The Effects of Vitamin D Supplementation and 25-hydroxyvitamin D Levels on The Risk of MI and Mortality

Prakash Acharya M.D.*, Tarun Dalia M.D.*, Sagar Ranka M.D.*, Prince Sethi M.D.*, Olurinde A. Oni M.B.B.S., M.P.H.†, Maya S. Safarova M.D., PhD, * Deepak Parashara M.D. *†‡, Kamal Gupta M.D. *, Rajat S. Barua M.D., Ph.D.*†‡

* Department of Cardiovascular Medicine, University of Kansas Medical Center, Kansas City, KS

† Division of Cardiovascular Research, Kansas City VA Medical Center, Kansas City, MO

‡ Division of Cardiovascular Medicine, Kansas City VA Medical Center, Kansas City, MO

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Address for correspondence:
Rajat S. Barua, MD, PhD
Division of Cardiovascular Medicine,
Kansas City Veterans Affairs Medical Center,
4801 E. Linwood Blvd, Kansas City, MO 64128.
Phone: 816 922 2441
Fax: 816 922 4745
E-mail: rajat.barua@va.gov

Abstract

Objective: Aim of the study was to examine the effects of the vitamin D (Vit-D) treatment and non-treatment on Vit-D-deficient patients without a prior history of myocardial infarction (MI).

Materials and Methods: This is an retrospective, observational, nested case-control study of patients (N=20,025) with low 25-hydroxyvitamin D [(25-OH)D] levels (<20 ng/ml) who received care at the Veterans Health Administration from 1999-2018. Patients were divided into three groups: Group A (untreated, levels ≤20 ng/ml), Group B (treated, levels 21-29 ng/ml), and Group C (treated, levels ≥30 ng/ml). The risk of MI and all-cause-mortality were compared utilizing propensity score-weighted cox-proportional hazard models.

Results. Among the cohort of 20,025 patients, the risk of MI was significantly lower in Group C, compared to Group B [hazard ratio (HR) 0.65, 95% CI; 0.49-0.85, *P*=.002] and Group A (HR 0.73, 95% CI; 0.55-0.96), *P*=.02). There was no difference in the risk of MI between Group B and Group A (HR 1.14, 95% CI; 0.91-1.42, *P*=.24]. Compared to Group A, both Group B (HR 0.59, 95% CI; 0.54-0.63, *P*<.001] and Group C (HR 0.61, 95% CI; 0.56-0.67, *P*<.001] had significantly lower all-cause-mortality. There was no difference in all-cause-mortality between Group B and Group C (HR 0.99, 95% CI; 0.89-1.09, *P*=.78).

Conclusions. In patients with Vit-D-deficiency and no prior history of MI, treatment to the (25-OH)D level of >20 ng/ml and >30 ng/ml was associated with a significantly lower risk of all-cause-mortality. The lower risk of MI was observed only in individuals maintaining the (25-OH)D levels ≥30 ng/ml.

Keywords: Vitamin D, myocardial infarction, all-cause-mortality, primary prevention, cardiovascular disease

Abbreviation

(25-OH)D: 25-hydroxyvitamin D

CDW: Corporate Data Warehouse

ICD: International Classification of Disease

IPTW: Inverse Probability of Treatment Weights

RCT: Randomized Controlled Trial

VDT: Vitamin D Treatment

VHA: Veterans Health Administration

VIDA: Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in The Vitamin D Assessment Study

VINCI: Veterans Administration Informatics and Computing Infrastructure

VITAL: Vitamin D supplements and prevention of cancer and cardiovascular disease

INTRODUCTION

There is substantial evidence implicating vitamin D (Vit-D) levels in the pathogenesis of cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, chronic kidney disease, and obesity.[1,2] Furthermore, experimental studies suggest that Vit-D may participate in pathways associated with atherosclerosis by influencing cellular growth, oxidative stress, membrane transport, cell adhesion and gene regulation. Direct effects of Vit-D on cardiomyocytes and vascular endothelial cells were reported via Vit-D receptors.[1] The Endocrine Society defines 25-hydroxyvitamin D [(25-OH)D] levels ≤ 20 ng/ml as deficiency, levels 21-29 ng/ml as insufficiency, and levels ≥ 30 ng/ml as optimal.[3] However, data regarding the association of the (25-OH)D levels and Vit-D supplementation with myocardial infarction (MI) and mortality remains controversial.[4-14]

Several meta-analyses of epidemiological studies suggested that Vit-D deficiency is associated with an increased risk of MI and cardiovascular mortality.[8,12,14] One meta-analyses suggested that there is generally a linear, inverse association between circulating (25-OH)D levels and the risk of cardiovascular disease.[13] A Cochrane meta-analysis showed that Vit-D treatment significantly reduced mortality in subgroups of patients with a pretreatment level below 20 ng/ml.[7] However, in several randomized controlled trials (RCTs), supplementation of Vit-D did not result in lower cardiovascular events and mortality.[4-6] It is important to note that majority of these RCTs have included patients who already had optimal baseline (25-OH)D levels, with most patients in these trials having pretreatment (25-OH)D levels above 25-30 ng/ml.[4,15] Additionally, in the majority of these clinical trials, post-treatment follow-up of (25-OH)D was not measured to account for effective supplementation and had a short-term follow-up.[4] Even in the VITAL (vitamin D and omega-3 trial) and the VIDA (vitamin D assessment) trials, only a small subset of the study population (6.3 and 8.6%, respectively)

had a repeat measurement of post-treatment (25-OH)D level performed.[5,6] It is also worth noting that in several studies, the association between Vit-D and the risk of MI was apparent only after long-term follow-up.[8,10,11] Additionally, there is limited data is available comparing the outcome of MI and mortality with respect to the levels of (25-OH)D achieved and maintained after Vit-D supplementation.

