Bone, Artery, & Renal Function in CKD

Supplementation of Calcium in Patients with Normal Renal Function

Disclosures: none

Objectives:

1. To assess the impact of Calcium supplementation on bone, colon, & CV system
2. To assess the impact of Calcium supplementation on CV events
3. To assess the impact of Calcium supplementation on CV function & coagulation

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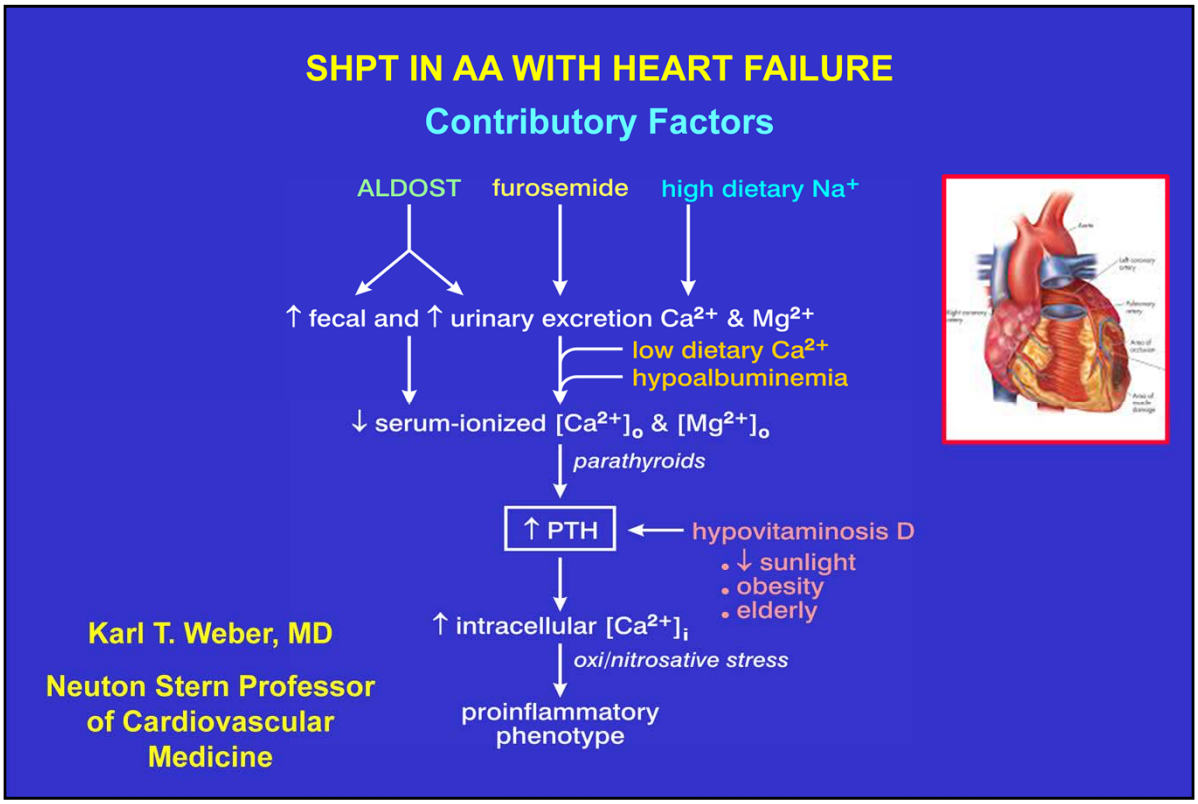
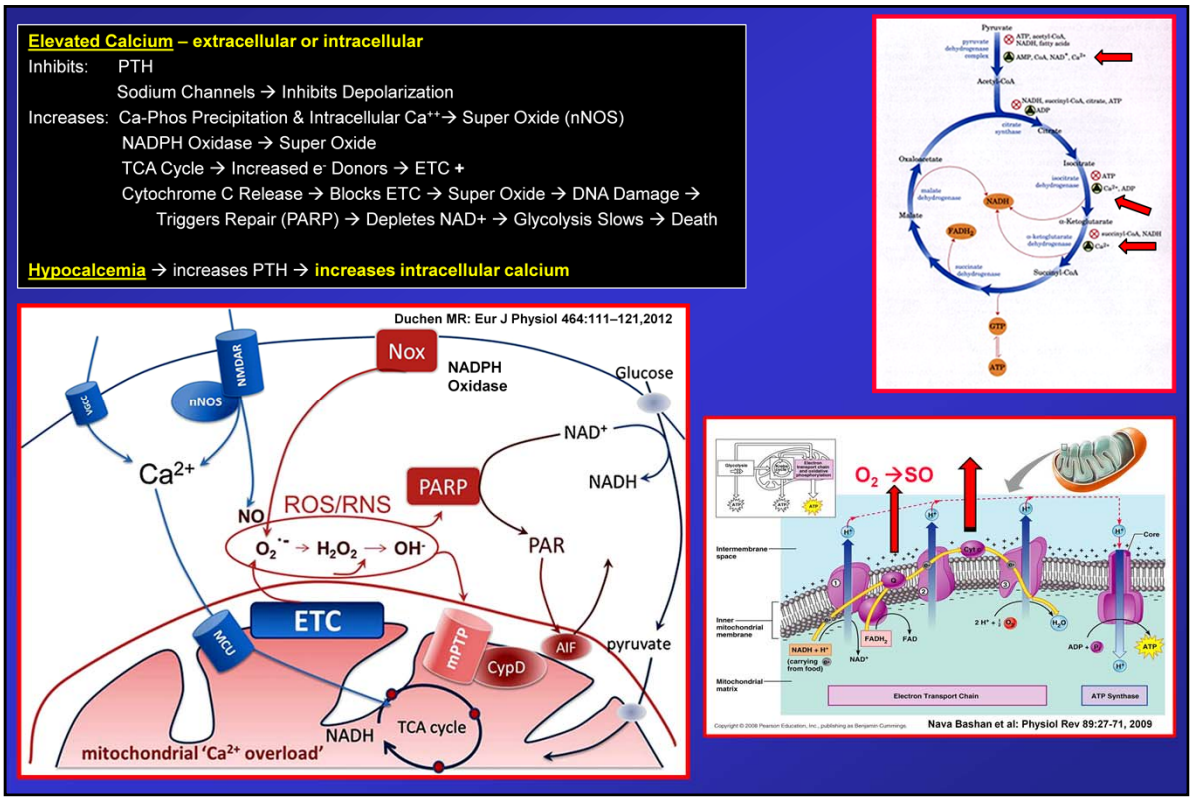


