Disorders Who Had and Had No Vitamin D Supplementation

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Background: Data regarding the prevalence of inadequate vitamin D status in ambulatory Thai population with cardiometabolic disorders (CMDs) are scarce.

Objective: To investigate the prevalence of hypovitaminosis D in ambulatory Thai patients with CMDs with and without vitamin D supplementation (DS).

Materials and Methods: This descriptive cross-sectional study randomly recruited patients with one or more CMDs that attended the outpatient clinic during December 2016 to May 2017. CMDs included type 2 diabetes (T2DM), hypertension (HT), dyslipidemia (DLP), and coronary artery disease (CAD). Serum 25-hydroxyvitamin D (25-OHD) levels were measured by electrochemiluminescence immunoassay.

Results: Four hundred and forty-four patients were included. Mean age was 65.79±10.12 years, 72.3% were aged >60 years, and 35.1% were male. CMDs included T2DM (75.9%), prediabetes (11.7%), HT (72.1%), DLP (88.3%), and CAD (7.4%). Mean serum 25-OHD was 26.12±10.10 ng/mL, with 29.7%, 42.1%, 25.5%, and 2.7% of patients having serum 25-OHD level of ≥30, 20-<30, 10-19.9, and <10 ng/mL, respectively. Twenty percent of patients had DS. Prevalence of 25-OHD <20 ng/mL and <30 ng/mL were lower in patients with DS than in patients without DS (19.1% *vs.* 30.6% and 61.7% *vs.* 72.6%, respectively, both p <0.05). Among the 350 patients without DS, prevalence of 25-OHD <10 ng/mL was higher in patients with HT and patients with CAD than in those without (3.9% *vs*. 0.0% and 14.8% *vs.* 1.9%, respectively, both p<0.05). Male patients had higher serum 25-OHD levels and lower prevalence of 25-OHD <30 ng/mL and 25-OHD <20 ng/mL than did the female patients (29.10±11.61 vs. 23.76±8.69 ng/mL, 57.4% *vs.* 81.4%, and 20.9% *vs.* 36.2%, respectively, all p <0.005). Non-elderly patients (age ≤60) had lower serum 25-OHD levels and higher prevalence of 25-OHD <30 ng/mL and 25-OHD <20 ng/mL than did the elderly patients (age >60) (23.23±9.20 *vs.* 26.81±10.41 ng/mL, 82.1% *vs.* 68.4%, and 43.4% *vs.* 25.0%, respectively, all p<0.01).

Conclusion: Prevalence of inadequate vitamin D status in ambulatory Thai patients with one or more CMDs was high in patients with and without DS. It was higher in patients without DS than in both patients with DS and all patients regardless of DS status. Factors associated with higher prevalence of inadequate vitamin D status in patients with CMDs included HT, CAD, age ≤60 years, and female gender.

Keywords: Thailand prevalence, Inadequate vitamin D status, Ambulatory Thai patients, Cardiometabolic disorders, Vitamin D supplementation

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In addition to calcium and bone metabolism-related problems, vitamin D deficiency (D-DEF) can cause musculoskeletal diseases like growth retardation, rickets, osteomalacia, and osteoporosis, and non-musculoskeletal diseases like infections, autoimmune diseases, cancers, and metabolic diseases[1]. In order to find solutions to health related problems caused by D-DEF, it is necessary to know the prevalence of vitamin D insufficiency (D-INSUFF) and D-DEF in populations, and to identify individuals, subpopulations, and populations that are at risk for developing these disorders. Over the past two decades, a number of studies have reported different rates of prevalence of D-INSUFF and D-DEF in various populations worldwide[2].

In Thailand, which is a tropical country that is bathed in sunlight most days of the year, previous studies reported rates of vitamin D insufficiency ranging from 13.6% to 64.6%[3-8]. The large disparity in

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the prevalence of insufficient vitamin D status among Thai population might be due to differences in the cut-off serum 25-hydroxyvitamin D (25-OHD) levels used for determining vitamin D status among studies. In addition, some of those studies did not clearly state whether their subjects had medical problems, or whether their patients were taking medications known to directly or indirectly affect vitamin D metabolism (particularly vitamin D supplementation) at the time of their study. Studies that fail to differentiate patients that are from those that are not taking vitamin D supplementation may underestimate the real prevalence of inadequate vitamin D status. Data relating to the prevalence of D-INSUFF and D-DEF in Thai populations with specific medical problems are limited. Among all of the cardiometabolic disorders (CMDs), type 2 diabetes mellitus (T2DM), hypertension (HT), dyslipidemia (DLP), and coronary artery disease (CAD) are the conditions in which inadequate vitamin D status has been reported[9-13]. Accordingly, the aim of this study was to investigate the prevalence of inadequate vitamin D status in ambulatory Thai patients with cardiometabolic disorders with and without vitamin D supplementation.

Materials and Methods

Patient recruitment

This descriptive cross-sectional study randomly recruited ambulatory Thai patients with one or more CMDs that attended the outpatient clinic of the Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand for regularly scheduled ongoing care and treatment during December 2016 to May 2017. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 163/2016). This study complied with the principles set forth in the Declaration of Helsinki (1964) and all of its subsequent amendments. Written informed consent was obtained from all study participants.

Each patient was interviewed for medical history, medications, health status, daily activities, and any possibility of receiving direct or indirect vitamin D supplementation. Included patients met all of the following inclusion criteria: 1) well-treated and stable CMDs; 2) attends regularly scheduled appointments at our outpatient clinic; 3) doing well generally and able to perform normal daily indoor and outdoor activities; and 4) having no conditions known to directly affect vitamin D metabolism, including inability to perform normal daily activities, current anticonvulsant therapy, corticosteroid therapy, inadequate or excessive thyroxine replacement, untreated hyperthyroidism, inflammatory bowel diseases, chronic diarrhea, liver diseases defined by serum aspartate aminotransferase and alanine aminotransferase of >3 times the upper normal limit, kidney diseases defined by eGFR of <30 mL/min/1.73 m^2 calculated by the Chronic Kidney Disease Epidemiology Collaboration equation[14], overt hyperparathyroidism or hypoparathyroidism, and granulomatous diseases. CMDs encountered in this study included T2DM, prediabetes, HT, DLP, and CAD. Type 2 diabetes mellitus was diagnosed by the presence of fasting plasma glucose levels of ≥126 mg/dL and/or hemoglobin A1C levels of ≥6.5%, or being treated with glucose-lowering agents. Prediabetes was defined by the presence of fasting plasma glucose levels of 100-125 mg/dL. Hypertension was diagnosed by the presence of blood pressure of >140/90 mmHg or being treated with antihypertensive agents. Dyslipidemia was defined by the presence of one or more of the following: serum total cholesterol levels of >250 mg/dL, serum triglyceride >250 mg/dL, and/or serum HDL-cholesterol of <40 mg/dL. Coronary artery disease was diagnosed according to the results of one or more of the following: electrocardiogram, transthoracic echocardiogram, and coronary angiography. Blood samples were collected for measurement of serum 25-OHD levels.