To address this gap in knowledge, we conducted a large retrospective analysis with long-term follow-up in patients with low baseline Vit-D level who had at least two separate measurements of (25-OH)D levels to confirm their status and to measure the effect of Vit-D supplementation on (25-OH)D levels.. The goal of our study was to examine the effects of Vit-D treatment (VDT) and lack of VDT on all-cause-mortality and MI in Vit-D deficient patients without prior history of MI in relation to three different reference levels of (25-OH)D as defined by the Endocrine Society .

METHODS

In this retrospective, observational, nested case-control study we leveraged clinical data ascertained from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW) through the Veterans Administration Informatics and Computing Infrastructure (VINCI) [16]. VINCI hosts the data, facilitates analysis while ensuring the privacy of Veterans as well as data security.[16] This study was approved by the Institutional Review Board of the Kansas City Veterans Affairs Medical Center, MO, USA.

Study design

This study was designed to examine the association of Vit-D with MI and all-cause-mortality among different sub-populations of treated and untreated patients. The incidence of MI and co-existing conditions were based on the International Classification of Disease 9th and 10th

revision (ICD-9 and ICD-10) codes. All the study population had (25-OH)D levels checked on at least two separate occasions to be included in the study.

Study population

Inclusion criteria:

Our study included veterans i) who received their medical care at the Veterans Health Administration (VHA) between December 1999 and December 2018, ii) who were tested for (25-OH)D levels, iii) those whose baseline level of (25-OH)D was ≤ 20 ng/ml and iv) whose age was >18 years.

Exclusion criteria:

We excluded i) patients on VDT prior to the index (25-OH)D level, ii) those who had MI before the first study date, and iii) those who did not have follow-up 25(OH)D testing done after initiation of treatment. We also excluded patients who had a baseline or follow up 25(OH)D level ≥100 ng/ml. Although the safe upper level of (25-OH)D for avoiding hypercalcemia is uncertain, vitamin D intoxication is usually observed in (25-OH)D above 150 ng/ml.[17] Hence, an upper limit of 100 ng/ml has been suggested to provide a safety margin in reducing effects of hypercalcemia.[3]

The study population was divided into three groups: i) patients who did not receive VDT and their (25-OH)D levels remained ≤ 20 ng/ml on follow up (untreated, level ≤ 20) [Group A], ii) patients who received VDT and their (25-OH)D levels remained between 21-29 ng/ml upon follow up (treated, level 21-29) [Group B], and iii) patients who received VDT and their (25-OH)D level remained ≥30 ng/ml upon follow up (treated, level ≥30) [Group C]. (Figure 1)

Rationale for the 25-hydroxyvitamin vitamin D cut-off levels

In general population, the Endocrine Society clinical practice guidelines define vitamin D deficiency as the (25-OH)D levels ≤ 20 ng/ml, levels 21-29 ng/ml as insufficiency, and levels ≥ 30 ng/ml as optimal.[3] We utilized these definitions in our study, and patients with baseline (25-OH)D level ≤ 20 ng/ml were defined to have low Vit-D.

Ascertainment of the vitamin D treatment exposure

The use of Vit-D supplementation was ascertained from the medication prescription of patient medical records. Any patient who received cholecalciferol or ergocalciferol (capsule or tablet), defined by release of the medication by the pharmacy, was considered to have been treated.

Outcome measures

The outcomes of the study were all-cause-mortality and MI across Vit-D levels. Deaths from any cause were determined using dates of death in CDW data augmented with vital status files. MI was identified using the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) code system. All serum (25-OH)D levels were measured at the VA healthcare clinical laboratories utilizing uniform standardized techniques.

Statistical analysis

All categorical and continuous variables were reported as percentages and mean with standard deviation (SD), respectively. Differences in mean and percentage were assessed using the Student's t-test and Pearson chi-squared test. Univariate and multivariable Cox proportional hazard regression models were utilized to assess the differences between the tested groups. Propensity scores were used to correct for potential systematic differences between the comparison groups. The patient's propensity scores for receiving VDT were

computed and adjusted for the covariates in a logistic regression analysis. The covariates included were age, sex, body mass index (BMI), HTN, diabetes, coronary artery disease (CAD), congestive heart failure (CHF), peripheral arterial disease (PAD), CKD, chronic obstructive pulmonary disease (COPD), smoking, concomitant therapies (aspirin, statin, and beta-blockers) and the low density lipoprotein-cholesterol (LDL-C) levels.

Additionally, we utilized propensity score-weighted, stabilized inverse probability of treatment weights (IPTW) to obtain unbiased estimates of the treatment effects.[18,19] IPTW accounts for confounding, distributing the weights according to the sample representation in which the treatment is independent of the measured confounders. The use of stabilized IPTW helped control for the imbalances between the comparison groups as shown in Table 1. Stabilized IPTW was also applied to the survival analysis to derive Kaplan-Meier (KM) survival curves comparing event-free survival time. STATA 15 (Stata Corp, College Station, TX) was used for statistical analysis. A two-sided *P*-value of <.05 was chosen as the level of statistical significance.

