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Statin Use and Calcific Uremic Arteriopathy: A Matched Case-Control Study

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Abstract

Background—Calcific uremic arteriopathy (CUA), also known as calciphylaxis, is characterized by vascular calcification, thrombosis and intense inflammation. Prior research has shown that statins have anticalcification, antithrombotic and antiinflammatory properties; however, the association between statin use and CUA has not been investigated.

Methods—This matched case-control study included 62 adult maintenance hemodialysis (HD) patients with biopsy-confirmed CUA diagnosed between the years 2002 and 2011 (cases). All cases were hospitalized at the time of diagnosis. Controls (n = 124) were hospitalized maintenance HD patients without CUA (matched to cases by gender and timing of hospitalization). Univariate and multivariable logistic regression models were applied to compute odds ratio (OR) and 95% confidence intervals (CI) for CUA in statin users, and also to examine previously described associations.

Results—The mean age of cases was 58 years. Most were females (68%), and of white race (64%). Statin use was more common in controls than in cases (39 vs. 19%, $p < 0.01$). Statin use was associated with lower odds of CUA in unadjusted (OR 0.38, 95% CI 0.18–0.79) and adjusted (OR 0.20, 95% CI 0.05–0.88) analyses. Hypercalcemia (OR 2.25, 95% CI 1.14–4.43), hypoalbuminemia (OR 5.73, 95% CI 2.79–11.77), calcitriol use (OR 5.69, 95% CI 1.02–31.77) and warfarin use (OR 4.30, 95% CI 1.57–11.74) were positively associated with CUA in adjusted analyses whereas paricalcitol and doxercalciferol were not (OR 1.33, 95% CI 0.54–3.27).

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Disclosures Statement

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Conclusion—Statin use may be negatively associated with odds of CUA. Further large prospective studies with attention to potential confounders are needed to confirm these findings.

Keywords

Calcific uremic arteriolopathy; Calciphylaxis; Case control; Statin; Vitamin D

Introduction

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare but highly fatal disorder of the skin and subcutaneous tissue [1, 2]. The exact incidence of CUA is unknown [2], but it is predominantly seen in patients with end-stage renal disease [3] with only sporadic reports in patients with preserved renal function [4, 5]. Although CUA was first described over 5 decades ago [6], it remains a poorly understood phenomenon with an obscure pathogenesis and no effective treatment [2, 7].

Histologically, CUA is characterized by dermal arteriolar calcification and thrombosis accompanied by intense inflammation of the subcutaneous adipose tissue [2, 3]. Reactive oxygen species, endothelial dysfunction and transdifferentiation of vascular smooth muscle cells into osteoblast-like cells (leading to vascular calcification and a prothrombotic state) are postulated to play significant roles in its pathogenesis [8, 9]. Statins, potent lipid lowering agents, have been shown to exert antioxidant effects and improve endothelial function in uremic animals [10] and in maintenance hemodialysis (HD) patients [11]. Statins have also been shown to have antithrombotic properties [12] and to prevent vascular calcification in experimental models [13]. However, it is not known whether these properties enable statins to offer any protection against the CUA development.

We performed a matched case-control study to define the relationship between statin use and CUA development in maintenance HD patients. We also examined associations described in prior studies [14–17] and analyzed the trend in the number of CUA cases over the study period.

Methods

Study Design and Subjects

Patients were identified from Partners Healthcare System's Research Patient Data Registry (RPDR) using natural language processing software. The RPDR has information on patient demographics, diagnoses, laboratory data and procedures, and serves as a central clinical data warehouse for over 1.8 million patients [18]. We also validated our case identification strategy by performing an independent query of histopathology records at pathology departments of the participating institutions for biopsy-confirmed CUA cases. The study protocol was approved by the Partners Institutional Review Board.

