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Calcium Supplementation and the Risks of Atherosclerotic Vascular Disease in Older Women: Results of a 5-Year RCT and a 4.5-Year Follow-up

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ABSTRACT

Concern has been expressed that calcium supplementation, a key intervention for preventing osteoporotic fracture in older women, may increase the risk of atherosclerotic vascular disease. To evaluate the risk further, an examination of complete verified atherosclerotic vascular hospitalization and mortality data from a 5-year randomized, controlled trial (RCT) of calcium carbonate and 4.5 years of posttrial follow-up was undertaken. This study used data from a published 5-year randomized, double-blinded, placebo-controlled trial [Calcium Intake Fracture Outcome Study (CAIFOS)]. The participants were 1460 women aged 75.1 $\pm$ 2.7 years at baseline (1998) recruited from the general population and randomized to receive 1200 mg of calcium carbonate daily or an identical placebo. All hospital admission and deaths during the 5-year study and the 4.5-year follow-up were derived from the Western Australian Data Linkage Service (WADLS). Hazard ratios (HRs) for the combined endpoint of atherosclerotic vascular mortality or first hospitalization were calculated using prespecified intention-to-treat and per-protocol models. The intervention group that received calcium supplementation did not have a higher risk of death or first-time hospitalization from atherosclerotic vascular disease in either the 5-year RCT [multivariate-adjusted HR = 0.938, 95% confidence interval (CI) 0.690–1.275] or during the 9.5 years of observational study (multivariate-adjusted HR = 0.919, 95% CI 0.737–1.146). Further analysis suggested that calcium supplementation may reduce the risk of hospitalization and mortality in patients with preexisting atherosclerotic cardiovascular disease. This trial provides compelling evidence that calcium supplementation of 1200 mg daily does not significantly increase the risk of atherosclerotic vascular disease in elderly women. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: CALCIUM SUPPLEMENTATION; RANDOMIZED; CONTROLLED TRIAL; POSTMENOPAUSAL WOMEN; ATHEROSCLEROTIC VASCULAR DISEASE; WESTERN AUSTRALIAN DATA LINKAGE SYSTEM

Introduction

Recently, Bolland and colleagues[(1)] reported that "Healthy older women randomised to calcium supplementation showed increased rates of myocardial infarction. This effect could outweigh any benefits on bone from calcium supplements." A recent reanalysis of the Kuopio Osteoporosis Risk Factor and Prevention Study[(2)] also reported an increased hazard rate for coronary heart disease morbidity and mortality among participants taking calcium supplements after, but not before, adjustment for hormone therapy, age, parity, body mass index (BMI), hypertension, diabetes, hypercholesterolemia/hyperlipidemia, smoking history, time since menopause, and dietary calcium intake. These reports have caused concern among patients and clinicians in view of the fact that calcium therapy is a key part of the public health approach to fracture prevention.

It is generally considered that myocardial infarction is a subcategory of atherosclerotic vascular disease (ASVD), a disease of the circulatory system affecting the heart and blood vessels that encompasses coronary heart disease, cerebrovascular disease, and peripheral arterial disease. Thus a reasonable, inclusive, testable hypothesis is that calcium increases ASVD.

Western Australia is fortunate in having a system that captures coded diagnosis data pertaining to all public and private inpatient contacts and death, known as the Western Australian Data Linkage System (WADLS), a division of the Health Department of Western Australia. The WADLS provides a comprehensive, population-based linkage system that connects nearly 40

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years of data from over 30 health-related data sets of residents of Western Australia.[3] The use of this data system allows complete ascertainment of verified ASVD events independent of patient report with the associated problems of loss to follow-up and inaccurate patient reporting. Thus WADLS data were used to examine ASVD hospitalization and death outcomes in a 5-year randomized, controlled trial (RCT) of calcium carbonate 1200 mg/day compared with an identical placebo.[4] Complete event data were available for a further 4.5-year observational follow-up, providing the most comprehensive and long-term follow-up of this issue yet available.