RESULTS

Description of the patient cohort

Figure 1 outlines the study subject enrollment details. A total of 142,784 patients had (25-OH)D levels tested. There were 273 patients with baseline or follow up (25-OH)D level above 100 ng/ml who were excluded to avoid the effect of VTD toxicity. We then excluded 5,942 patients whose pretreatment baseline (25-OH)D level could not be ascertained. Subsequently, we excluded 3,040 patients who had prior MI as our study was focused on role of vitamin D in primary prevention. Among the remaining 133,529 patients, 44.99% (60,088) patients had normal (25-OH)D at baseline and were excluded. There were 73,441 patients with low (25-OH)D at baseline, among those 38.91% (28,576) patients received VDT and

61.09% (44,865) patients were identified as naïve. From these two groups of patients, 54,349 patients were excluded as i) they did not have a follow-up (25-OH)D level measured, ii) a follow-up (25-OH)D level fluctuated above the pre-specified threshold for the group, or iii) the timestamp for the follow-up (25-OH)D level was missing . The remaining 19,092 patients were categorized into three study groups. There were 11,119 who did not receive treatment and had (25-OH)D levels which remained below 20 ng/ml (Group A). Among the patients who received VDT, 5,623 patients had follow-up (25-OH)D level that remained between 20-29 ng/ml (Group B) and 3,277 patients had a follow-up (25-OH)D level that remained >30 ng/ml (Group C). The mean time between the diagnosis of low 25(OH)D level and follow up (25-OH) D level was 2.14 years (SD 2.06). The mean numbers of times (25-OH)D levels were repeated after the diagnosis of low baseline (25-OH) D level was 2.62 (SD 2.48). The median time between the last sample collection for (25-IH) D level and MI was 1.17 (25-75% 0.42-2.52) years.

Baseline characteristics of the patients

The baseline characteristics of the three comparison groups are shown in Table 1. Utilizing the stabilized IPTW, we balanced and matched for differences in age, sex, BMI, patients' comorbidities, concomitant therapies with aspirin, statin and beta blockers as well as LDL level by ensuring that the cohorts were well matched (P-value >.05). (Table 1)

Association of (25-OH)D levels with myocardial infarction

The risk of myocardial infarction in the study groups is presented in Table 2. The risk of MI in the Group B (treated, level 20-29 ng/ml) was not different from that of the Group A (untreated, level <20 ng/ml) [HR 1.14, 95% CI (0.91-1.42), P=0.24]. However, Group C (treated, level >30 ng/ml) had a lower risk of MI compared to both the Group B (treated, Level 20-29 ng/ml) [HR 0.65, 95% CI (0.49-0.85), P=0.002] as well as the Group A

(untreated, level <20 ng/ml) [HR 0.73, 95% CI (0.55-0.96), P=0.02]. A comparison of the probability of MI-free survival with a KM curve among the three groups is shown in Figure 2. KM curves show that the Group C (treated, level >30 ng/ml group) had significantly higher MI free survival compared with the Group B (treated, level 20-29 ng/ml) (log-rank P<0.001) and the Group A (untreated, level <20 ng/ml) (log-rank P=0.03) group. There was no significant difference in MI-free survival between the Group B (treated, level 20-29 ng/ml) and the Group A(untreated, level <20 ng/ml) (log-rank P=0.10).

Association of (25-OH)D levels with and all-cause-mortality

Table 2 summarizes study-group stratified risk distribution for all-cause-mortality. Compared to the Group A (untreated, level <20 ng/ml), the risk of all-cause-mortality was significantly lower in both the Group C (treated, level >30 ng/ml) [HR 0.61, 95% CI (0.56-0.67), p<0.001] and Group B (treated, level 20-29 ng/ml) [HR 0.59, 95% CI (0.54-0.63), p<0.001] . However, there was no significant difference in the risk of all-cause-mortality between the Group C (treated, level >30 ng/ml) and Group B (treated, level 20-29 ng/ml) [HR 0.99, 95% CI (0.89-1.09), p=0.78]. Survival analysis with KM curve shows that the probability of survival was significantly higher in the Group B (treated, Level 20-29 ng/ml) (log-rank p<0.001) and the Group C (treated, level >30 ng/ml) (log-rank p<0.001) compared to the Group A (untreated, level <20 ng/ml). The probability of survival was not different between Group B (treated, level 20-29 ng/ml and Group C (treated, level >30 ng/ml) (log-rank p=0.78). (Figure 3)

DISCUSSION

The current study examined the effects of non-treatment and treatment in Vit-D deficient patients without a prior history of MI in-relation to three different reference levels of (25-OH)D. Based on the long-term follow-up, our study found that the patients with post-treatment (25-OH)D levels at or above 30 ng/ml had lower incidence of MI and all-cause-mortality. These results suggest that targeting 25(OH)D levels above 30 ng/ml might improve prognosis in the primary prevention setting among individuals with Vit-D deficiency.