CUA cases in this study were defined as adult (age >18 years) maintenance HD patients with biopsy-confirmed CUA diagnosed between January 2002 and December 2011 at one of the participating institutions (Brigham and Women's Hospital and Massachusetts General Hospital, Boston, Mass., USA). Biopsy confirmation was performed by a dermatopathologist

after reviewing Hematoxylin and Eosin and von Kossa stains. In cases with uncertainty, diagnosis of CUA was conferred only if consensus from other dermatopathologists was obtained. Patients with clinically suspected CUA who lacked biopsy confirmation and patients who were not on maintenance HD were excluded. All cases that we identified were hospitalized at the time of CUA diagnosis. Controls were hospitalized maintenance HD patients with no known or suspected CUA. Controls were randomly selected from the RPDR to match cases by gender (since CUA is predominantly described in females [16]). The timing of the control hospitalization was also matched to that of the CUA diagnosis (± 6 months). For example, given a maintenance HD female patient with CUA diagnosed in July 2009, the control would be a female maintenance HD patient hospitalized between January 2009 and December 2009. A case:control ratio of 1: 2 was used.

Study Data

Study data were obtained from the RPDR and from comprehensive review of medical records. Captured variables included demographics, comorbidities such as diabetes mellitus, obesity, autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, polymyositis, Sjögren syndrome, antiphospholipid antibody syndrome, or giant cell arteritis), macrovascular disease (coronary artery disease, cerebrovascular disease, or peripheral vascular disease), HD vintage, HD access, month/year of diagnosis (cases), CUA lesion characteristics, relevant laboratory parameters, medications (statins, calcium-based phosphate binders, vitamin D receptor agonists (VDRAs), cinacalcet, iron therapy, warfarin and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker), and 1-year mortality since diagnosis of CUA for cases and corresponding 1-year mortality for controls. Statins included all available HMG-CoA reductase inhibitors (atorvastatin, simvastatin, pravastatin, lovastatin, rosuvastatin and fluvastatin). Serum calcium levels were corrected for albumin using the following formula: corrected serum calcium = measured serum calcium + $0.8(4 - \text{measured serum albumin})$ [19]. Corrected serum calcium values were used for all analyses and results were verified using uncorrected serum calcium values. Laboratory data and medication use were abstracted at the time of CUA diagnosis for cases and at the time of hospital admission for controls. VDRAs were categorized as selective (paricalcitol, doxercalciferol) or non-selective (calcitriol).

Statistical Analyses

Categorical variables were summarized by frequency. Mean and standard deviation values were reported for normally distributed continuous variables. Median and interquartile ranges were reported for nonnormally distributed data. Categorical variables were compared between cases and controls using a χ^2 test. Normally distributed continuous variables were compared using independent samples t test and nonnormally distributed variables were compared using Mann-Whitney U test. Comparisons were also made between statin users and statin nonusers.

Logistic regression models were applied to compute odds ratio (OR) and 95% confidence intervals (CI) for CUA in statin users with statin nonusers as a reference. The selection of covariates for multivariable-adjusted models was based upon significance in unadjusted analyses, CUA associations described in prior studies [14–17], significant differences

between statin users and nonusers, and clinical relevance. Sensitivity analyses were conducted to compare rates of CUA per 100 patient-years of dialysis in statin users and nonusers using Poisson regression models. Analyses were also conducted with VDRA users subgrouped into selective and non-selective VDRA. Mineral bone parameters, calcium-based phosphate binders and cinacalcet use were compared between selective and nonselective VDRA users.

To address the pattern of CUA incidence at our institutes, we counted the number of newly diagnosed CUA cases during each year of the study period. To account for potential changes in the number of hospitalized maintenance HD patients over the study period, we computed incidence rate of CUA by dividing the number of CUA cases by total number of maintenance HD patients hospitalized for each year. A correlation coefficient (r_s) between year of diagnosis and number of newly diagnosed CUA cases was calculated using Spearman correlation.

All analyses were performed using the SAS program (version 9.2, Cary, N.C., USA). Statistical significance was set as $p < 0.05$.

Results

We identified 73 patients with clinically suspected or biopsy-confirmed CUA over the 10-year study period. We excluded patients on peritoneal dialysis ($n = 2$), patients with functioning renal allograft ($n = 2$), patients with nonuremic calciphylaxis ($n = 2$) and maintenance HD patients with clinically suspected CUA for whom biopsy confirmation was either not performed ($n = 4$) or was negative ($n = 1$). After these exclusions, 62 patients satisfied eligibility criteria (cases). Involvement of proximal body parts (abdomen, thighs, back and breasts) was seen in 76% of cases, distal body parts (hands and feet) were involved in 21% of cases, and both proximal and distal body parts were involved in the remaining cases. Skin ulceration prior to CUA diagnosis was noted in 70% of cases. Reasons for hospitalizations for controls included cardiovascular (35%), access-related infections and complications (34%), nonaccess-related infections (25%) and other causes such as gastrointestinal disease and cancer (6%).