Materials and Methods

Subjects

Fourteen hundred and sixty women were recruited from the electoral role for the Calcium Intake Fracture Outcome Study (CAIFOS), a 5-year population-based study of ambulatory Western Australian women aged over 70 years designed to investigate the efficacy of calcium supplementation in preventing fracture. A recruitment letter was sent to 24,800 potentially eligible women using the electoral roll. Because voting is compulsory for adult Australians, nearly 100% of women of this age are registered. Potential participants were excluded if they had an illness likely to limit involvement in the study for 5 years or they were taking bone-active agents such as bisphosphonates or estrogen. The disposition of the participants is shown in Fig. 1. The treatment phase concluded in 2003, and the major findings were published in 2006.[4] Informed consent was obtained from each participant, including consent to access linked administrative health data from WADLS. The Human Rights Committee of the University of Western Australia approved the study.

Baseline data

At baseline, information was obtained from the patient on previous medical history and current medications; the participants were asked to verify this information with their general practitioner where available. These data then were coded using the International Classification of Primary Care—Plus (ICPC-Plus) method.[5] The coding methodology allows aggregation of different terms for similar pathologic entities, as defined by the ICD-10 coding system. This data set then was used to determine the presence of preexisting atherosclerotic vascular disease, including ischemic heart disease, heart failure, arrhythmia, stroke (excluding hemorrhagic stroke), and peripheral vascular disease (K74000–99011). Additionally, the presence of baseline risk factors for atherosclerotic vascular disease were recorded, including preexisting diabetes (T89001–90009); previous or current smoking, defined as smoking of at least 1 cigarette per day for at least 3 months at any time, and cardiovascular medications, which included beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, HMG-CoA reductase inhibitors, and antiplatelet agents. A semiquantitative food-frequency questionnaire developed by the Cancer Council of Victoria was used to assess calcium and alcohol intake.[6] Weight was assessed using digital scales, and height was assessed using a stadiometer. Total cholesterol, HDL cholesterol and triglyceride levels were determined using a Hitachi 917 auto analyser (Roche Diagnostics GmbH, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's method.[7] Baseline renal function was determined from the serum creatinine determined on a BM/Hitachi 747 Analyser (Boehringer Mannheim GmbH, Mannheim, Germany) by calculating the revised 175 Modification of Diet in Renal Disease (MDRD) study equation to estimate glomerular filtration rate (eGFR).[8-10]

Randomization

Patients received 600-mg calcium carbonate tablets or identical placebo tablets (Wyeth Consumer Healthcare, Baulkham Hills, Australia) twice daily with the morning and evening meals for 5 years. Medication was dispensed according to a block randomization design using blocks of 10. A random-number generator was used to produce the treatment order both within the blocks and then for ordering the blocks. The pharmacy

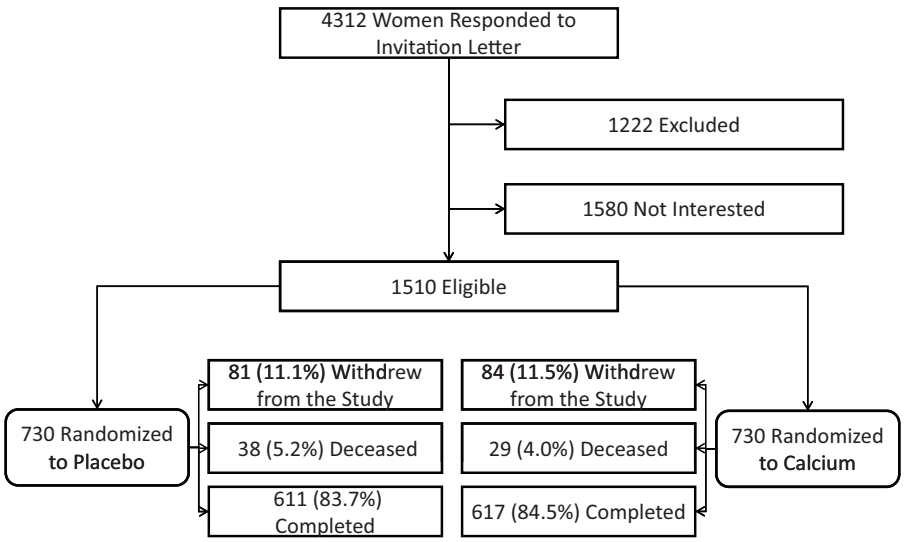

Fig. 1. Details of the recruitment, randomization, and follow-up process of participants who remained in the placebo and calcium groups for the 5-year treatment phase of the study.

dispensed the appropriate medications to the patient in study number order according to this list. The randomization code was not joined to outcome data files until the data had been verified and finalized. Compliance with tablet consumption was assessed by medication return and tablet counting. Average tablet compliance of greater than 80% was used as the definition of adherence for the patients in the per-protocol analysis.