There are conflicting data related to low Vit-D level and all-cause-mortality.[4-14] Our study appears to unify and provide an explanation for some of the contradictory data related to Vit-D and its association with MI and all-cause-mortality. This data also provides a possible unique perspective regarding the association of MI and mortality in relation to Vit-D deficiency and Vit-D supplementation. Our finding of a significantly lower all-cause-mortality when the Vit-D levels were maintained >20 ng/ml post-treatment as compared to patients who were untreated and whose levels remained ≤20 ng/ml, is consistent with several prior prospective studies with long term follow up and meta-analyses of randomized studies.[7,9,20,21] The Cochrane meta-analyses showed Vit-D supplementation in patients with (25-OH)D levels <20 ng/ml significantly lower all-cause-mortality and this benefit was not seen in patients with (25-OH)D levels above 20 ng/ml.[7] In a 20-year-follow-up of the Third National Health and Nutrition Examination Survey (NHANES III) participants, (25-OH)D levels above 17.5 ng/ml were associated with lower all-cause-mortality.[22] On the contrary, the VITamin D and OmegA-3 TriaL (VITAL) followed by the subsequent meta-analyses of clinical trials did not show any reduction in all-cause-mortality with Vit-D supplementation.[4,5] In these studies, however, all-cause-mortality as an outcome was not specifically looked at in patients with baseline (25-OH)D levels ≤ 20 ng/ml.[4,20,23] The other

reason for the difference could be that in these study population the baseline (25-OH)D levels were > 20 ng/ml when VDT was initiated. For example, in the VITAL trial, the majority of patients had baseline (25-OH)D levels above 25-30 ng/ml, with only 12.7% of the population having (25-OH)D levels <20 ng/ml and 32% of patients between 20-29 ng/ml.[5] In our study, we found there was no difference in all-cause-mortality among groups with (25-OH)D levels between 21-29ng/ml and >30 ng/ml post-treatment. When the post-treatment (25-OH)D level >20 ng/ml was achieved, there was no added benefit on all-cause-mortality with higher (25-OH)D levels. Therefore, it may be hypothesized that in Vit-D deficient patients, a target (25-OH)D level of >20 ng/ml would be sufficient to obtain a mortality benefit.

We found a lower incidence of MI events in patients who had (25-OH)D levels at or above 30 ng/ml compared to those with the levels in the range of 21-29 ng/ml as well as those with levels ≤ 20 ng/ml. These findings are consistent with prior studies demonstrating varying risk of MI upon long term follow up in patients according to their baseline (25-OH)D levels.[8,10,11] There was no difference in the risk of MI between patients with (25-OH)D levels maintained at ≤ 20 ng/ml and 21-29 ng/ml. Our findings suggest that (25-OH)D target level ≥30 ng/ml may provide protection against MI. Study by Brøndum-Jacobsen et al also showed graded increase in MI and mortality with drop in (25-OH)D levels.[8] In our study, when compared to the ≤ 20 ng/ml group of patients, those with ≥30 ng/ml had both mortality and MI benefit. On the other hand, no significant difference in all-cause-mortality was noted between the groups with (25-OH)D levels 20-29 ng/m and ≥30 ng/ml, but there was a significant difference in the MI event-rate suggesting that the MI events between these two groups may not contribute significantly to the mortality. While observational studies demonstrate similar findings of lower MI risk with Vit-D supplementation,[10,11] this effect has not been replicated yet in randomized clinical trials.[4,5] It is plausible that this discrepancy stems from the lack of standardized target levels for (25-OH)D across the studies. Further,

risk reduction in the MI events has been reported with longer periods of observation (>10 years)[4-6,10,11] compared to the clinical trials terminating at 5-6 years.

The pathophysiological mechanism for our findings remains speculative. The predominant cause of mortality in patients with (25-OH)D levels ≤ 20ng/ml is likely multifactorial, and possibly related to the pleiotropic effect of Vit-D on immunity, cardiovascular health and metabolic abnormalities associated with its deficiency.[24-29]Additionally, our data suggest that in Vit-D deficient patients, post-treatment (25-OH)D levels of 21-29 ng/dl may provide inadequate protection against MI and to derive significant MI benefit post-treatment (25-OH)D levels should be >30ng/dl. Experimental studies have demonstrated that Vit-D inhibits the transformation of macrophages to foam cells, increases cholesterol efflux in macrophages, improves endothelial nitric oxide formation, promotes vascular repair and decreases thrombogenicity as well as inflammation. All these mechanisms may play a role in providing a protective effect against the atherothrombotic process such as MI. [1,27,30]

Limitations and Strengths

This was an observational study because of which unmeasured confounding or hidden bias might be present. We were unable to account for seasonal variability in the (25-OH)D levels or the methodology utilized to measure (25-OH)D levels in each individual cases. We were unable to account for the use of over the counter vitamin D supplements that were not listed in the medical record. Our database does not have all the clinical data regarding indications for initiating and not initiating Vit-D treatment. Additionally, we were unable to determine the compliance and duration of therapy. The cause of death could not be ascertained because of which cardiovascular cause of mortality was not measured. Furthermore, outcomes were

determined using ICD-9 and ICD-10 codes which could have its own limitations. The results of our study may not be applicable to other populations as this study only included veterans, which is an unique population. Race variable is not available in the database available to us, hence racial differences in the population could not be accounted for.