Baseline Characteristics

Table 1 summarizes the baseline characteristics for cases and controls. The average age of cases and controls was similar (58 ± 14 vs. 58 ± 13 years, $p = 0.94$). Most cases were white (64%) and female (68%). The median HD vintage for cases was 1.7 years and 2.0 years for controls ($p = 0.71$). HD access distribution (catheter vs. arteriovenous fistula or graft) was comparable between the cases and controls ($p = 0.80$). The prevalence of diabetes mellitus, obesity, autoimmune disease and macrovascular disease were similar between cases and controls. Serum calcium (both uncorrected and albumin corrected; $p = 0.03$), phosphorous ($p < 0.01$) and the calcium-phosphorous product ($p < 0.01$) were higher for cases compared to controls, and serum albumin levels were significantly lower ($p < 0.01$). Serum parathyroid hormone (PTH), alkaline phosphatase, 25-hydroxyvitamin D and low-density lipoprotein (LDL) were similar between the two groups.

Statin use was more common in controls than in cases (39 vs. 19%, $p < 0.01$). Overall VDRA use was similar between cases and controls (55 vs. 52%, $p = 0.76$); however, use of calcitriol was greater in cases compared to controls (15 vs. 3%, $p < 0.01$). Warfarin use was also more prevalent in cases (44 vs. 19%, $p < 0.01$).

Statin Use and CUA

In unadjusted analyses, statin use was negatively associated with CUA (OR 0.38, 95% CI 0.18–0.79; table 2). CUA rate per 100 patient-years of dialysis was lower in the statin users compared to nonusers (7.5 vs. 15.3; $p = 0.03$). Statin users, when compared to nonusers, had a higher prevalence of obesity (53 vs. 27%, $p < 0.01$) and macrovascular disease (97 vs. 21%, $p < 0.01$), lower LDL levels (91 vs. 102 mg/dl, $p = 0.02$) and higher albumin levels (3.5 vs. 3.2 g/dl, $p = 0.02$). The prevalence of autoimmune disease was similar between statin users and nonusers (8 vs. 9%, $p = 0.10$). Iron use was more common among statin users compared to nonusers (32 vs. 17%, $p = 0.02$), whereas warfarin, VDRA, calcium-based phosphate binder, cinacalcet and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was similar between the two groups.

Statin use continued to be associated with lower odds of CUA (OR 0.20, 95% CI 0.05–0.88) in analyses adjusted for age, HD vintage, obesity, autoimmune disease, macrovascular disease, serum levels of mineral bone parameters, LDL, albumin, VDRA, warfarin and iron therapy (table 3). Although statin use was associated with reduced odds of CUA, it was not associated with a significant reduction in 1-year mortality when compared to nonusers (30 vs. 34%, $p = 0.67$).

Other Associations for CUA

In unadjusted logistic regression analyses, higher albumin-corrected serum calcium, higher serum phosphorous, higher calcium-phosphorous product, higher alkaline phosphatase, lower serum albumin, calcitriol use and warfarin use were positively associated with CUA (table 2). Uncorrected serum calcium was also positively associated with CUA (OR 1.93, 95% CI 1.15–3.24). No significant associations were observed with other covariates.

Higher albumin-corrected serum calcium, lower serum albumin, calcitriol use, and warfarin use continued to be positively associated with CUA in adjusted analyses (table 3). Uncorrected serum calcium levels were also positively associated with CUA in adjusted analyses (OR 2.23, 95% CI 1.10–4.21). No significant associations with CUA were observed with serum phosphorous, calcium-phosphorous product, serum alkaline phosphatase and serum PTH.