Serum 25-OHD measurement

Serum 25-OHD levels were measured by electrochemiluminescence (ECLIA) immunoassay using an Elecsys 2010 automated immunoassay analyzer (Roche Diagnostics, Risch-Rotkreuz, Switzerland) that measures both 25-hydroxyergocalciferol ($25\text{-}OHD_2$) and 25-hydroxycholecalciferol ($25\text{-}OHD_3$). Results were reported in nanograms per milliliter (ng/mL). All serum 25-OHD measurements were performed in a laboratory accredited by the International Organization for Standardization (ISO 15189), and were monitored using the Randox International Quality Assessment Scheme (RIQAS). Serum 25-OHD levels of 20 to <30 ng/mL, 10 to <20 ng/mL, and <10 ng/mL were defined as vitamin D insufficiency (D-INSUFF), vitamin D deficiency (D-DEF)[15,16], and severe vitamin D deficiency (D-DEF)[15-17], respectively.

Statistical analysis

SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA) was used to perform all data analyses in this

study. Results are expressed as percentage, number and percentage, range, or mean ± standard deviation. Chi-square test or Fisher exact test were used to compare prevalence of D-INSUFF and D-DEF between groups. Independent samples *t*-test was used to compare normally distributed data between groups. A *p*-value less than 0.05 was regarded as being statistically significant.

Results

A total of 444 well-managed and stable ambulatory Thai patients with one or more CMDs were studied for vitamin D status. Demographic characteristics, vitamin D status, and clinical characteristics of all patients, and vitamin D status of patients that did and that did not receive vitamin D supplementation were shown in Table 1. The mean age was 65.79±10.12 years (range: 34-92), 72.3% were aged >60 years, and 35.1% were male. The mean eGFR was 71.70±20.25 mL/min/1.73 m^2 (range: 30.82-119.76). Just over thirty percent of patients had an eGFR of <60 mL/min/1.73 m^2. Patient underlying CMDs included T2DM (75.9%), prediabetes (11.7%), HT (72.1%), DLP (88.3%), and CAD (7.4%). Serum 25-OHD levels ranged from 3.00-70.00 ng/mL (mean: 26.12±10.10 ng/mL). Regarding vitamin D status, 29.7% of patients had sufficient vitamin D status, 42.1% had serum 25-OHD of 20 to <30 ng/mL, 25.5% had serum 25-OHD of 10 to <20 ng/mL, and 2.7% had serum 25-OHD of <10 ng/mL. Ninety-four of our patients (21.2%) had vitamin D supplementation, and 350 (78.8%) did not. Prevalence of serum 25-OHD <20 ng/mL and 25-OHD <30 ng/mL was significantly lower in patients with vitamin D supplementation than in patients without vitamin D supplemention (19.1% *vs.* 30.6%; $p = 0.029$ and 61.7% *vs.* 72.6%; $p = 0.041$, respectively) (Table 2). However, there was no difference in mean serum 25-OHD between patients with and without vitamin D supplementation (27.56±9.72 *vs.* 25.72±10.18 ng/mL; $p>0.05$).

To determine the real prevalence of inadequate vitamin D status, 94 patients with history of vitamin D supplementation were excluded from the analysis. Among the 350 patients without vitamin D supplementation, the prevalence of serum 25-OHD <10 ng/mL was significantly higher in patients with HT than in patients without HT (3.9% *vs*. 0%; $p = 0.05$). Similarly, the prevalence of serum 25-OHD <10 ng/mL was significantly higher in patients with CAD than in patients with no CAD (14.8% *vs*. 1.9%; $p<0.001$) (Table 3). Serum 25-OHD levels and prevalence of inadequate vitamin D status using different cut-off values in patients with different combinations of underlying CMDs that received no vitamin D supplementation are shown in Table 4. Patients who had coexisting T2DM, HT, and CAD had significantly higher prevalence of serum 25-OHD <10 ng/mL than those who had other combinations of CMDs (33.3% *vs.* 2.6%; $p<0.001$). Moreover, patients that had coexisting T2DM, HT, DLP, and CAD had significantly higher prevalence of serum 25-OHD <10 ng/mL than patients who had other combinations of CMDs (17.6% *vs.* 2.1%; $p<0.001$).

When male and female patients without vitamin D supplementation were compared, male patients had significantly higher serum 25-OHD levels than female patients (29.10±11.61 *vs.* 23.76±8.69 ng/mL; $p<0.001$) (Table 5). In addition, the prevalence of serum 25-OHD <30 ng/mL and 25-OHD <20 ng/mL were significantly lower in male patients than in female patients (57.4% *vs.* 81.4%; $p<0.001$ and 20.9% *vs.* 36.2%; $p = 0.003$, respectively). When patients were subcategorized into non-elderly patients (age ≤60 years) and elderly patients (age >60 years), non-elderly male patients tended to have higher serum 25-OHD levels than non-elderly female patients, and they had significantly lower prevalence of serum 25-OHD <30 ng/mL than non-elderly female patients (25.46±8.99 *vs.* 21.99±9.15 ng/mL; $p = 0.062$ and 68.2% *vs.* 88.2%; $p = 0.027$, respectively) (Table 5). Elderly male patients had higher serum 25-OHD levels, and lower prevalence of serum 25-OHD <30 ng/mL and 25-OHD <20 ng/mL than elderly female patients (30.62±12.27 *vs.* 24.55±8.39 ng/mL, 51.6% *vs.* 78.4%, and 14.3% *vs.* 31.4%, respectively; all $p<0.005$). There was no significant difference in the prevalence of serum 25-OHD <10 ng/mL between male and female patients in the all patients, non-elderly, and elderly subgroups (Table 5).