Outcome data

The primary outcome of interest was an atherosclerotic event causing either death or hospitalization (combined endpoint). Atherosclerotic deaths and first-time hospitalizations were retrieved from WADLS for each of the study participants from 1998 when the participant was randomized until 9.5 years after the baseline visit. Atherosclerotic events were defined using diagnosis codes from the *International Classification of Diseases, Injuries and Causes of Death: Clinical Modification* (ICD-9-CM)[11] and the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision, *Australian Modification* (ICD-10-AM).[12] These codes included ischemic heart disease, which includes myocardial infarction (ICD-9-CM codes 410–414 and ICD-10-AM codes I20–I25); atrial fibrillation, flutter, or ventricular tachycardia (ICD-9-CM code 427.3 and ICD-10-AM codes I48, 427.1, and I47.2); heart failure (ICD-9-CM code 428 and ICD-10-AM code I50); cerebrovascular disease, excluding hemorrhage (ICD-9-CM codes 433–438 and ICD-10-AM codes I63–69, G45.9); and peripheral arterial disease, excluding hemorrhage (ICD-9-CM codes 440–444 and ICD-10-AM codes I70–I74). The search for atherosclerotic vascular ICD codes included all available diagnostic information that comprised parts 1 and 2 of the death certificate and the principal diagnosis in the inpatient data. All diagnosis text fields from the death certificate were used to ascertain the cause(s) of recent deaths where these data were not yet available from the WADLS.

Statistical analysis

Before beginning the analysis, a prespecified analytical protocol was produced. Time to first event was calculated in days from baseline divided into months to obtain time to event with the cutoffs of 5 or fewer years for the calcium supplementation study and 9.5 or fewer years for the extended observational study. The primary outcome was specified to be the hazard ratio (HR) of the time to first atherosclerotic vascular event (ie, hospitalization or death) using an intention-to-treat model after adjusting for age or all prespecified covariates. The method selected was a Cox proportional hazards model with the level of clinical significance set at $p \leq .05$ in a two-tailed test. The proportional hazards assumption was tested for each covariate, and no violations were detected. A fully adjusted model also was tested using potential atherosclerotic vascular risk factors determined at baseline, which included age, atherosclerotic vascular disease, diabetes, eGFR, previous or current smoking, receipt of cardiovascular medications, and calcium intake as covariates.

A per-protocol analysis of patients who had tablet compliance of 80% or above then was undertaken, including an age- and multivariate-adjusted analysis ($p \leq .025$ significance). Further specific analysis of the effects of calcium compared with placebo was undertaken in patients with each of the prespecified risk factors alone. Finally, a study of treatment effects on the incidence of individual components of atherosclerotic cardiovascular disease, including myocardial infarction alone, was undertaken. Baseline variables were tested for differences using ANOVA or a chi-squared test where appropriate, and differences in ASVD events over 5 and 9.5 years were assessed by a chi-squared test, with a Yates-corrected chi-squared test used when appropriate. Any significant differences then were tested using age-adjusted logistic regression. The number of ASVD events divided by the number of person-years/1000 in the study censored for death or an ASVD event was used to calculate overall event rates for the 5 and 9.5 years of the study. The data were analyzed using SPSS (Version 15, SPSS, Inc., Chicago, IL, USA) and SAS (Version 9, SAS Institute, Inc., Chicago, IL, USA).

Results

The recruitment and disposition of the patients in the first 5 years of the study are shown in Fig. 1. The baseline characteristics of the participants are shown in Table 1. There were no significant differences between the calcium and placebo groups. The per-protocol group consisted of participants with 80% or greater tablet compliance and comprised 420 recruited to the calcium group (57.5%) and 410 recruited to the placebo group (56.2%), resulting in an overall tablet adherence of 56.8% for the 5-year study.