Aldosterone increases fecal & urinary calcium & magnesium excretion.

Furosemide potentiates these loses.

Vitamin D deficiency contributes to the low serum calcium → high PTH and increased intracellular calcium.



Mitochondria, calcium-dependent neuronal death and neurodegenerative disease. Eur J Physiol 464:111–121, 2012. Michael R. Duchen

Fig. 3 Scheme of pathways involved in glutamate-induced excitotoxicity. Calcium influx through voltage-gated or NMDAR-gated channels is followed by mitochondrial Ca2+ influx through the mitochondrial calcium uniporter (MCU). While the physiological consequence of raised intra-mitochondrial [Ca2+] is an increased activity of the three rate limiting enzymes of the TCA cycle, pathological and prolonged Ca2+ influx leads to mitochondrial Ca2+overload. NMDAR mediated Ca2+ influx is closely coupled to the generation of NO by nNOS; raised Ca2+ may activate the NADPH oxidase (Nox), while mitochondrial Ca2+ overload may also increase generation of superoxide by the electron transport chain (ETC). Nitrosative or oxidative stress arising either from the ETC or from Nox activation may cause over activation of PARP. PARP consumes NAD+ to form PAR polymers, causing depletion of NAD+, failure of glycolysis and so failure of mitochondrial substrate supply. This culminates in the loss of $\Delta\psi m$, ATP depletion, and cell death. The PAR polymers generated by PARP may also cause release of AIF which amplifies cell death following its translocation to the nucleus.

Abstract Understanding the mechanisms of neuronal dysfunction and death represents a major frontier in contemporary medicine, involving the acute cell death in stroke, and the attrition of the major neurodegenerative diseases, including Parkinson's, Alzheimer's, Huntington's and Motoneuron diseases. A growing body of

evidence implicates mitochondrial dysfunction as a key step in the pathogenesis of all these diseases, with the promise that mitochondrial processes represent valuable potential therapeutic targets. Each disease is characterised by the loss of a specific vulnerable population of cells--dopaminergic neurons in Parkinson's disease, spinal motoneurons in Motoneuron disease, for example. We discuss the possible roles of cell type-specific calcium signalling mechanisms in defining the pathological phenotype of each of these major diseases and review central mechanisms of calcium-dependent mitochondrial-mediated cell death.