When non-elderly and elderly patients without vitamin D supplementation were compared, non-elderly patients had lower serum 25-OHD levels than elderly patients (23.23±9.20 *vs.* 26.81±10.41 ng/mL; $p = 0.002$) (Table 6). In addition, the prevalence of serum 25-OHD <30 ng/mL and 25-OHD <20 ng/mL were higher in non-elderly patients than in the elderly patients (82.1% *vs.* 68.4% and 43.4% *vs.* 25.0%, respectively; both $p<0.01$). Non-elderly male patients had significantly lower serum 25-OHD levels and higher prevalence of serum 25-OHD <30 ng/mL and 25-OHD <20 ng/mL than elderly male patients (25.46±8.99 *vs.* 30.62±12.27 ng/mL, 71.1%

Table 1. Demographic characteristics, vitamin D status, and clinical characteristics of all patients, and vitamin D status of patients that did and that did not receive vitamin D supplementation

Characteristics	Mean±SD or n (%)	Range (min–max)
Age (years)	65.79±10.12	(34 to 92)
Elderly patients (age >60 years)	321 (72.3%)	
Male gender	156 (35.1%)	
Having vitamin D supplementation	94 (21.2%)	
All patients	(N=444; 100%)	
Serum 25-OHD (ng/mL)	26.12±10.10	(3.00 to 70.00)
25-OHD ≥30 ng/mL	132 (29.7%)	
25-OHD = 20 to <30 ng/mL	187 (42.1%)	
25-OHD = 10 to <20 ng/mL	113 (25.5%)	
25-OHD <10 ng/mL	12 (2.7%)	
Patients with vitamin D supplementation	(n=94; 21.2%)	
Serum 25-OHD (ng/mL)	27.56±9.72	(11.74 to 45.71)
25-OHD ≥30 ng/mL	36 (38.3%)	
25-OHD = 20 to <30 ng/mL	40 (42.6%)	
25-OHD = 10 to <20 ng/mL	16 (17.0%)	
25-OHD <10 ng/mL	2 (2.1%)	
Patients without vitamin D supplementation	(n=350; 78.8%)	
Serum 25-OHD (ng/mL)	25.72±10.18	(3.00 to 70.00)
25-OHD ≥30 ng/mL	96 (27.4%)	
25-OHD = 20 to <30 ng/mL	147 (42.0%)	
25-OHD = 10 to <20 ng/mL	97 (27.7%)	
25-OHD <10 ng/mL	10 (2.9%)	
Underlying diseases		
Type 2 diabetes mellitus	337 (75.9%)	
Prediabetes	52 (11.7%)	
Hypertension	320 (72.1%)	
Dyslipidemia	392 (88.3%)	
Coronary artery disease	33 (7.4%)	

Abbreviations: SD, standard deviation; serum 25-OHD, serum 25-hydroxyvitamin D

Table 2. Vitamin D status in patients with cardiometabolic disorders compared between patients with and without vitamin D supplementation

Patients	Serum 25-OHD (ng/mL) Mean±SD	25-OHD <10 ng/mL n (%)	25-OHD <20 ng/mL n (%)	25-OHD <30 ng/mL n (%)
All patients (N=444)	26.12±10.10	12 (2.7%)	125 (28.2%)	254 (70.3%)
Patients with vitamin D supplementation (n=94; 21.2%)	27.56±9.72	2 (2.1%)	18 (19.1%)[a]	58 (61.7%)[b]
Patients without vitamin D supplementation (n=350; 78.8%)	25.72±10.18	10 (2.9%)	107(30.6%)[a]	253 (72.6%)[b]

A *p*-value<0.05 indicates statistical significance

[a] denotes statistically significant difference between patients with and without vitamin D supplementation (p=0.029)

[b] denotes statistically significant difference between patients with and without vitamin D supplementation (p=0.041)

Abbreviations: serum 25-OHD, serum 25-hydroxyvitamin D; SD, standard deviation

Table 3. Vitamin D status in 350 patients with cardiometabolic disorders that did not receive vitamin D supplementation stratified by specific disorders

Metabolic disorder	n (%)	Serum 25-OHD (ng/mL) Mean±SD	25-OHD <10 ng/mL n (%)	25-OHD <20 ng/mL n (%)	25-OHD <30 ng/mL n (%)
All patients	350 (100%)	25.72±10.18	10 (2.9%)	107 (30.6%)	254 (72.6%)
Type 2 diabetes mellitus	264 (75.4%)	25.85±10.33	9 (3.4%)	78 (29.5%)	189 (71.6%)
Prediabetes	40 (11.4%)	25.23±8.32	1 (2.5%)	12 (30.0%)	32 (80.0%)
No diabetes mellitus	46 (13.2%)	25.46±10.99	0 (0.0%)	17 (37.0%)	33 (71.7%)
Hypertension	255 (72.9%)	25.85±10.45	10 (3.9%)[a]	74 (29.0%)	186 (72.9%)
No hypertension	95 (27.1%)	25.65±9.46	0 (0.0%)[a]	31 (32.6%)	66 (69.5%)
Dyslipidemia	309 (88.3%)	25.81±10.14	8 (2.6%)	93 (30.1%)	223 (72.2%)
No dyslipidemia	41 (11.7%)	25.63±10.61	2 (4.9%)	12 (29.3%)	29 (70.7%)
Coronary artery disease	27 (7.7%)	26.15±13.93	4 (14.8%)[b]	9 (33.3%)	18 (66.7%)
No coronary artery disease	323 (92.3%)	25.76±9.82	6 (1.9%)[b]	96 (29.7%)	234 (72.4%)

A *p*-value<0.05 indicates statistical significance

[a] denotes statistically significant difference between patients with and without HT (p=0.05)

[b] denotes statistically significant difference between patients with and without coronary artery disease (p<0.001)

Abbreviations: serum 25-OHD, serum 25-hydroxyvitamin D; SD, standard deviation

Table 4. Vitamin D status in 350 patients with multiple cardiometabolic disorders that did not receive vitamin D supplementation