Combined atherosclerotic vascular hospitalizations and deaths (Table 2 and Fig. 2)

In the 5-year intention-to-treat (ITT) analysis, 104 participants (31.4/1000 person-years) in the calcium supplementation group and 103 (30.9/1000 person-years) in the placebo group sustained either hospitalization or death from ASVD (age-adjusted ITT HR = 1.005, 95% CI 0.766–1.320; multivariate-adjusted ITT HR = 0.938, 95% CI 0.690–1.275). At 9.5 years, 195 participants (33.9/1000 person-years) in the calcium supplementation group and 200 participants (34.5/1000 person-years) in the placebo group sustained hospitalization or death from ASVD (age-adjusted ITT HR = .975, 95% CI 0.800–1.187; multivariate-adjusted ITT HR = 0.919, 95% CI 0.737–1.146).

In the 5-year per-protocol (PP) analysis in the calcium supplementation group, there were 49 participants who sustained vascular hospitalizations or death compared with 48 participants in the placebo group (age-adjusted PP HR = 1.014, 95% CI 0.681–1.511; multivariate-adjusted PP HR = 1.051, 95% CI 0.678–1.630). In the 9.5-year per-protocol analysis, there were 96 participants who sustained at least one vascular event in the calcium supplementation group compared with 102 participants in the placebo group (age-adjusted PP HR = 0.944, 95% CI 0.714–1.247, multivariate-adjusted PP HR 0.953 95% CI 0.702–1.296).

The effect of calcium therapy on the risks of each of the subsets of atherosclerotic cardiovascular disease is shown in Table 2. At 9.5 years but not 5 years, calcium therapy was associated with significantly fewer heart failure death events [9.5-year age-adjusted odds ratio (OR) = 0.503, 95% CI 0.261–0.968, $p = .040$]. Examination of ischemic heart disease events

Table 1. Baseline Variables by Treatment Group

Characteristics	Calcium	Placebo	*p* Value
Number of subjects	730	730	
Age (years)	75.2 ± 2.7	75.1 ± 2.7	.512
Body mass index (kg/m^2)	27.1 ± 4.76	27.4 ± 4.7	.212
Smoking ever (yes)	280 (38.4%)	259 (35.5%)	.215
Diabetes (yes)	48 (6.6%)	47 (6.4%)	.940
Atherosclerotic vascular disease (yes)	108 (14.8%)	104 (14.2%)	.882
Cardiovascular medication (yes)	439 (60.1%)	458 (62.7%)	.307
Calcium intake (mg/day)	961 ± 356	970 ± 352	.697
Alcohol intake (g/day)	6.6 ± 9.5	7.1 ± 10.5	.401
Cholesterol (mmol/L)	5.8 ± 1.1	5.9 ± 1.1	.703
HDLC (mmol/L)	1.4 ± 0.4	1.5 ± 0.4	.587
LDLC (mmol/L)	3.7 ± 1.0	3.7 ± 1.0	.943
Triglycerides (mmol/L)	1.6 ± 0.7	1.6 ± 0.7	.662
Estimated GFR[a] (mL/min/1.73 m^2)	65.8 ± 14.6	64.73 ±14.4	.204

Note: Results are mean and SD or number (%). HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol.
[a]eGFR available for 1239 participants (calcium group $n = 629$; placebo $n = 610$).

alone, which included myocardial infarction, showed that there was no difference in either the 5- or 9.5-year analysis (5-year age-adjusted OR = 0.918, 95% CI 0.616–1.369, 9.5-year age-adjusted OR = 0.998. 95% CI 0.724–1.374).

In Fig. 3 the effects of treatment are shown for those participants with baseline prespecified risk factors for atherosclerotic vascular disease. In those who had ASVD at baseline, the 5-year analysis showed that calcium supplementation was associated with a significant decrease in the risk of participants sustaining ASVD events (age-adjusted HR = 0.637, 95% CI 0.392–1.034; multivariate-adjusted HR = 0.438, 95% CI 0.246–0.781, $p = .005$). This effect dissipated in the 9.5-year analysis. No other baseline risk factor was associated with an increase or decrease in risk associated with consuming calcium tablets.