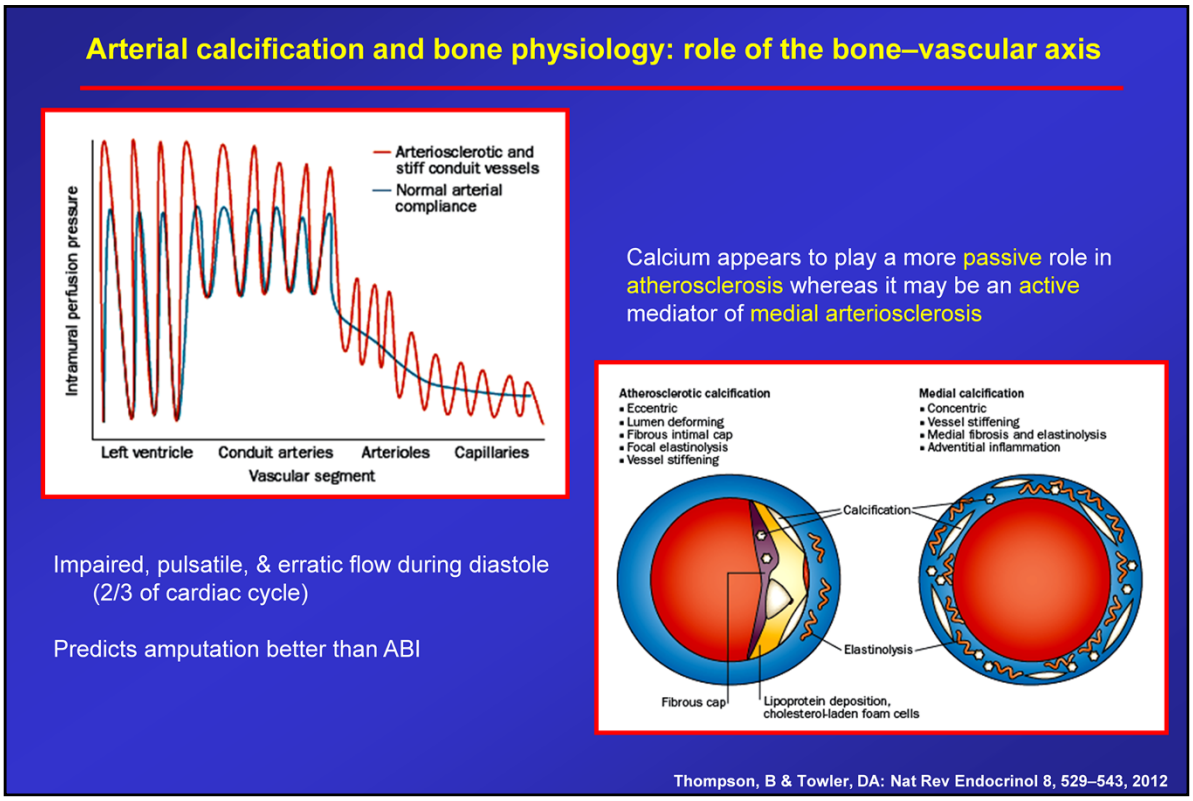
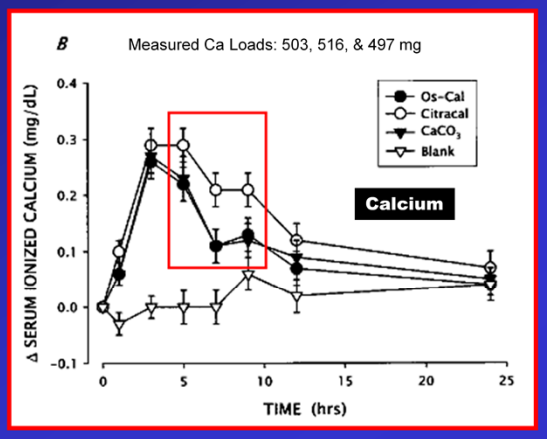