Cardiometabolic disorder combinations	n (%)	Serum 25-OHD (ng/mL) Mean±SD	25-OHD <10 ng/mL n (%)/n (%)	25-OHD <20 ng/mL n (%)/n (%)	25-OHD <30 ng/mL n (%)/n (%)
All patients	350 (100%)	25.72±10.18	12 (2.9%)	125 (28.2%)	254 (72.6%)
T2DM+HT	13 (3.7%)	27.06±8.75	0 (0%)/ 10 (3.0%)	3 (23.1%)/ 104 (30.9%)	10 (76.9%)/ 244 (72.4%)
T2DM+DLP	47 (13.4%)	26.05±9.83	0 (0%)/ 10 (3.3%)	12 (25.5%)/ 95 (31.4%)	33 (70.2%)/ 221 (72.9%)
T2DM+CAD	0 (0.0%)	-	-	-	-
HT+DLP	35 (10.0%)	25.75±8.52	0 (0%)/ 10 (3.2%)	8 (22.9%)/ 99 (31.4%)	25 (71.4%)/ 229 (72.7%)
HT+CAD	0 (0.0%)	-	-	-	-
DLP+CAD	0 (0.0%)	-	-	-	-
T2DM+HT+DLP	169 (48.3%)	25.85±10.20	5 (3.0%)/ 5 (2.8%)	50 (29.6%)/ 57 (31.5%)	123 (72.8%)/ 131 (72.4%)
T2DM+HT+CAD	3 (0.9%)	23.64±17.32	1 (33.3%)/ 9 (2.6%)[a]	1 (33.3%)/ 106 (30.5%)	2 (66.7%)/ 252 (72.6%)
T2DM+DLP+CAD	3 (0.9%)	20.99±9.70	0 (0%)/ 10 (2.9%)	1 (33.3%)/ 106 (30.5%)	2 (66.7%)/ 252(72.6%)
HT+DLP+CAD	4 (1.1%)	32.97±16.16	0 (0%)/ 10 (2.9%)	1(25.0%)/ 106(30.6%)	2 (50.0%)/ 252 (72.8%)
T2DM+HT+DLP+CAD	17 (4.9%)	25.90±14.12	3 (17.6%)/ 7 (2.1%)[b]	6(35.3%)/ 101(30.3%)	12 (70.6%)/ 242 (72.7%)

n (%)/ n (%) = number and (proportion) of patients with combination of diseases/ number and (proportion) of patients without combination of diseases

A *p*-value<0.05 indicates statistical significance

[a, b] denotes statistically significant differences between patients with and without stated multiple underlying diseases (p<0.001)

Abbreviations: serum 25-OHD, serum 25-hydroxyvitamin D; SD, standard deviation; T2DM, type 2 diabetes mellitus; HT, hypertension; DLP, dyslipidemia; CAD, coronary artery disease

Table 5. Vitamin D status stratified by age group compared between male and female patients with cardiometabolic disorders that did not receive vitamin D supplementation

Patient Group	Serum 25-OHD status	Male (n = 129) Mean±SD or n (%)	Female (n = 221) Mean±SD or n (%)	***p*-value**
All patients	Serum 25-OHD levels (ng/mL)	29.10±11.61	23.76±8.69	<0.001
	25-OHD <30 ng/mL	74 (57.4%)	180 (81.4%)	<0.001
	25-OHD <20 ng/mL	27 (20.9%)	80 (36.2%)	0.003
	25-OHD <10 ng/mL	2 (1.6%)	8 (3.6%)	0.262
Non-elderly patients	Serum 25-OHD levels (ng/mL)	25.46±8.99	21.99±9.15	0.062[a]
(age ≤60; male: n = 38, female: n = 68)	25-OHD <30 ng/mL	27 (71.1%)	60 (88.2%)	0.027
	25-OHD <20 ng/mL	14 (36.8%)	32 (47.1%)	0.309
	25-OHD <10 ng/mL	0 (0.0%)	3 (4.4%)	0.189
Elderly patients	Serum 25-OHD levels (ng/mL)	30.62±12.27	24.55±8.39	<0.001
(age >60; male: n = 91, female: n = 153)	25-OHD <30 ng/mL	47 (51.6%)	120 (78.4%)	<0.001
	25-OHD <20 ng/mL	13 (14.3%)	48 (31.4%)	0.003
	25-OHD <10 ng/mL	2 (2.2%)	5 (3.3%)	0.628

A *p*-value<0.05 indicates statistical significance

[a] denotes factor with trend towards statistically significant difference between male and female patients

Abbreviations: serum 25-OHD, serum 25-hydroxyvitamin D; SD, standard deviation

Table 6. Vitamin D status stratified by gender compared between non-elderly and elderly patients with cardiometabolic disorders that did not receive vitamin D supplementation

Patient group	Serum vitamin D status	Non-elderly patients (age ≤60; n=106) Mean±SD or n (%)	Elderly patients (age >60; n = 244) Mean±SD or n (%)	***p*-value**
All patients	Serum 25-OHD levels (ng/mL)	23.23±9.20	26.81±10.41	0.002
	25-OHD <30 ng/mL	87 (82.1%)	167 (68.4%)	0.009
	25-OHD <20 ng/mL	46 (43.4%)	61 (25.0%)	0.001
	25-OHD <10 ng/mL	3 (2.8%)	7 (2.9%)	0.984
Male (non-elderly: n = 38, elderly: n = 91)	Serum 25-OHD levels (ng/mL)	25.46±8.99	30.62±12.27	0.021
	25-OHD <30 ng/mL	27 (71.1%)	47 (51.6%)	0.042
	25-OHD <20 ng/mL	14 (36.8%)	13 (14.3%)	0.004
	25-OHD <10 ng/mL	0 (0.0%)	2 (2.2%)	0.357
Female (non-elderly: n = 68, elderly n = 153)	Serum 25-OHD levels (ng/mL)	21.99±9.15	24.55±8.39	0.043
	25-OHD <30 ng/mL	60 (88.2%)	120 (78.4%)	0.084
	25-OHD <20 ng/mL	32 (47.1%)	48 (31.4%)	0.025
	25-OHD <10 ng/mL	3 (4.4%)	5 (3.3%)	0.674

A *p*-value<0.05 indicates statistical significance

Abbreviations: SD, standard deviation; serum 25-OHD, serum 25-hydroxyvitamin D

vs. 51.6%, and 36.8% *vs*. 14.3%, respectively; all $p<0.05$) (Table 6). Non-elderly female patients had significantly lower serum 25-OHD levels and higher prevalence of serum 25-OHD <20 ng/mL than elderly female patients (21.99±9.15 *vs*. 24.55±8.39 ng/mL and 47.1% *vs*. 31.4%, respectively; both $p<0.05$) (Table 6). No significant difference in the prevalence of serum 25-OHD <30 ng/mL was observed between non-elderly and elderly patients in the female subgroup. Moreover, no significant difference in the prevalence of serum 25-OHD <10 ng/mL was observed between non-elderly and elderly patients among the all patients, male patient, and female patient subgroups.