Discussion

In this study, the incidence of overall ASVD and the subset of ischemic heart disease including myocardial infarction was the same in the calcium group as in the placebo group. The strengths of this study over previous studies include the complete follow-up of all 1460 participants and the comprehensive evaluation of ASVD risk factors both at baseline and over 9.5 years using validated hospital admission and mortality data. The prespecified covariate analysis provides further reassurance in that the participants with preexisting cardiovascular disease, a group already at higher risk of ASVD, if randomized to the calcium supplementation group had a reduced risk of ASVD compared with placebo over the first 5 years, an effect that dissipated over

Table 2. Number of Individuals (%) With at Least One Atherosclerotic Vascular Disease Event at 5 or 9.5 Years in 730 Participants in Each Treatment Group

	5 Years		9.5 Years	
Atherosclerotic vascular disease events	Calcium	Placebo	Calcium	Placebo
Total vascular hospitalization and deaths	104 (14.2%)	103 (14.1%)	195 (26.7%)	200 (27.4%)
Total vascular deaths	18 (2.5%)	24 (3.3%)	59 (8.1%)	72 (9.9%)
Ischemic heart disease	13 (1.8%)	9 (1.2%)	34 (4.7%)	36 (4.9%)
Arrhythmia	1 (0.1%)	3 (0.4%)	10 (1.4%)	16 (2.2%)
Heart failure	6 (0.8%)	9 (1.2%)	14 (1.9%)[b]	27 (3.7%)[b]
Cerebrovascular disease[a]	6 (0.8%)	8 (1.1%)	20 (2.7%)	22 (3.0%)
Peripheral arterial disease[a]	1 (0.1%)	1 (0.1%)	1 (0.1%)	4 (0.5%)
Total vascular hospitalization	91 (12.5%)	91 (12.5%)	160 (21.9%)	169 (23.2%)
Ischemic heart disease	50 (6.8%)	54 (7.4%)	85 (11.6%)	85 (11.6%)
Arrhythmia	21 (2.9%)	16 (2.2%)	39 (5.3%)	40 (5.5%)
Heart failure	7 (1.0%)	9 (1.2%)	22 (3.0%)	28 (3.8%)
Cerebrovascular disease[a]	30 (4.1%)	25 (3.4%)	45 (6.2%)	57 (7.8%)
Peripheral arterial disease[a]	10 (1.4%)	12 (1.6%)	19 (2.6%)	18 (2.5%)

[a]Excluding hemorrhage.
[b]Significantly different by chi-squared test $p = .039$, OR = 0.503, 95% CI 0.261–0.968, $p = .040$. Total event categories are less than the sum of the individual groups because some individuals sustained more than one disorder.

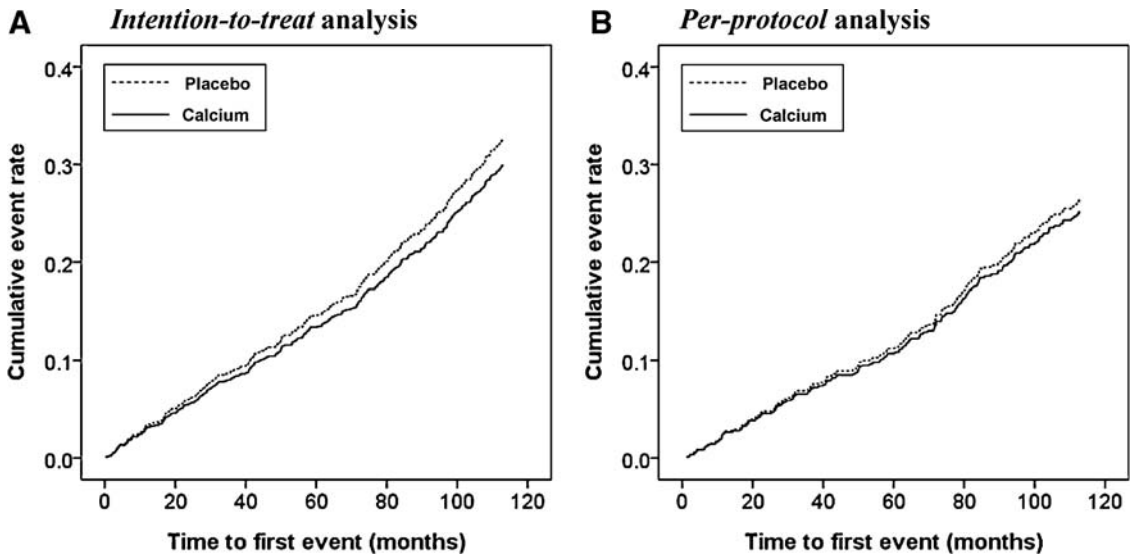

Fig. 2. Cox proportional hazards analysis for combined atherosclerotic vascular disease events (incident hospitalization or death) over 9.5 years adjusted for age, calcium intake at baseline, compliance, baseline atherosclerotic vascular disease, eGFR, diabetes, previous or current smoking, and cardiovascular medications. (*A*) Intention-to-treat analysis (calcium group $n = 730$; placebo $n = 730$) multivariate-adjusted HR = 0.919, 95% CI 0.737–1.146. (*B*) Per-protocol analysis (calcium group n = 420; placebo $n = 410$) multivariate-adjusted HR = 0.953, 95% CI 0.702–1.296.