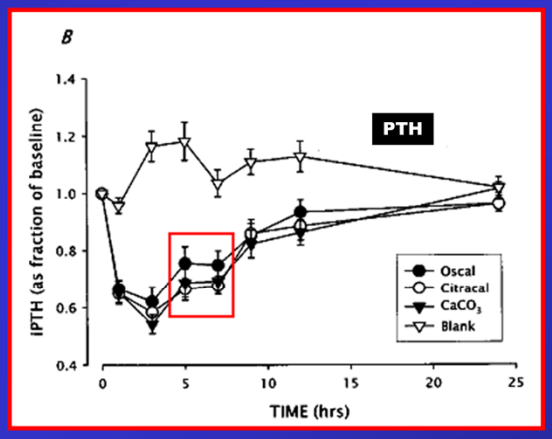
Figure 1 | Consequences of arterial stiffening and impaired Windkessel physiology. During systole, some kinetic energy is stored as potential energy in the elastic conduit arteries. This stored energy permits not only coronary perfusion but also smooth distal capillary perfusion during diastole (blue tracing). With arteriosclerotic stiffening (red tracing), less potential energy is stored during systole, giving rise to impaired, pulsatile and erratic flow during diastole (two-thirds of the cardiac cycle). Systolic blood pressure is also increased.

Calcium Supplementation

"The Good"

Absorbability and Cost Effectiveness in Calcium Supplementation





24 Post-Meno Women
Age ~56 yrs
BMI ~29 & Healthy

Supplemented w/
10 mcg 25VitD for 1 week
Ca served with light meal

Table 3. Urine Calcium Increments after Ingestion of Test Calcium Sources*

	0–5 hours			5–24 hours			0–24 hours		
	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM
Os-Cal	23	21	3	22	22	8	22	43	10
Citracal	23	16	3	22	30	10	22	46	9
$CaCO^3$	21	20	4	20	20	10	20	38	9

* mg Ca above the corresponding excretion following the blank load.

Heaney RP et al: J Amer Coll Nutrition 20(3):239–246, 2001

Background: Cost-effectiveness of calcium supplementation depends not only on the cost of the product but on the efficiency of its absorption. Published cost-benefit analyses assume equal bioavailability for all calcium sources. Some published studies have suggested that there are differences in both the bioavailability and cost of the major calcium supplements.

Design: Randomized four period, three-way cross-over comparing single doses of off-the-shelf commercial calcium supplements containing either calcium carbonate or calcium citrate compared with a no-load blank and with encapsulated calcium carbonate devoid of other ingredients; subjects rendered fully vitamin D-replete with 10 mg/day 25(OH)D by mouth, starting one week prior to the first test.

Subjects: 24 postmenopausal women

Methods: Pharmacokinetic analysis of the increment in serum total and ionized calcium and the decrement in serum iPTH induced by an oral calcium load, based upon multiple blood samples over a 24-hour period; measurement of the rise in urine calcium excretion. Data analyzed by repeated measures ANOVA. Cost calculations based on average retail prices of marketed products used in this study from April through October, 2000.

Results: All three calcium sources (marketed calcium carbonate, encapsulated calcium carbonate and marketed calcium citrate) produced identical 24-hour time courses for the increment in total serum calcium. Thus, these were equally absorbed and had equivalent bioavailability. Urine calcium rose slightly more with

the citrate than with the carbonate preparations, but the difference was not significant. Serum iPTH showed the expected depression accompanying the rise in serum calcium, and there were no significant differences between products.

Conclusion: Given the equivalent bioavailability of the two marketed products, the cost benefit analysis favors the less expensive carbonate product.

VII. Meta-Analysis of Calcium Supplementation for the Prevention of Postmenopausal Osteoporosis

15 Trials: 1,806 Menopausal Women - Most w/o VitD supplements
Calcium Supplements (~1,000 mg) vs Usual Intake (~400-900 mg)

Small Positive Effect
Especially in Secondary Prevention

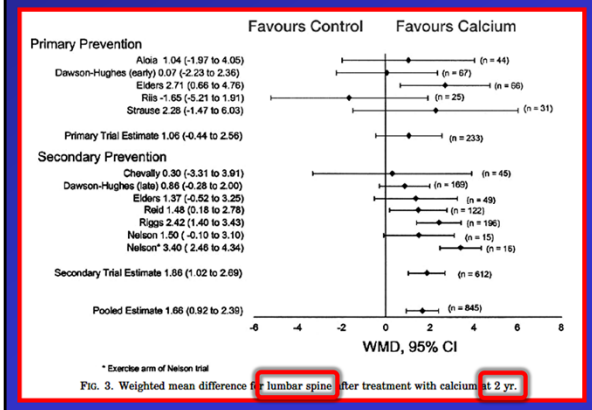


FIG. 3. Weighted mean difference for lumbar spine after treatment with calcium at 2 yr.

