

Effect of monthly 100,000 IU vitamin D supplementation on persistence with long-term statin therapy: results from the Vitamin D Assessment study

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Abstract. Long-term persistence with statin use is far from satisfactory. The main reason for discontinuing statins has been attributed to pain-related adverse effects, called statin myalgia. Studies have linked statin myalgia with vitamin D deficiency. This secondary analysis found that monthly vitamin D supplementation improved persistence with statin use.

Introduction

Clinical trials have shown that long-term statin use significantly reduces the risk of coronary heart disease, stroke, and all-cause mortality (Mihaylova et al. 2012). However, long-term adherence and persistence of taking statin therapy are far from satisfactory, with adherence varying from 33% to 85% after 1-year. This less than ideal adherence decreases the effectiveness of statins in disease prevention.

Previous studies show that one of the main reasons for discontinuing statins is pain-related adverse effects, such as myalgia. Although the pathophysiology of statin-related pain remains unclear, a number of observational studies have linked statin myalgia with vitamin D deficiency (Mergenhagen et al. 2014, Buettner et al. 2015, Michalska-Kasiczak et al. 2015).

Our aim was to determine if monthly vitamin D supplementation (100,000-IU) improves the persistence with long-term statin use in older adults.

Method

Study design

This study is a secondary analysis of the Vitamin D Assessment (ViDA) study, a population-based, randomized, double-blinded, placebo-controlled trial to evaluate the effect of monthly vitamin D supplementation on health outcomes (Scragg et al. 2016). Participants were mainly recruited from Auckland general practices from 05 April 2011 to 06 November 2012, and followed to 31 July 2015.

Eligibility criteria

Inclusion criteria were: age range of 50–84 years; able to give informed consent; being resident in Auckland at recruitment; and anticipated residence in New Zealand for the 4-year study period.

Participants were included in this analysis of statin persistence if, after randomization, they had two or more

prescriptions for statins, equal to 90 days or more of statin treatment.

Intervention

Vitamin D3 (100,000-IU) or identical placebo oral capsules were mailed to participants' homes. Two capsules were sent in the first mail after randomization (200,000-IU), followed by a 100,000-IU capsule of vitamin D3 (or placebo) to be taken monthly thereafter.

Outcome

Prescription data for statins during follow-up after randomization were provided by the Ministry of Health, with linkage to individual study participants by National Health Index (NHI) numbers.

The outcome of this secondary analysis was persistence in taking statins 18 months after first statin prescription. Statin persistence was defined as non-discontinuation of all statin medication, allowing for a 30-day gap between refills.

Statistical Method

The Cox proportional hazards model was used to investigate any differences in persistence probability between the two groups, along with Kaplan-Meier curves of survival (persistence with taking statin).

Results

Study Population

From all 5110 participants randomized into the main trial, 2648 participants were excluded because of not meeting the statin inclusion criteria for analysis. Of the 2494 selected participants, 1243 were in the vitamin D group and 1251 in the placebo group; and of these, 1235 in the vitamin D group and 1227 in the placebo group were taking statins at baseline.

Baseline Characteristics

There were no significant differences in the baseline characteristics of participants between the vitamin D and placebo groups among those taking statins at baseline (Table 1). The deseasonalized 25-hydroxyvitamin D (25(OH)D) concentration was similar between the two groups, with an overall average of 64.9 nmol/L (SD 22.4).

About 8% of all ViDA participants (n=441) returned at 6, 12, 24, and 36 months after randomization for collection of blood samples to measure 25(OH)D levels. For the 220 included in this secondary analysis, observed serum 25(OH)D levels during follow-up were much higher (by

>50.0 nmol/L) in the vitamin D group compared with placebo.

Table 1 Baseline characteristics of the selected participants.

Variables	Vitamin D (N=1235)*	Placebo (N=1227)*
Female, n (%)	420 (34.0)	425 (34.6)
Age (y), mean (SD)	67.3 (8.1)	67.6 (7.8)
Age (y), n (%)		
50-59	218 (17.7)	188 (15.3)
60-69	509 (41.2)	522 (42.5)
70-79	416 (33.7)	427 (34.8)
80-84	92 (7.4)	90 (7.3)
Ethnicity n (%)		
European/Other	988 (80.0)	1003 (81.7)
Māori	69 (5.6)	64 (5.2)
Pacific	102 (8.3)	91 (7.4)
South Asian	76 (6.2)	69 (5.6)
25OHD (nmol/l), mean (SD)	65.6 (22.6)	64.5 (22.2)
25OHD (nmol/l), n (%)		
0-24.9	23 (1.9)	18 (1.5)
25.0-49.9	291 (23.6)	322 (26.3)
50.0-74.9	549 (44.5)	508 (41.4)
75.0-99.9	371 (30.1)	378 (30.8)
Missing	1	1

* Numbers are participants taking statins at follow-up.

Outcomes

The persistence probability of taking all types of statins (combined), during the 18-month follow-up period, for vitamin D treatment and placebo groups, is shown in **Fig. 1**. This figure shows that non-persistence was higher in the placebo group than the vitamin D group.

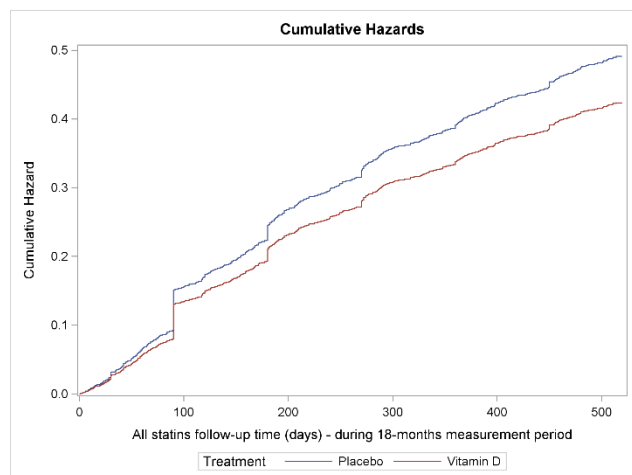


Figure 1. Cumulative hazard function plot of non-persistence with statins during 18-month measurement period (after first prescription).

Monthly 100,000 IU vitamin D3 supplementation significantly improved the persistence with taking all statins up to the end of the 18-month measurement period after the statin index date, compared with placebo (hazard

ratio 1.2; 95% CI 1.0, 1.3; $p=0.03$) (61.1% vs 65.3%). Findings were consistent, though not statistically significant in vitamin D-deficient participants who had a baseline deseasonalized 25(OH)D <50 nmol/L ($n=670$, hazard ratio 1.1; 95% CI 0.9, 1.4; $p=0.48$).

Conclusions

Among participants with long-term statin therapy in general population, we found that 100,000 IU monthly vitamin D3 supplementation significantly improved the persistence with taking statin therapy during an 18-month follow-up period, compared to placebo. The full results for 24-months follow-up have been recently published (Wu et al. 2018).

The role of vitamin D supplementation as an adjunct therapy for patients on long-term statins merits further investigation.

References

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