In adjusted analyses, selective VDRA were not associated with CUA whereas calcitriol was positively associated with CUA (table 3). Serum PTH levels were significantly higher in calcitriol users compared to selective VDRA users (412 vs. 232 pg/ml, $p = 0.04$), whereas serum calcium (9.0 vs. 8.8 mg/dl, $p = 0.80$), phosphorous (5.8 vs. 5.5 mg/dl, $p = 0.10$) and calcium-phosphorous product (51.1 vs. 46.1, $p = 0.10$) were similar in calcitriol users compared to selective VDRA users. Calcium-based phosphate binder (21 vs. 24%, $p = 0.56$), and cinacalcet (14 vs. 12%, $p = 0.74$) use was similar between calcitriol and VDRA users.

CUA Incidence and Mortality

Figure 1 shows a trend in CUA incidence over the study period. We observed an increasing trend in newly diagnosed CUA cases over time ($r_s = 0.84$, $p < 0.01$). The average annual incidence rate over the study period was 0.78 per 100 hospitalized maintenance HD patients, and in recent years the incidence rate was noted to be slightly above 1% compared to approximately 0.6% a decade ago.

One-year mortality was 54% in CUA subjects and 22% in control subjects ($p < 0.001$). In CUA cases where cause of death was available ($n = 25$), most deaths (74%) were attributable to infection.

Discussion

CUA is a rare but highly devastating and fatal condition with 1-year mortality between 45 and 80% [2, 7, 14]. At present, there is no known effective treatment and there is an urgent need to explore strategies that can effectively prevent CUA. We designed this matched case-control study primarily to investigate associations between statin use and CUA. We identified 62 biopsy-confirmed CUA cases and observed that statin use was negatively associated with odds of CUA. As described in prior studies, we also observed positive association for CUA with hypoalbuminemia and warfarin use [14, 15]. In addition, we detected a possible differential CUA odds with VDRA use; calcitriol was positively associated with CUA odds whereas no association was noted with selective VDRA (paricalcitol and doxercalciferol). An increase in the number of CUA cases was noted over the study period.

There is a biological plausibility to our data, as statins are known to have antioxidant [10, 11, 20, 21], antiinflammatory [22], anticalcification [10, 13] and antithrombotic properties [12, 23]. We speculate that this constellation of statin actions may attribute to reduction in CUA risk. In fact, CUA is considered to be a dermal analogue of acute myocardial infarction and statins have been shown to have major beneficial actions in acute myocardial infarction [24]. Although statins have not been found to offer significant cardiovascular events or mortality reduction in randomized controlled trials conducted in HD population [25–27], and anticalcification properties are yet to be confirmed in this population, it is possible that pleiotropic actions of statins may be important in preventing complications such as CUA. In addition, as noted from SHARP study results, limitations derived from low modifiable vascular event rate and sample size may have been responsible for negative results of earlier statin trials in HD patients and it is necessary to conduct further prospective studies to evaluate statins in HD patients [28].

Our study findings regarding VDRA are novel. Prior studies have reported mixed results on association between VDRA and CUA [15, 29]. These prior studies did not evaluate selective VDRA and calcitriol separately, and it is possible that differences in their findings are possibly due to different VDRA evaluated. Calcitriol in prior studies has been associated with higher serum calcium, phosphorous and PTH levels compared to selective VDRA [30, 31], and in nephrectomized rats high doses of calcitriol have been shown to cause more vascular calcification compared to high doses of selective VDRA [32]. In fact,

we observed higher serum calcium levels in CUA cases compared to controls, a finding consistent with some earlier studies [15], but discrepant from other studies that report low serum calcium at the time of CUA diagnosis (attributed to tissue deposition of calcium) [33, 34]. However, no significant differences in serum calcium, phosphorous or calcium-phosphorous product were noted between calcitriol users compared to selective VDRA users. Whether differences in CUA odds noted in our study represent diverse effects of VDRA on vasculature is unknown and needs further investigation.

Warfarin, a vitamin K antagonist, is commonly used in HD patients. Warfarin is associated with increased risk of major bleeding in this population and also has gained recognition as a risk factor for vascular calcification [35, 36]. Although exact mechanisms underlying vascular calcification remain under investigation, inhibition of vitamin K-dependent carboxylation of calcification inhibitor such as matrix Gla protein has been implicated [36]. Our study confirms association between warfarin use and CUA that is described previously [15] and emphasizes individualizing risk benefit discussion regarding warfarin therapy in HD patients.