The strength of our study is that we only included patients with low (25-OH)D levels (≤20 ng/ml) with extensive follow up of up to 14 years. Each patient had at least two separate measurements of (25-OH)D levels to confirm the status and to measure the effect of vitamin D supplementation. We only included patients with consistent levels within each group. We were also able to stratify the patient population according to the (25-OH)D level that was maintained over the years of follow up rather than relying only on the baseline (25-OH)D level or the dose and type of Vit-D treatment received.

Conclusion

Results from our current study suggest in patients with Vit-D deficiency and no prior history of MI, treatment to the (25-OH)D level of >20 ng/ml was associated with a significantly lower risk of all-cause-mortality. Our study also highlights that in this population reduction in the risk of MI was observed only with the increase in the (25-OH)D levels to≥30 ng/ml. In the future, adequately powered, prospective, well-designed trials with a long-term follow-up will be needed to reach a conclusive agreement regarding the effect of Vit-D supplementation, and post supplement (25-OH)D target levels on MI risk.

CONFLICTS OF INTEREST DISCLOSURES

The authors have no conflict of interest regarding the contents of the paper. The contents of this article are those of authors and do not necessarily reflect the position and policy of the Department of Veterans Affairs or the United States Government.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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FIGURE LEGENDS

Figure 1. Methodology and patients selection process

Figure 1 shows the selection of the study population. We excluded 123,692 patients who met various exclusion criteria. 19092 patients met our inclusion criteria and were divided into three subgroups according to their treatment status and follow-up (25-OH)D levels : Group A- untreated, level <20 ng/ml , Group B- treated, level 20-29 ng/ml, and Group C- treated, level ≥30 ng/ml.

Figure 2. Kaplan–Meier curve depicting the myocardial infarction free survival among propensity-matched study groups of patients.

Figure 2 shows the comparison of myocardial infarction (MI) free survival. Kaplan Meier curves and log-rank test were utilized. Group C (treated, level ≥30 ng/ml group) had higher probability of MI free survival when compared with the Group B (treated, level 20-29 ng/ml group) (log-rank p<0.001) and Group A (untreated, level <20 ng/ml group) (log-rank p=0.03) group. There was no significant difference in MI free survival upon comparison of Group A versus Group B (log-rank p=0.10).

Figure 3. Kaplan–Meier curve depicting survival probability among propensity-matched study groups of patients.

Figure 3 compares survival probability between the three groups. Kaplan Meier curves and log-rank test were utilized. Compared to the Group A (untreated, level <20 ng/ml), the probability of survival was significantly higher in Group B (treated, Level 20-29 ng/ml) (log-rank p<0.001) and Group C (treated, level ≥30 ng/ml) (log-rank p<0.001). The probability of survival was not different between Group B and Group C (log-rank p=0.78).

Table1: Baseline characteristics of all patients in the study unadjusted and stabilized inverse probability of treatment weight adjusted.

Patient characteristics	Unmatched cohort			Propensity matched cohort (stabilized IPTW)		
	Untreated, level ≤ 20 ng/ml vs Treated, level 21-29 ng/ml (Group A vs Group B)					
	Untreated, level ≤20 (Group A)	Treated, level 21-29 (Group B)	*P*-value	Untreated, level ≤20 (Group A)	Treated, level 21-29 (Group B)	*P*-value
Number of patients (N)	11119	5623		10064	5067	
Age ≥50 years, n(%)	7946 (71.5)	4000 (71.1)	0.67	7256 (72.1)	3663 (72.3)	0.73
Age, mean years (SD)	57.7 (17.9)	56.9 (16.3)		57.6 (17.5)	58 (16.5)	
Male, n(%)	8537 (76.8)	3715 (66.1)	<0.001	7367 (73.2)	3694 (72.9)	0.75
Body mass index, kg/m2, mean (SD)	29.9 (6.7)	31.3 (6.7)	<0.001	30.5 (6.8)	30.6 (6.6)	0.61
BMI >=30	5560 (50)	3138 (55.8)	<0.001	4992 (49.6)	2513 (49.6)	0.97
Follow-up time (years), mean (SD)	3.6 (2.9)	4.6 (2.8)		3.6 (3)	4.5 (2.8)	
Comorbidities						
Hypertension, n(%)	6266 (56.4)	3299 (58.7)	0.004	6089 (60.5)	3071 (60.6)	0.88
Diabetes mellitus, n(%)	3201 (28.8)	1712 (30.5)	0.03	3150 (31.3)	1586 (31.3)	0.97
Coronary artery disease, n(%)	1669 (15.0)	816 (14.5)	0.39	1600 (15.9)	801 (15.8)	0.92
Congestive heart failure, n(%)	807 (7.3)	338 (6.0)	0.003	725 (7.2)	365 (7.2)	0.88
Peripheral vascular disease, n(%)	889 (8.0)	425 (7.6)	0.32	835 (8.3)	421 (8.3)	0.93
Chronic kidney disease, n(%)	1097 (9.9)	479 (8.5)	0.005	976 (9.7)	502 (9.9)	0.79
Chronic obstructive pulmonary disease, n(%)	495 (4.5)	201 (3.6)	0.007	453 (4.5)	228 (4.5)	0.97
Smoking, n(%)	2675 (24.1)	1447 (25.7)	0.02	2647 (26.3)	1338 (26.4)	0.90
Concomitant therapy						
Aspirin, n(%)	6776 (60.9)	4164 (74.1)	<0.001	6783 (67.4)	3435 (67.8)	0.63
Statin, n(%)	5996 (53.9)	3697 (65.8)	0.001	6059 (60.1)	3060 (60.4)	0.81
Beta blockers, n(%)	4475 (40.3)	2606 (46.4)	<0.001	4398 (43.7)	2224 (43.9)	0.73
Laboratory findings						
Low density lipoprotein, mg/dl, mean (SD)	107.3 (36.5)	109.4 (36.5)	<0.001	107.7 (36.4)	107.6 (36.3)	0.91
	Treated, level 21-29 ng/ml vs Treated, level ≥30 ng/ml					