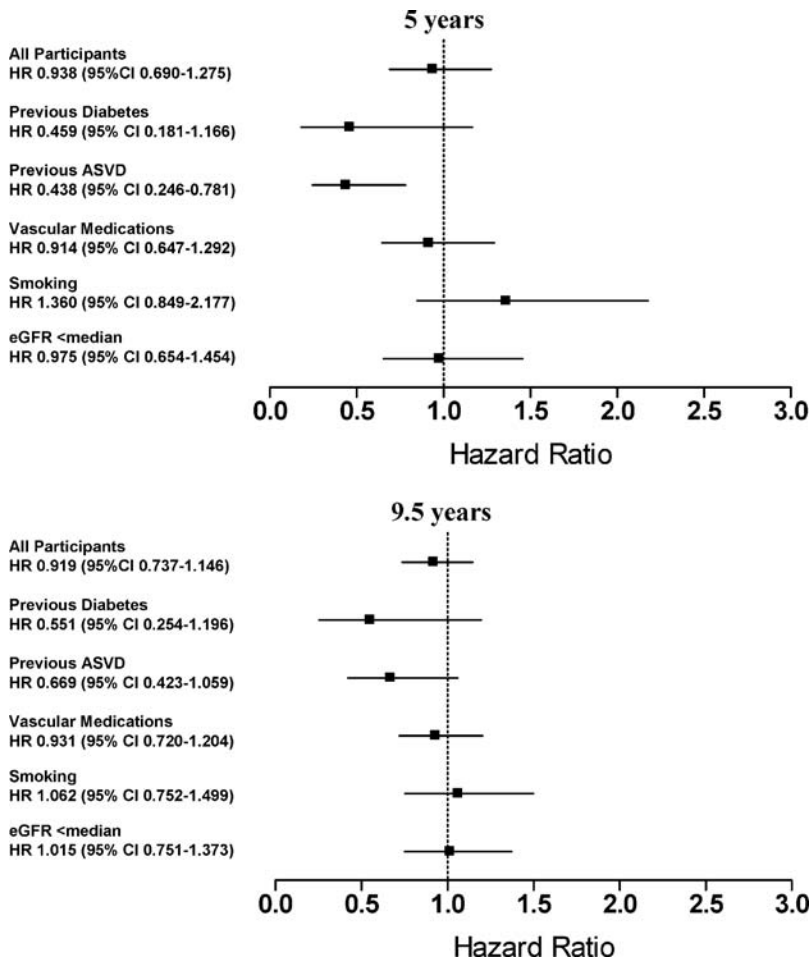

Fig. 3. The effect of calcium treatment compared with placebo on all atherosclerotic vascular disease hospitalizations and death outcomes over 5 and 9.5 years. The analyses used groups with the named baseline risk factor. Analyses adjusted for baseline age, calcium intake, compliance, cardiovascular disease, eGFR, diabetes, previous or current smoking, and baseline cardiovascular medications unless that covariate was the subject of the analysis. eGFR refers to estimated glomerular function rate, whereas ASVD refers to atherosclerotic vascular disease.

the next 4.5 years. In addition, the incidence of the heart failure outcome was reduced in calcium-treated patients at 9.5 years but not 5 years. The apparent beneficial effect of calcium needs to be treated with caution because it could be argued that because of testing of multiple outcomes, a more rigorous *p* value than .05 should be used.