One of the biggest challenges in any case-control study is selection of an appropriate control group. We selected maintenance HD patients as controls since all the cases in this study were hospitalized at the time of CUA diagnosis and comparison with ambulatory maintenance HD patients may have introduced a healthy control bias. We believe that selecting hospitalized HD patients as controls reduced potential selection bias for statin exposure, as factors that commonly dictate statin use (such as macrovascular disease, diabetes mellitus, serum LDL levels) were equally distributed between the cases and controls. Controls were randomly selected from the available source population and did not differ from the source population in terms of demographics and relevant laboratory characteristics (data not shown). By matching cases and controls by time period, we further limited bias that can be introduced by temporal trends in practice management.

Our study has important limitations. Although ours is one of the largest studies on this topic, we did not have adequate sample size to conduct analyses to address specific types of statins and to conduct dose-response analyses. We could not conduct subgroup analyses to evaluate proximal versus distal CUA due to sample size limitations. Temporal data on laboratory and medication covariates for weeks or months prior to CUA diagnosis were not available; hence, we could not conduct longitudinal analyses. Although we constructed multivariable models adjusted for potential confounders including covariates such as hypoalbuminemia that were more common in statin users than nonusers and observed an independent negative association with statin use, residual confounding cannot be definitively excluded in any association study of this nature and causality cannot be inferred. Over one third of control patients were hospitalized for cardiovascular complications. It is possible that adherence to medications such as statins may have been lower in this group and this may have introduced potential residual confounding. Data on markers of inflammation (e.g. C-reactive protein) and oxidative stress (oxidized LDL) were not available; hence, we could not provide any mechanistic explanations for the observed associations. Lastly, assessing the true incidence of CUA remains difficult. Although in our study increase in the number of CUA cases was

noted, we could not distinguish whether this represented a true increase in disease incidence, improved detection, or a combination of the two.

Due to these limitations, we consider our study findings as preliminary and propose their confirmation in future larger prospective studies. Only a large randomized controlled trial can definitively confirm causality, though the rarity of CUA poses a challenge for the design of such a trial. In the absence of a clinical trial, larger prospective observational studies are needed to confirm associations from this study. In this regard, we propose that CUA registries should systematically collect longitudinal data on medications and laboratory parameters to verify associations observed in this study.

In conclusion, statin use is negatively associated with CUA in maintenance HD patients. Hypercalcemia, hypoalbuminemia, warfarin and calcitriol use are positively associated with CUA, whereas no such association was noted with selective VDRAs. These findings are preliminary and study of this condition will benefit from disease registries. Confirmation of these associations in future prospective studies will not only offer potential prevention strategies, but also significant insights into the pathobiology of this highly lethal condition, and may have significant treatment implications for HD patients.

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Fig. 1.
Increasing trend in CUA cases over the study period.

Table 1

Comparison of baseline characteristics of CUA cases and controls

Characteristic	Cases (n = 62)	Controls (n = 124)	p value
Age, years	58 ± 14	58 ± 13	0.94
Female gender, %	68	68	Not applicable
White race, %	64	59	0.62
Hemodialysis vintage, years	1.7 (0.6–3.8)	2.0 (0.7–3.8)	0.71
Catheter access, %	48	49	0.80
Diabetes mellitus, %	44	42	0.88
Obesity, %	37	35	0.75
Autoimmune disease, %	9	8	0.82
Macrovascular disease, %	45	44	0.97
Serum calcium ^I , mg/dl	8.9 (8.4–9.4)	8.8 (8.1–9.1)	0.03
Serum phosphorous, mg/dl	5.7 (5.2–5.9)	5.4 (4.6–5.7)	<0.01
Serum calcium-phosphorous product	49.7 (43.5–55.6)	45.4 (40.3–49.2)	<0.01
Serum alkaline phosphatase, U/l	123 (84–186)	120 (67–165)	0.11
Serum intact PTH, pg/ml	297 (129–453)	285 (136–421)	0.60
Serum 25-hydroxyvitamin D, ng/ml	16 (11–24)	19 (13–24)	0.24
Serum albumin, g/dl	2.9 (2.5–3.4)	3.6 (3.1–3.9)	<0.01
Serum LDL, mg/dl	98 (67–110)	103 (64–118)	0.33
Statin, %	19	39	<0.01
VDRA, %	55	52	0.76
Calcitriol, %	15	3	<0.01
Selective VDRA, %	47	48	0.92
Calcium-based phosphate binders, %	32	33	0.91
Cinacalcet, %	18	22	0.67
Warfarin, %	44	19	<0.01
Iron therapy, %	19	23	0.61
ACE inhibitor/ARB, %	25	27	0.52