Discussion

Several clinical practice guidelines and experts have recommended different serum 25-OHD cut-off values for determining vitamin D status[15-19]. The Institution of Medicine 2011[15] and The Endocrine Society Clinical Practice Guideline 2011[16] defined D-INSUFF and D-DEF as serum 25-OHD levels of 21-29 ng/mL and lower than 20 ng/mL, respectively. Those recommendations were based on evidence from previous laboratory and clinical studies that showed that serum 25-OHD levels were inversely related to serum PTH levels until serum 25-OHD reaches 20 ng/mL. They also reported that serum 25-OHD levels of >30 ng/mL are not consistently associated with increased benefit relative to PTH suppression and incremental increase in $1,25(OH)_2D$ level[15,16,18]. Several factors are known to affect vitamin D status, including sunlight exposure; skin pigmentation; dietary vitamin D intake; vitamin D supplementation; genetic predisposition; medications, such as phenytoin, rifampicin, and corticosteroids; and, underlying diseases or conditions, such as obesity, liver and kidney diseases, intestinal malabsorption, granulomatous diseases, hypoparathyroidism, and hyperparathyroidism[20].

The prevalence of insufficient vitamin D status reported in different subgroups of Thai population ranged from 13.6% to as high as 64.6%[3-8]. This large difference in prevalence of insufficient vitamin D status among Thai population may be due to differences in the serum 25-OHD cut-off levels used for determining vitamin D status; characteristics of the studied population, such as age, gender, daily activities, and geographical areas; and lack of information relative to participant health status and medications (particularly vitamin D supplementation) at the time of the study that could lead to inhomogeneity within the studied population. Data specific to the prevalence of D-DEF and D-INSUFF in Thai population with specific medical problems and no vitamin D supplementation are lacking. CMDs, such as T2DM, HT, DLP, and CAD, are the commonly reported medical problems in which insufficient vitamin D status has been reported[9-13]. To the best of our knowledge and based on our review of the literature, this is the first descriptive study to investigate the prevalence of D-DEF and D-INSUFF in ambulatory Thai medical patients with well-treated CMDs and no vitamin D supplementation. In the present study, serum 25-OHD levels of <30 ng/mL and <20 ng/mL were used to define and determine D-INSUFF and D-DEF status, respectively, because most studies in the prevalence of D-INSUFF and D-DEF worldwide (including Thailand) have used these cut-off values. The fact that these values are widely used enables us to compare our results with those reported in other studies.

Comparison of the prevalence of inadequate vitamin D status in non-vitamin D supplemented patients with CMDs to previous vitamin D studies conducted in Thailand

Previous studies in Thailand reported different rates of prevalence of D-INSUFF and D-DEF in different subgroups of Thai population using different serum 25-OHD cut-off levels (Table 7). One large study in 2011 by Chailurkit, et al in 2,641 subjects randomly sampled from 21,960 subjects (age range: 15 to 98 years) who participated in the Thai 4th National Health Examination Survey during August 2008 to March 2009[3] showed the prevalence of D-INSUFF (serum 25-OHD level <30 ng/mL) by geographic region to be 66.7%, 43.1%, 39.1%, 34.2%, and 43.8% in the Bangkok, central, northern, northeastern, and southern regions of Thailand, respectively[3]. The prevalence of D-INSUFF reported in Chailurkit's study in Bangkok was comparable to that of the 70.3% rate observed in our study using the same serum 25-OHD cut-off level of 30 ng/mL (75 nmol/L). Chailurkit's study also classified subjects into subgroups according to age, body mass index (<25 *vs*. ≥25 kg/m^2), municipal area (rural *vs*. urban), and religion (Muslim *vs*. non-Muslim)[3]. That study also showed that subjects aged <60 years had mean 25-OHD levels lower than elderly subjects aged >60 years (age 15-29, 74.4±0.9 nmol/L; age 30-44, 79.9±1.1 nmol/L; and, age 45-59, 80.6±1.0 nmol/L *vs*. age 60-69, 85.1±1.0 nmol/L; age 70-79, 88.6±1.2 nmol/L; and, age >80, 88.2±1.4 nmol/L).[3]

Table 7. Summary of prevalence of inadequate vitamin D status in different population subgroups in Thailand

Authors	Year	Sample size	Type of population	Prevalence of inadequate vitamin D status	Cut-point (ng/mL)	Method of 25-OHD measurement
Chailurkit. et al.	2011	2,641	Thai population	34.2-64.6%	<30	LC/MS/MS ($25\text{-}OHD_2+D_3$)
Chailurkit, et al.	2011	446	Thai elderly women	54.0%	<30	RIA ($25\text{-}OHD_2+D_3$)
Kruavit, et al.	2012	93	Thai nursing home residents	61.3%	<28	RIA ($25\text{-}OHD_2+D_3$)
Nimitphong, et al.	2013	1,449	Male subjects	13.9%	<20	LC/MS/MS
		541	Female subjects	43.1%		($25\text{-}OHD_2+D_3$)
Soontrapa, et al.	2015	66	Rural elderly males	13.6%	<40	ECLIA
		100	Urban elderly males	48.0%		($25\text{-}OHD_2+D_3$)
The present study	2018	444	Adult ambulatory patients with cardiometabolic disorders	70.3% 28.2%	<30 <20	ECLIA ($25\text{-}OHD_2+D_3$)

Abbreviations: 25-OHD, serum 25-hydroxyvitamin D; LC/MS/MS, liquid chromatography tandem mass spectrometry; RIA, radioimmunoassay; ECLIA, electrochemiluminescence immunoassay

Those results agree with our finding that non-elderly patients (age <60 years) had lower serum 25-OHD levels and higher prevalence of D-DEF (25-OHD <20 ng/mL) and D-INSUFF (25-OHD <30 ng/mL) than elderly patients (age ≥60 years) (23.23±9.20 *vs*. 26.81±10.41 ng/mL, 82.1% *vs*. 68.4%, and 43.4% *vs*. 25.0%, respectively; all $p<0.01$) (Table 6). The lower serum 25-OHD in non-elderly adults observed by both Chailurkit's study and our study may be due to different amounts of sunlight exposure between elderly and non-elderly Thais. However, no data regarding health conditions, most notably CMDs and the use of vitamin D supplementation, were reported in their study[3].