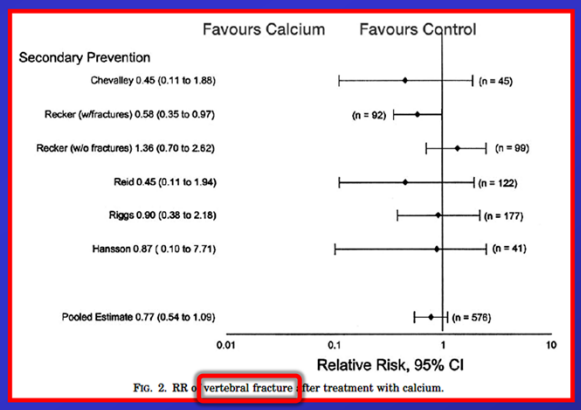


FIG. 2. RR of vertebral fracture after treatment with calcium.

TABLE 2. Weighted RR of fracture After treatment with calcium

Fracture site	No. of trials	Sample size	RR (95% CI)	RR *P* value	Heterogeneity *P* value
Vertebral	5	576	0.77 (0.54,1.09)	0.14	0.40
Non vertebral	2	222	0.86 (0.43,1.72)	0.66	0.54

We interpreted $P \leq 0.05$ as indicating important between-study differences in results.

Shea B et al: Endocrine Reviews 23(4):552–559, 2002

Objective: To summarize controlled trials examining the effect of calcium on bone density and fractures in postmenopausal women.

Data Source: We searched MEDLINE and EMBASE up to 1998 and the Cochrane Controlled Register up to 2000, and we examined citations of relevant articles and proceedings of international meetings. We contacted osteoporosis investigators to identify additional studies, and primary authors for unpublished data.

Study Selection: We included 15 trials (1806 patients) that randomized postmenopausal women to calcium supplementation or usual calcium intake in the diet and reported bone mineral density of the total body, vertebral spine, hip, or forearm, or recorded the number of fractures, and followed patients for at least 1 yr.

Data Extraction: For each trial, three independent reviewers assessed the methodological quality and extracted data.

Data Synthesis: We found calcium to be more effective than placebo in reducing rates of bone loss after two or more years of treatment. The pooled difference in percentage change from baseline was 2.05% [95% confidence interval (CI) 0.24 – 3.86] for total body bone density, 1.66% (95% CI 0.92–2.39) for the lumbar spine, 1.64% (95% CI 0.70 –2.57) for the hip, and 1.91% (95% CI 0.33–3.50) for the distal radius. The relative risk (RR) of fractures of the vertebrae was 0.77, with a wide CI (95% CI 0.54 –1.09); the RR for nonvertebral fractures was 0.86 (95% CI 0.43–1.72).

Conclusions: Calcium supplementation alone has a small positive effect on bone

density. The data show a trend toward reduction in vertebral fractures, but do not meaningfully address the possible effect of calcium on reducing the incidence of nonvertebral fractures.

Calcium plus Vitamin D Supplementation and the Risk of Fractures (WHI)

36,282 Post-Meno Women
Age 50-79 yo & Healthy
$CaCO_3$ 1,000 mg + 400 IU VitD

Current HRT users – 52%
Assigned to HRT arm – 22%
Normal Hip BMD ~60%
Osteopenia ~36%

Average follow-up – 7 years

Jackson RD et al: NEJM 354(7):669-683, 2006

Table 1. Characteristics of the Participants in the Calcium with Vitamin D Trial at the Time of the WHI Screening, According to Randomly Assigned Group.*