Age is reported as mean ± SD, all other continuous variables are reported as median with interquartile range in parentheses. ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

^I Albumin-corrected serum calcium.

Table 2

Results from unadjusted logistic regression analyses

Covariate	OR	95% CI	p value
Statin	0.38	0.18–0.79	<0.01
Age (per 1 year increment)	1.01	0.9–1.02	0.94
White race	0.81	0.42–1.57	0.54
Hemodialysis vintage (per 1 month increment)	0.99	0.99–1.00	0.86
Diabetes Mellitus	0.94	0.51–1.73	0.83
Obesity	1.11	0.59–2.10	0.75
Autoimmune disease	1.04	0.75–1.81	0.78
Macrovascular disease	0.99	0.54–1.85	0.99
Serum calcium ^I (per 1 mg/dl increment)	1.83	1.13–2.98	0.02
Serum phosphorous (per 1 mg/dl increment)	1.39	1.02–1.88	0.04
Serum calcium-phosphorous product (per 1 unit increment)	1.05	1.01–1.08	<0.01
Serum alkaline phosphatase (per 10 U/l increment)	1.10	1.00–1.11	0.03
Serum intact PTH (per 10 pg/ml increment)	1.01	0.99–1.10	0.21
Serum 25-hydroxyvitamin D (per 1 ng/ml reduction)	1.01	0.96–1.06	0.77
Serum albumin (per 1 g/dl reduction)	4.68	2.64–8.28	<0.01
Serum LDL (per 10 mg/dl increment)	1.03	0.79–1.10	0.33
VDRA	1.14	0.62–2.10	0.68
Calcitriol	5.09	1.50–17.28	<0.01
Selective VDRA	0.97	0.53–1.78	0.92
Calcium-based phosphate binders	0.96	0.50–1.85	0.91
Cinacalcet	0.75	0.38–1.66	0.66
Warfarin	3.39	1.72–6.66	<0.01
Iron therapy	0.82	0.39–1.76	0.61
ACE inhibitor/ARB	0.73	0.42–1.63	0.55

^I Albumin-corrected serum calcium.

ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Table 3

Results from multivariable-adjusted logistic regression analyses

Covariate	OR	95% CI	p value
Statin	0.20	0.05–0.88	0.02
Age (per 1 year increment)	0.99	0.97–1.03	0.85
White race	1.76	0.70–4.39	0.23
Diabetes Mellitus	0.86	0.35–2.11	0.74
Obesity	0.82	0.31–2.19	0.69
Macrovascular disease	2.80	0.85–9.25	0.09
Serum calcium ^I (per 1 mg/dl increment)	2.25	1.14–4.43	0.02
Serum phosphorous (per 1 mg/dl increment)	1.09	0.75–1.59	0.21
Serum calcium-phosphorous product (per 1 unit increment)	1.03	0.97–1.07	0.20
Serum alkaline phosphatase (per 10 U/l increment)	1.01	0.99–1.01	0.09
Serum intact PTH (per 10 pg/ml increment)	1.00	0.99–1.00	0.39
Serum albumin (per 1 g/dl reduction)	5.73	2.79–11.77	<0.01
Serum LDL (per 10 mg/dl increment)	0.99	0.96–1.01	0.50
VDRA	1.38	0.57–3.33	0.47
Calcitriol	5.69	1.02–31.77	0.03
Selective VDRA	1.33	0.54–3.27	0.39
Warfarin	4.30	1.57–11.74	<0.01
Iron therapy	0.45	0.16–1.30	0.14

^I Albumin-corrected serum calcium.