	(Group B vs Group C)					
	Treated, level 21-29 (Group B)	**Treated, level ≥30 (Group C)**	***P*-value**	**Treated, level 21-29 (Group B)**	**Treated, level ≥30 (Group C)**	***P*-value**
Number of patients (N)	5623	3277		5266	3088	
Age ≥50 years, n(%)	4000 (71.1)	2703 (82.5)	<0.001	3997 (75.9)	2331 (75.5)	0.66
Age, mean years (SD)	56.9 (16.3)	62.2(15.5)		58.9 (16.2)	59.5 (15.8)	
Male, n(%)	3715 (66.1)	2272 (69.3)	0.002	3538 (67.7)	2084 (67.5)	0.88
Body mass index, kg/m2, mean (SD)	31.3 (6.7)	29.3 (6.2)	<0.001	30.6 (6.6)	30.7 (6.8)	0.61
BMI >=30	3138 (55.8)	1432 (43.7)	<0.001	2623 (49.9)	1547 (50.1)	0.9
Follow-up time (years), mean (SD)	4.6 (2.8)	4.9 (3.1)		4.6 (2.8)	4.9 (3.0)	
Comorbidities						
Hypertension, n(%)	3299 (58.7)	2178 (66.5)	<0.001	3365 (63.9)	1967 (63.7)	0.89
Diabetes mellitus, n(%)	1712 (30.5)	1023 (31.2)	0.45	1690 (32.1)	997 (32.3)	0.88
Coronary artery disease, n(%)	816 (14.5)	621 (18.9)	<0.001	885 (16.8)	513 (16.6)	0.79
Congestive heart failure, n(%)	338 (6.0)	241 (7.4)	0.01	3581 (6.8)	207 (6.7)	0.90
Peripheral vascular disease, n(%)	425 (7.6)	258 (7.9)	0.59	427 (8.1)	244 (7.9)	0.83
Chronic kidney disease, n(%)	479 (8.5)	281 (8.6)	0.93	469 (8.9)	278 (9.0)	0.87
Chronic obstructive pulmonary disease, n(%)	201 (3.6)	144 (4.4)	0.05	216 (4.1)	127 (4.1)	0.96
Smoking, n(%)	1447 (25.7)	927 (28.3)	0.009	1464 (27.8)	853 (27.6)	0.86
Concomitant therapy						
Aspirin, n(%)	4164 (74.1)	2367 (72.2)	0.06	3913 (74.3)	2297 (74.4)	0.93
Statin, n(%)	3697 (65.8)	2342 (71.5)	<0.001	3639 (69.1)	2125 (68.8)	0.74
Beta blockers, n(%)	2606 (46.4)	1609 (49.1)	0.01	2538 (48.2)	1482 (48.0)	0.88
Laboratory findings						
Low density lipoprotein, mg/dl, mean (SD)	109.4 (36.5)	101.9 (35.3)	<0.001	106.5 (36.0)	106.7 (36.7)	0.84
	Untreated, level ≤20 ng/ml vs Treated, level ≥30 ng/ml (Group A vs Group C)					
	Untreated, level ≤20 (Group A)	**Treated, level ≥30 (Group C)**	***P*-value**	**Untreated, level ≤20 (Group A)**	**Treated, level ≥30 (Group C)**	***P*-value**
Number of patients (N)	11119	3277		10014	2942	
Age ≥50 years, n(%)	7946 (71.5)	2703 (82.5)	<0.001	7480 (74.7)	2218 (75.4)	0.53