Characteristic	Calcium+Vitamin D (N=18,176)	Placebo (N=18,106)
Age at screening		
Mean — yr	62.4±7.0	62.4±6.9
50 to 59 yr — no. (%)	6,728 (37.0)	6,694 (37.0)
60 to 69 yr — no. (%)	8,275 (45.5)	8,245 (45.5)
70 to 79 yr — no. (%)	3,173 (17.5)	3,167 (17.5)
Race or ethnic group — no. (%)†		
White	15,047 (82.8)	15,106 (83.4)
Black	1,682 (9.3)	1,635 (9.0)
Hispanic	789 (4.3)	718 (4.0)
American Indian or Native American	77 (0.4)	72 (0.4)
Asian or Pacific Islander	369 (2.0)	353 (1.9)
Unknown or not identified	212 (1.2)	222 (1.2)
Family history of fracture after 40 yr of age — no. (%)	6,835 (37.6)	6,692 (37.0)
History of fracture — no. (%)		
At any age	6,311 (34.7)	6,228 (34.4)
At age ≥55 yr	1,948 (10.7)	1,968 (10.9)
Calcium supplementation ≥500 mg/day — no. (%)	5,192 (28.6)	5,313 (29.3)
Total calcium intake (supplements, diet, and medications)		
Mean — mg/day	1148±654	1154±658
<800 mg/day — no. (%)	6,104 (33.6)	6,003 (33.2)
800 to <1200 mg/day — no. (%)	4,715 (25.9)	4,655 (25.7)
≥1200 mg/day — no. (%)	7,002 (38.5)	7,095 (39.2)
Total vitamin D intake (supplements and diet)		
Mean — IU/day	365±265	368±266
<200 IU/day	6,827 (37.6)	6,671 (36.8)
200 to <400 IU/day	3,379 (18.6)	3,423 (18.9)
400 to <600 IU/day	4,188 (23.0)	4,295 (23.7)
≥600 IU/day	3,427 (18.9)	3,364 (18.6)

Background The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women remains equivocal.

Methods We recruited 36,282 postmenopausal women, 50 to 79 years of age, who were already enrolled in a Women's Health Initiative (WHI) clinical trial. We randomly assigned participants to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D3 daily or placebo. Fractures were ascertained for an average follow-up period of 7.0 years. Bone density was measured at three WHI centers.

Results Hip bone density was 1.06 percent higher in the calcium plus vitamin D group than in the placebo group ($P<0.01$). Intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture (95 percent confidence interval, 0.72 to 1.08), 0.90 for clinical spine fracture (0.74 to 1.10), and 0.96 for total fractures (0.91 to 1.02). The risk of renal calculi increased with calcium plus vitamin D (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34). Censoring data from women when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (95 percent confidence interval, 0.52 to 0.97). Effects did not vary significantly according to prerandomization serum vitamin D levels.

Conclusions Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones.

Calcium plus Vitamin D Supplementation and the Risk of Fractures (WHI)

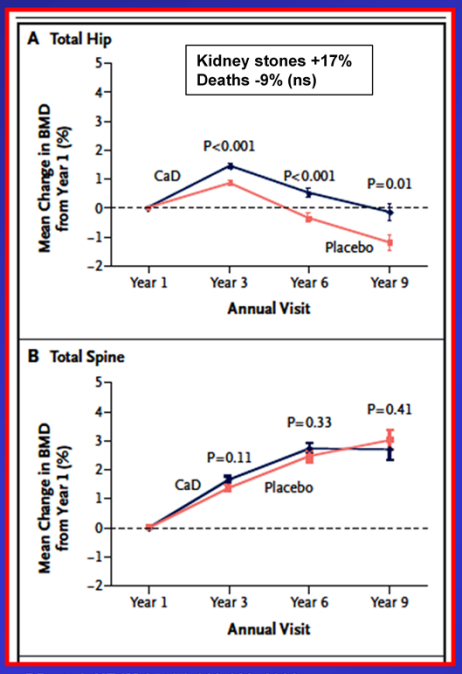


Table 2. Effect of Calcium with Vitamin D Supplementation on Clinical Outcomes, According to Randomly Assigned Group.*