This study overcomes many of the problems of previous studies of this issue. First, misclassification of myocardial infarction and stroke and poor concordance between self-reported events and adjudicated or validated events, particularly with angina, congestive heart failure, and peripheral arterial disease, have been reported in other studies.[1,13,14] As is done in pharmaceutical trials, our analysis chose to analyze serious adverse events, that is, verified hospitalization and death data attributed to ASVD, to provide a more robust analytical endpoint. It should be noted that the validity of Western Australian Hospital Morbidity Data System (HMDS) data has been verified exhaustively with over 250 publications,[3] whereas cardiovascular endpoints have been assessed against self-reported and adjudicated medical records and found to be as accurate as adjudicated medical records.[13,15]

Another problem with reporting ASVD is that it consists of several categories, including coronary heart disease, cerebrovascular disease, and peripheral arterial disease.[16] These broad categories of atherosclerotic vascular disease are further broken down into subcategories of disease by the ICD coding system. Given the relatively low frequency of events in these subcategories of disease, it is possible to find statistical differences between groups owing to the problem of multiple statistical testing. To overcome this problem, an overall analysis of all ASVD events was prespecified. Finally, because some participants had multiple events over 9.5 years, which may introduce bias into the statistical analyses, we used a proportional hazards model that allowed only one event per participant.

Previous RCT analyses have not met these stringent study design criteria. The Auckland study used three different event endpoints and three different types of event ascertainments that gave three different event rates. Under these circumstances, it can be calculated that a *p* value suggesting that an effect is unlikely to be related to chance is .006. Using this criterion, none of the analyses reported in this study would have demonstrated an adverse effect of calcium. The Randomised Evaluation of Calcium or Vitamin D (RECORD) trial, suggested in the Auckland article to support the hypothesis that calcium has adverse effects on mortality, is based on a reported increased death rate from 16.3% in the placebo group to 18.5% in the calcium group.[17] Unfortunately, the RECORD investigators did not explain exactly how the deaths were ascertained or the causes of death. The Women's Health Initiative (WHI) study is also suggested to support the adverse effect of calcium hypothesis, this time using another classification and composite endpoint of myocardial infarction, coronary heart disease death, coronary artery bypass graft, or percutaneous coronary intervention.[18] The major findings were that calcium plus vitamin D did not significantly increase or decrease the incidence of coronary or cerebrovascular disease over the 7-year period of the study. Interestingly, the investigators reported a beneficial interaction of calcium and vitamin D supplementation to reduced stroke risk in a subset of women with increased baseline cardiovascular risk.

In contrast to the Kuopio observational study,[2] other observational studies have found that calcium intake was inversely associated with ischemic heart disease in elderly women[19] and inversely associated with mortality from stroke but not cardiovascular disease[20] or had no effect.[21] Interventional studies of calcium supplementation have shown beneficial changes to the circulating lipid profile of elderly women, reduced visceral adipose tissue accumulation, transient reductions in blood pressure, and an increased rate of weight loss in obese patients.[22-28]

In addition to methodologic differences, another explanation for our differences from the Bolland report may relate to lower bioavailability of calcium from calcium carbonate 600 mg with meals twice a day compared with calcium citrate 400 mg in the morning before breakfast and 600 mg in the evening. However, Lappe and Heaney,[29] using either 1400 mg of calcium citrate per day or 1500 mg of calcium carbonate per day, reported a decrease from 6.94 events per 1000 person-years in the placebo group to 4.76 events per 1000 person-years in the calcium group. Thus there is no clear dose-response effect.

Increased compliance may increase the patient's exposure to deleterious consequences of interventions. We addressed this by preplanning a per-protocol analysis, setting the compliance level at 80% or more of the medication. Bolland and colleagues[1] also report a per-protocol analysis of those consuming 60% or more of the medication, and the rate ratio for adverse events increased and the confidence interval increased, but the results again were nonsignificant.

In conclusion, it would appear that concerns that have been raised previously that calcium supplementation may cause or potentiate atherosclerotic cardiovascular disease depend on studies that have used comparisons of multiple endpoints in varying populations, often with less than ideal methods of ascertainment. Our study, which was designed to specifically address this issue, found no evidence that calcium supplementation increased the risk of atherosclerotic cardiovascular disease.

It would be unfortunate if reports of increased risk of calcium supplements alone dissuaded patients and clinicians from using calcium supplementation and vitamin D. This combination has been shown in meta-analyses to reduce the risk of any clinical fracture by 12% in patients not selected for osteoporosis (risk ratio = 0.88, 95% CI 0.83–0.95, $p = .0004$).[30]

Disclosures

All the authors state that they have no conflicts of interest.

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