Age, mean years (SD)	57.7 (17.9)	62.2 (15.5)		58.8 (17.5)	60.1 (16.2)	
Sex, n(%)	8537 (76.8)	2272 (69.3)	<0.001	7540 (75.3)	2198 (74.7)	0.52
Body mass index, kg/m2, mean (SD)	29.9 (6.7)	29.3 (6.2)	<0.001	29.9 (6.6)	29.8 (6.5)	0.72
BMI >=30	5560 (50)	1432 (43.7)	<0.001	4586 (45.8)	1315 (44.7)	0.31
Follow-up time (years), mean (SD)	3.6 (2.9)	4.9 (3.1)		3.6 (3)	4.7 (3.1)	
Comorbidities						
Hypertension, n(%)	6266 (56.4)	2178 (66.5)	<0.001	6239 (62.3)	1853 (63.0)	0.51
Diabetes mellitus, n(%)	3201 (28.8)	1023 (31.2)	0.007	3135 (31.3)	936 (31.8)	0.65
Coronary artery disease, n(%)	1669 (15)	621 (18.9)	<0.001	1702 (17)	503 (17.1)	0.95
Congestive heart failure, n(%)	807 (7.3)	241 (7.4)	0.87	771 (7.7)	232 (7.9)	0.79
Peripheral vascular disease, n(%)	889 (8)	258 (7.9)	0.82	841 (8.4)	247 (8.4)	0.99
Chronic kidney disease, n(%)	1097 (9.9)	281 (8.6)	0.03	991 (9.9)	300 (10.2)	0.59
Chronic obstructive pulmonary disease, n(%)	495 (4.5)	144 (4.4)	0.89	481 (4.8)	153 (5.2)	0.52
Smoking, n(%)	2675 (24.1)	927 (28.3)	<0.001	269 (26.9)	809 (27.4)	0.58
Concomitant therapy						
Aspirin, n(%)	6776 (60.9)	2367 (72.2)	<0.001	6559 (65.5)	1951 (66.3)	0.46
Statin, n(%)	5996 (53.9)	2342 (71.5)	<0.001	6028 (60.2)	1774 (60.3)	0.99
Beta blockers, n(%)	4475 (40.2)	1609 (49.1)	<0.001	4366 (43.6)	1294 (44.0)	0.69
Laboratory findings						
Low density lipoprotein, mg/dl, mean (SD)	107.3 (36.5)	101.9 (35.3)	<0.001	105.7 (36.1)	105.6 (36.9)	0.97

The covariates included were age, sex, body mass index (BMI), risk factors hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), congestive heart failure (CHF), peripheral vascular disease (PVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and smoking, concomitant therapies (aspirin, statin, and beta-blockers) and low density lipoprotein (LDL).

Table 2: Hazard ratio for all-cause-mortality and myocardial infarction among the propensity matched, stabilized inverse probability of treatment weighted subgroups.

Outcomes	**All-cause-mortality**			**Myocardial infarction**		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Comparing Untreated, level ≤20 ng/ml (Group A) vs Treated, level 21-29 ng/ml (Group B) [reference= Untreated, level ≤ 20 ng/ml]						
Propensity matched (stabilized IPTW) N=10,064 vs. 5,067	0.59	0.54-0.63	<0.001	1.14	0.91-1.42	0.24
Comparing Treated, level 21-29 ng/ml (Group B) vs Treated, level ≥30 ng/ml (Group C) [reference=Treated, level 21-29 ng/ml]						
Propensity matched (stabilized IPTW) N=5,266 vs. 3,088	0.99	0.89-1.09	0.78	0.65	0.49-0.85	0.002
Comparing Untreated, level ≤20 ng/ml (Group A) vs Treated, level ≥30 ng/ml (Group C) [reference= Untreated, level ≤20 ng/ml]						
Propensity matched (stabilized IPTW) N=10,014 vs. 2,942	0.61	0.56-0.67	<0.001	0.73	0.55-0.96	0.02