Analysis	Calcium + Vitamin D	Placebo	Hazard Ratio (95% CI)†
Intention-to-treat analysis			
Follow-up time — yr	7.0±1.4	7.0±1.4	
Rate of fracture — no. of cases (annualized %)			
Hip	175 (0.14)	199 (0.16)	0.88 (0.72–1.08)
Clinical vertebral	181 (0.14)	197 (0.15)	0.90 (0.74–1.10)
Lower arm or wrist	565 (0.44)	557 (0.44)	1.01 (0.90–1.14)
Total	2102 (1.64)	2158 (1.70)	0.96 (0.91–1.02)
Analysis excluding follow-up time for participants 6 mo after nonadherence detected			
Follow-up time — yr	3.8±2.9	3.9±2.9	
Rate of fracture — no. of cases (annualized %)			
Hip	68 (0.10)	99 (0.14)	0.71 (0.52–0.97)
Clinical vertebral	91 (0.13)	104 (0.15)	0.89 (0.67–1.19)
Lower arm or wrist	312 (0.45)	308 (0.43)	1.05 (0.90–1.23)
Total	1119 (1.63)	1222 (1.72)	0.94 (0.87–1.02)

Benefit only seen in women assigned HRT
Fx Rate: 0.10 v 0.17 % annually
no HRT: 0.24 v 0.22 % annually

Jackson RD et al: NEJM 354(7):669-683, 2006

Background The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women remains equivocal.

Methods We recruited 36,282 postmenopausal women, 50 to 79 years of age, who were already enrolled in a Women's Health Initiative (WHI) clinical trial. We randomly assigned participants to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D3 daily or placebo. Fractures were ascertained for an average follow-up period of 7.0 years. Bone density was measured at three WHI centers.

Results Hip bone density was 1.06 percent higher in the calcium plus vitamin D group than in the placebo group (P<0.01). Intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture (95 percent confidence interval, 0.72 to 1.08), 0.90 for clinical spine fracture (0.74 to 1.10), and 0.96 for total fractures (0.91 to 1.02). The risk of renal calculi increased with calcium plus vitamin D (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34). Censoring data from women when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (95 percent confidence interval, 0.52 to 0.97). Effects did not vary significantly according to prerandomization serum vitamin D levels.

Conclusions Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones.

Calcium/Vitamin D Supplementation and Cardiovascular Events - WHI

36,282 Post-menopausal Woman → $CaCO_3$ 500 mg + VitD 200 IU BID for 7 yrs

TABLE 1. Baseline Characteristics by Treatment Group Assignment

	Calcium/Vitamin D (N=18 176)	Placebo (N=18 106)	*P*
Age, y	62.4±7.0	62.4±6.9	0.97
Body mass index, kg/m²	29.1±5.9	29.0±5.9	0.24
Waist circumference, cm	88.9±13.7	88.8±13.7	0.46
Systolic blood pressure, mm Hg	127±17	128±17	0.48
Diastolic blood pressure, mm Hg	76±9	76±9	0.56
Total calcium intake (supplements, diet, and medications), mg/d	1148±654	1154±658	0.40
Total vitamin D intake (supplements and diet), IU/d	365±265	368±266	0.36
Vitamin D intake (supplements), IU/d	190±235	192±235	0.46
Vitamin D intake (diet), IU/d	175±117	176±117	0.47
Ethnicity			0.45
White	15 047 (82.8)	15 106 (83.4)	
Black	1682 (9.3)	1635 (9.0)	
Hispanic	789 (4.3)	718 (4.0)	
American Indian/Alaskan native	77 (0.4)	72 (0.4)	
Asian/Pacific islander	369 (2.0)	353 (1.9)	
Unknown	212 (1.2)	222 (1.2)	

LDL = 127 mg/dl
HDL = 60 mg/dl
TGs = 160 mg/dl

Hsia J et al: Circulation 115:846-854, 2007

Background—Individuals with vascular or valvular calcification are at increased risk for coronary events, but the relationship between calcium consumption and cardiovascular events is uncertain. We evaluated the risk of coronary and cerebrovascular events in the Women's Health Initiative randomized trial of calcium plus vitamin D supplementation.

Methods and Results—We randomized 36 282 postmenopausal women 50 to 79 years of age at 40 clinical sites to calcium carbonate 500 mg with vitamin D 200 IU twice daily or to placebo. Cardiovascular disease was a prespecified secondary efficacy outcome. During 7 years of follow-up, myocardial infarction or coronary heart disease death was confirmed for 499 women assigned to calcium/vitamin D and 475 women assigned to placebo (hazard ratio, 1.04; 95% confidence interval, 0.92 to 1.18). Stroke was confirmed among 362 women assigned to calcium/vitamin D and 377 assigned to placebo (hazard ratio, 0.95; 95% confidence interval, 0.82 to 1.10). In subgroup analyses, women with higher total calcium intake (diet plus supplements) at baseline were not at higher risk for coronary events (*P*0.91 for interaction) or stroke (*P*0.14 for interaction) if assigned to active calcium/vitamin D.