Another study in 2011 by Chailurkit, et al in 497 healthy elderly women (age >60 years) who lived in Bangkok (subjects with serum creatinine level >132.6 µmol/L, serum glutamic oxaloacetic transferase >27 U/L, and/or overt hyperparathyroidism or hypoparathyroidism were excluded) showed a prevalence of D-INSUFF (serum 25-OHD <30 ng/mL) of 54.0%[4]. Our study, which included 153 elderly women (age >60 years) with CMDs, found a prevalence of D-INSUFF (serum 25-OHD <30 ng/mL) of 78.4% (Table 5), which was higher than the 54% reported in Chailurkit's 2011 study[4].

A cross-sectional study in 2013 by Nimitphong, et al in 1,449 male and 541 female young (age range: 25-54) healthy employees of the Electrical Generating Authority of Thailand (EGAT) found that male subjects had higher serum 25-OHD levels than female subjects (65.0±0.5 *vs*. 53.5±0.5 nmol/L; $p<0.001$), and that the prevalence of D-DEF defined as serum 25-OHD <20 ng/mL (<50 nmol/L) was 13.9% in men and 43.1% in women[6]. The present study included 106 patients aged <60 years (Table 5) and found a prevalence of D-DEF defined as serum 25-OHD <20 ng/mL of 43.4% overall and 36.8% in men (Table 6), which were both higher than the 21.8% and 13.9% rates reported by Nimitpong, et al. However, the prevalence of 25-OHD <20 ng/mL was comparable in non-elderly women between our study and the study by Nimitpong, et al (47.1% *vs*. 43.1%). This suggests that young adult ambulatory patients with CMDs tended to have a higher rate of D-DEF than healthy young adults. However, the prevalence of D-DEF reported by Nimitphong, et al may not represent the overall healthy young Thai adult population, as that study included only employees of EGAT. More specifically, that group of employees of the same company may have a similar socioeconomic status and different outdoor physical activities than the general Thai population. Two cross-sectional studies from Northeastern Thailand by Soontrapa, et al in 2011 and Soontrapa, et al in 2015 aimed to determine the prevalence of D-INSUFF in healthy elderly males. The first study was conducted in 100 healthy urban elderly males with a mean age 70.73 years. The later study was conducted in 66 healthy rural elderly males with a mean age 68.09 years. These studies reported that 48.0% of urban subjects and 13.6% of rural subjects had serum 25-OHD levels of <40 ng/mL[7,8]. Using a lower cut-off level of 30 ng/mL in our study, we found the prevalence of D-INSUFF in 91 elderly male subjects to be higher than the rates reported in both of Soontrapa's studies (51.6%; Table 5). A study by Kruavit, et al in 2012 conducted in 93 elderly Thai men and women (age range: 61-97 years) living in a long-term nursing home

set forth to determine the prevalence of D-INSUFF and low bone mineral density[5]. That study found that 77.4% of residents had serum 25-OHD <30 ng/mL and 21.5% had serum 25-OHD <20 ng/mL; however, no subjects had severe D-DEF (serum 25-OHD <10 ng/mL)[5]. The prevalence of serum 25-OHD <30 ng/mL in Kruavit's study was comparable to the rate found in our study in 153 elderly female patients (77.4% *vs.* 78.4%), while the prevalence of serum 25-OHD <20 ng/mL was lower in Kruavit's study than our study (21.5% *vs.* 31.4%; Table 6). Kruavit's study also reported that 9 of 93 subjects were receiving vitamin D supplementation, and no significant difference in serum 25-OHD levels was observed between those who were and were not receiving vitamin D supplementation[5]. However, the prevalence of D-INSUFF and D-DEF in patients without vitamin D supplement was not reported in that study[5].

The present study found relatively higher prevalence of D-INSUFF and D-DEF than most previous Thai studies in every subgroup. This may be explained by the following possible explanations. Firstly, our study excluded any patient with any form of proven or highly suspected vitamin D supplementation. Other studies in Thai population may have included subjects receiving some form of vitamin D supplementation, which might lead to improvement of vitamin D status and underestimation of D-INSUFF and D-DEF prevalence. Secondly, the present study was conducted in ambulatory patients with one or more CMDs. Several laboratory and observational studies discovered a link between the beneficial effects of vitamin D for helping to prevent CMDs[1,9,10,12]. Therefore, a higher prevalence of inadequate vitamin D status might be observed in patients with CMDs compared to the healthy individuals or the general population groups that were studied in most previous studies. Moreover, some factors associated with inadequate vitamin D status in patients with CMDs might differ from healthy individuals, such as limited physical activity, lower sunlight exposure, higher body mass index, and lower dietary intake of foods containing high vitamin D. Thirdly, the methods of serum 25-OHD measurement were varied among studies. These differences may contribute to differences in serum 25-OHD levels. Our study and Soontrapa's studies[7,8] used electrochemiluminescence immunoassay (ECLIA) to measure serum 25-OHD levels, Chailurkit's 2011[3] and Nimitphong's[6] studies used liquid chromatography tandem-mass spectrometry (LC/MS/MS), and Chailurkit's 2011[4] and Kruavit's[5] studies used radioimmunoassay (RIA) (Table 4.). However, all 3 of the described methods measured both 25-OHD_2 and 25-OHD_3 levels. Fourth and last, since most participants in our study lived in Bangkok, inadequate vitamin D status was more likely possibly due to less outdoor activity and less sunlight exposure.