IPTW: Inverse Probability of Treatment Weights

Figure 1

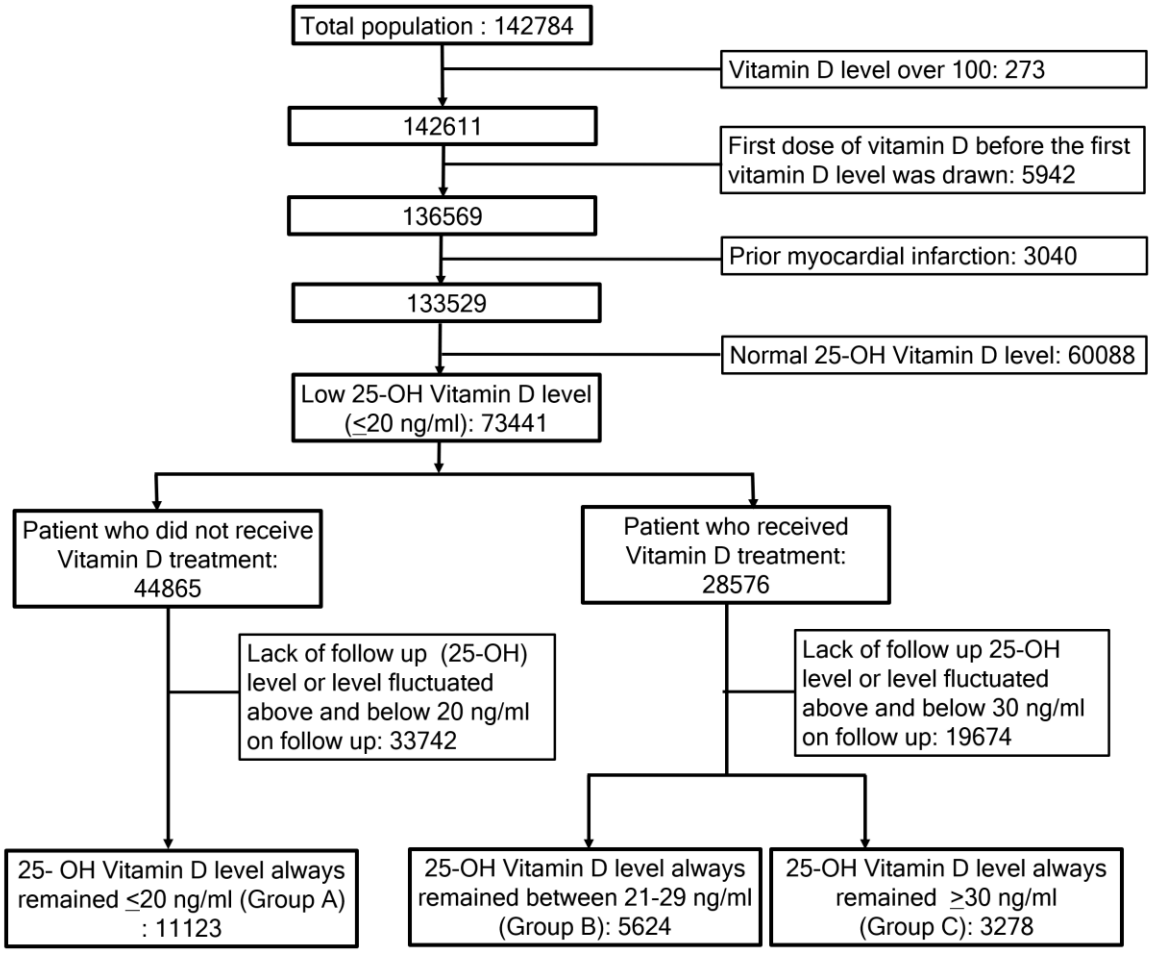

Figure 2

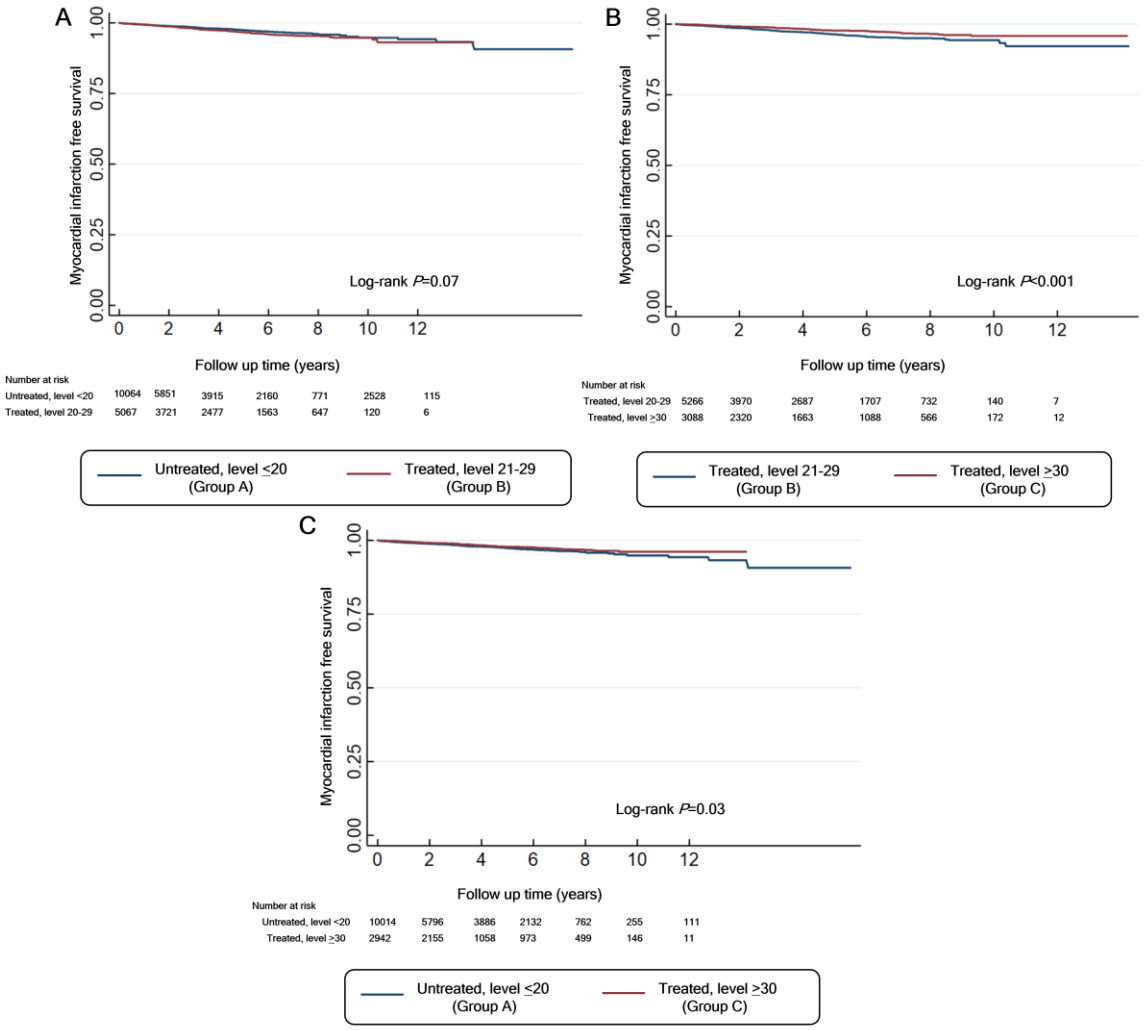

Figure 3