Studies in the prevalence of inadequate vitamin D status in South East Asia and East Asia

National population-based studies and epidemiologic studies from countries located in different latitudes revealed a wide range of prevalence of D-DEF. In India, which is located between 8.4 and 37.6°N, epidemiologic studies from different parts of the country showed a prevalence of D-DEF (25-OHD <20 ng/mL) higher than 70%, which is higher than the prevalence reported in all of the previous studies conducted in Thailand[3-8,21]. In Singapore, which is located at 1°N, the prevalence of D-DEF and D-INSUFF defined as serum 25-OHD levels of <20 and <30 ng/mL, respectively, in 504 subjects aged 45-74 years randomly selected from 63,257 participants enrolled in the Singapore Chinese Health Study, which was a population-based prospective cohort study conducted during 1993 to 1998, was 14% and 68%, respectively[22]. Those findings were comparable to the 28.2% and 70.3% rates in our study, and the 14.3% and 64.6% rates in Bangkok population reported in Chailurkit's 2011 Thai population-based study[3]. Although Thailand (5-20°N) and India (8.4-37.6°N) are located at similar latitudes and they receive comparable amounts of intense sunlight throughout a year, the higher prevalence of D-DEF in Indian population may be due to different cultural and environmental factors, such as clothing, sunlight exposure behavior, and dietary intake. Studies conducted in Bangkok and Singapore reported comparable rates of prevalence of inadequate vitamin D status, which might be explained by the comparable amount of sunlight and other similarities, such as ethnicity, dietary intake, and lifestyle factors[3,22]. In China, which has major cities located at 40°N (Beijing) and 31°N (Shanghai), a 2005 population-based study that was part of the Nutrition and Health of Aging Population in China (NHAPC) project conducted in 3,262 non-institutionalized Chinese participants (age range: 50-70 years) showed that 69% and 94% of the study population had serum 25-OHD levels of <20 ng/mL and <30 ng/mL, respectively[23]. In South Korea, which is located between 33°N and 38°N, the Korea National Health and Nutrition Examination Surveys

IV conducted in 2008 in 6,925 subjects found a prevalence of D-INSUFF (serum 25-OHD <30 ng/mL) of 87% in male subjects and 94% in female subjects, and a prevalence of D-DEF (serum 25-OHD <20 ng/mL) of 47% in male subjects and 65% in female subjects[24]. The prevalence of inadequate vitamin D status reported from Korea and China were higher than the rates reported in our study and from all previous epidemiologic studies conducted in Thailand[3-8].

Vitamin D status in patients with CMDs receiving vitamin D supplementation

The high prevalence of vitamin D supplementation (21.2%) in patients with CMDs who were randomly invited to participate in our study, and the higher prevalence of inadequate vitamin D status in patients without vitamin D supplementation compared to patients with vitamin D supplementation and all patients regardless of vitamin D supplementation observed in this study suggests that vitamin D supplementation is very common in Thai population, and this can result in underestimation of the real prevalence of inadequate vitamin D status in a studied population. Accordingly, vitamin D supplementation data and/or information should be included in any epidemiologic study of vitamin D status. The high prevalence of inadequate vitamin D status observed in our patients who received vitamin D supplementation indicates that a significant proportion of patients could not achieve sufficient vitamin D status despite receiving vitamin D supplementation. That observation concurs with observations reported in previous studies that found that only 32-45% of vitamin D deficient patients achieved adequate vitamin D status despite receiving high-dose vitamin D supplementation[22,23], which suggests that measurement of serum 25-OHD in individuals who are receiving vitamin D supplementation is required for assessment of the adequacy of supplementation. Inability to achieve sufficient vitamin D status during vitamin D supplementation may be due to inadequate supplement dosage, defect in vitamin D absorption, or both. The recommended daily allowance (RDA) of vitamin D introduced by the Institute of Medicine in 2011 is 600 IU/day for adults aged 50-70 years, and 800 IU/day for those older than 70 years[15]. These RDAs correspond to the amount of daily vitamin D intake that can maintain serum 25-OHD levels at 20 ng/mL or higher, even in conditions with minimal sunlight exposure[15]

However, our study has some mentionable limitations. First, we were unable to clarify and report the dosage and types of vitamin D supplementation (D_2 or D_3) that patients were receiving. Second and last, baseline serum 25-OHD levels prior to vitamin D supplementation were not available. Further well-designed studies in Thai population are needed to determine the effect of vitamin D supplementation on the prevalence of inadequate vitamin D status, and to establish recommendations for initiation of vitamin D supplementation, adjustment of vitamin D dosage, and assessment of vitamin D status during vitamin D supplementation.

Vitamin D status in non-vitamin D-supplemented patients with CMDs

Several laboratory and observational studies discovered the link between vitamin D and its beneficial effects on CMDs[1,9,10,12]. A meta-analysis of 28 studies that included 99,475 participants aged older than 18 years by Parker, et al that aimed to examine the effect of vitamin D on CMDs, including cardiovascular diseases, T2DM, and metabolic syndrome, showed that high levels of serum 25-OHD were associated with 43% reduction in CMDs (OR: 0.57, 95% CI: 0.45-0.68)[12]. The higher prevalence of inadequate vitamin D status in non-vitamin D-supplemented patients with CMDs observed in our study, as compared to other studies in Thai population without CMDs[3-6], supports the presence of relationships between vitamin D status and CMDs. However, the causal relationships between vitamin D and non-skeletal outcomes, such as CMDs, remain unclear due to the lack of large randomized controlled studies to verify this relationship[1]. Large-scale ongoing randomized trials of vitamin D supplementation are currently underway in the United States[25], Australia[26], Finland[27], and the United Kingdom[28] to examine the cause-effect relationship of vitamin D on reduction of cardiovascular diseases and mortality. Those studies are expected to conclude their 5-year follow-up by 2019.

A number of previous studies have reported the prevalence of inadequate vitamin D status in patients with each type of CMD, and each reported different results[29-38]. Our study found that each type of CMD affected vitamin D status differently, as patients with HT had a higher prevalence of severe D-DEF (serum 25-OHD <10 ng/mL) than those without HT (3.9% *vs.* 0%; $p = 0.05$), and patients with CAD had a much higher prevalence of severe D-DEF than those without CAD (14.8% *vs.* 1.9%; $p<0.001$). However and in contrast, there was no difference in vitamin D status between patients with and without T2DM, and between

patients with and without DLP. In contrast to the results of our study, the results from the third National Health and Nutrition Examination Survey (NHANES III) showed serum 25-OHD levels to be lower in women, elderly persons (age >60 years), and study participants with cardiovascular risk factors. In addition, the lowest quartile of serum 25-OHD levels (<21 ng/mL) significantly increased the risk of HT (odds ratio [OR]: 1.30), T2DM (OR: 1.98), obesity (OR: 2.29), and high serum triglyceride levels (OR: 1.47) (all $p<0.001$)[34]. The higher prevalence of severe D-DEF in patients with HT than in those without HT observed in our study suggests the potential role of vitamin D in the development of HT, and this is supported by the results of NHANES III and other previous epidemiologic studies[32,33,35,36]. NHANES III showed serum 25-OHD levels to be inversely associated with blood pressure[32,33], and the lowest quartile of serum 25-OHD (<21 ng/mL) to be associated with increased prevalence of HT (OR: 1.30)[34]. Our findings also agreed with those of Forman, et al who reported that low serum 25-OHD concentrations of <37.5 nmol/L (<15 ng/mL) were associated with increased risk of incident hypertension[35]. However, a relationship contrary to our finding was reported in a case-control study by Akbari, et al that showed that hypertensive patients had higher mean serum 25-OHD levels, and a lower prevalence of serum 25-OHD levels of <10 ng/mL and <30 ng/mL compared to controls[36]. Regarding the association between vitamin D status and CAD, several previous studies reported association between CAD and D-DEF[29-31] . NHANES 2001-2004 included 8,351 adults and found that D-DEF defined as 25-OHD <30 ng/mL was more prevalent in individuals at high risk for cardiovascular diseases (75%, OR: 1.32, 95% CI: 1.05-1.67), CAD (77%, OR: 1.48, 95% CI: 1.14-1.91), and both CAD and heart failure (89%, OR: 3.52, 95% CI: 1.58-7.84) than in individuals at low risk for cardiovascular disease (68%) after controlling for age, race, and gender. (30) In contrast, a cross-sectional study by Dhibar, et al in 315 patients who underwent coronary angiography (age range: 30-70 years) with no hemodynamic instability, shock, heart failure, diseases, or conditions that affect vitamin D and calcium metabolism, and who received vitamin D supplementation reported the prevalence of D-DEF (serum 25-OHD <20 ng/mL) and severe D-DEF (serum 25-OHD <10 ng/mL) in 240 patients with CAD *vs.* 75 patients without CAD to be 81.7% *vs.* 89.4% and 39.6% *vs.* 54.7%, respectively. (37) Unlike our study and most previous studies, the Dhibar, *et al*. study reported no significant difference in the prevalence of inadequate vitamin D status between patients with and without CAD[37]. Moreover, the prevalence of overall inadequate vitamin D status reported by Dhibar, et al is much higher than the overall rate reported in our study. Our study found no difference in vitamin D status between patients with and without T2DM, whereas a number of studies found a higher prevalence of inadequate vitamin D status in T2DM compared to individuals without diabetes[34,38]. Results of NHANES III showed the lowest quartile of serum 25-OHD levels to be significantly associated with increased risk of T2DM (OR: 1.98; $p<0.001$). (34) Consistent with the results of NHANES III, a case-control study by Kostoglou-Athanassiou, et al in 120 age and gender-matched T2DM patients and 120 non-diabetic subjects showed the prevalence of 25-OHD <10 ng/mL and 25-OHD <20 ng/mL to be higher in T2DM than in controls (17.5% *vs.* 5.8% and 63.3% *vs.* 23.3%, respectively[38]). The observed inconsistency in the prevalence of D-DEF among patients with CMDs across studies may be due to several factors, including age, gender, ethnicity, environmental factors, and the prevalence of coexisting comorbidities among the study groups. In this study, we subcategorized our patients according to various combinations of coexisting CMDs, and we found that patients with coexisting T2DM, HT, and CAD, and coexisting T2DM, HT, DLP, and CAD had markedly higher prevalence of severe D-DEF than patients with other combinations of CMD (33.3% *vs.* 2.6%, and 17.6% *vs.* 2.1%, respectively; all $p<0.001$) (Table 4). These results suggest that the presence of multiple CMDs may be more strongly correlated with prevalence of D-DEF than the presence of a single CMD. However, our study included a relatively small number of subjects with ≥3 CMDs, and previous data regarding vitamin D status in patients with multiple CMDs are limited. Accordingly, further studies in a much larger study population are needed to verify the results of this study, and to further elucidate the risk factors for inadequate vitamin D status in patients with CMDs.

Conclusion

The prevalence of D-INSUFF and D-DEF in medically well-controlled ambulatory Thai patients with one or more CMDs, including T2DM, HT, DLP, and/or CAD, was high in patients with and without vitamin D supplementation, and higher than the prevalence rates previously reported in other subgroups of Thai population in which the presence

of CMDs was not specified. The prevalence of inadequate vitamin D status was higher in patients without vitamin D supplementation than in those with vitamin D supplementation. In patients not receiving vitamin D supplementation, the factors associated with higher prevalence of inadequate vitamin D status were HT, CAD, female gender, and age less than 60 years. Patients with coexisting T2DM, HT, and CAD, and patients with coexisting T2DM, HT, DLP, and CAD had higher prevalence of severe D-DEF (25-OHD <10 ng/mL) than those with other combinations of CMDs. Further study in a larger CMD study population are needed to determine the role of each type of CMD and the risk factors associated with inadequate vitamin D status.

What is already known in this topic?

Previous studies in different subgroups of Thai population reported rates of prevalence of inadequate vitamin D status ranging from 13.6% to 64.6%. Cardiometabolic disorders, such as type 2 diabetes mellitus, hypertension, dyslipidemia, and coronary artery disease, are the common medical problems in which inadequate vitamin D status has been reported in various ethnic populations, but never in Thai population.

What this study adds?

To the best of our knowledge, this is the first study in the vitamin D status of ambulatory Thai patients with CMDs. Our results showed the prevalence of vitamin D insufficiency and vitamin D deficiency in patients with CMD to be high, both in patients with and without vitamin D supplementation, and higher than the prevalence in other subgroups of Thai population without specific medical problems. In addition, the prevalence of inadequate vitamin D status was higher in CMD patients without vitamin D supplementation than in those with vitamin D supplementation. Factors associated with higher prevalence of inadequate vitamin D status in patients with CMD included hypertension, coronary artery disease, age <60 years, and female gender.

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Potential conflicts of interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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