Conclusions—Calcium/vitamin D supplementation neither increased nor decreased coronary or cerebrovascular risk in generally healthy postmenopausal women over a 7-year use period.

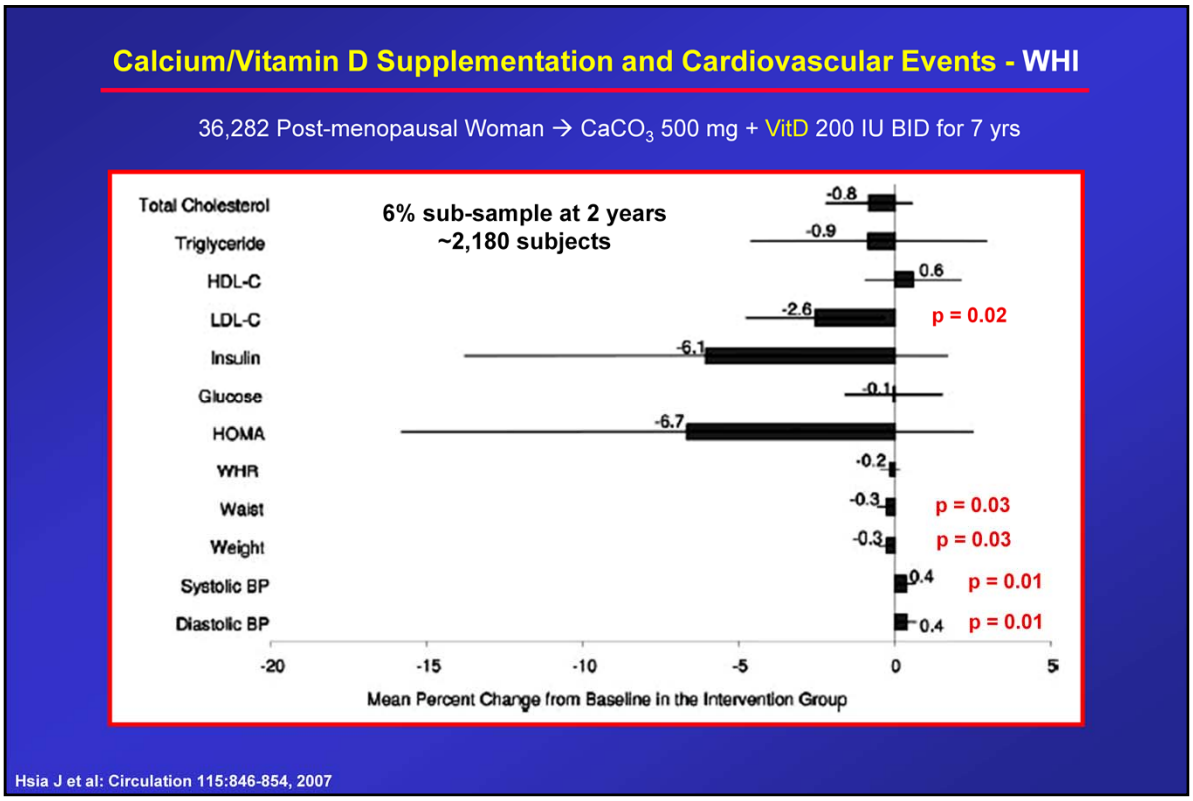


Figure 1. Differences in mean percent change from baseline to year 2 between women assigned to active calcium/vitamin D and those assigned to placebo for several intermediate outcomes. Horizontal lines represent 95% CIs. Physical measures were performed on the entire cohort; laboratory measures, in a random 6% subsample. Treatment group differences were significant for low-density lipoprotein cholesterol (LDL-C; *P*0.02), waist circumference and weight (both *P*0.03), and systolic (*P*0.01) and diastolic (*P*0.01) blood pressures. HDL-C indicates high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; WHR, waist-to-hip ratio; and BP, blood pressure.

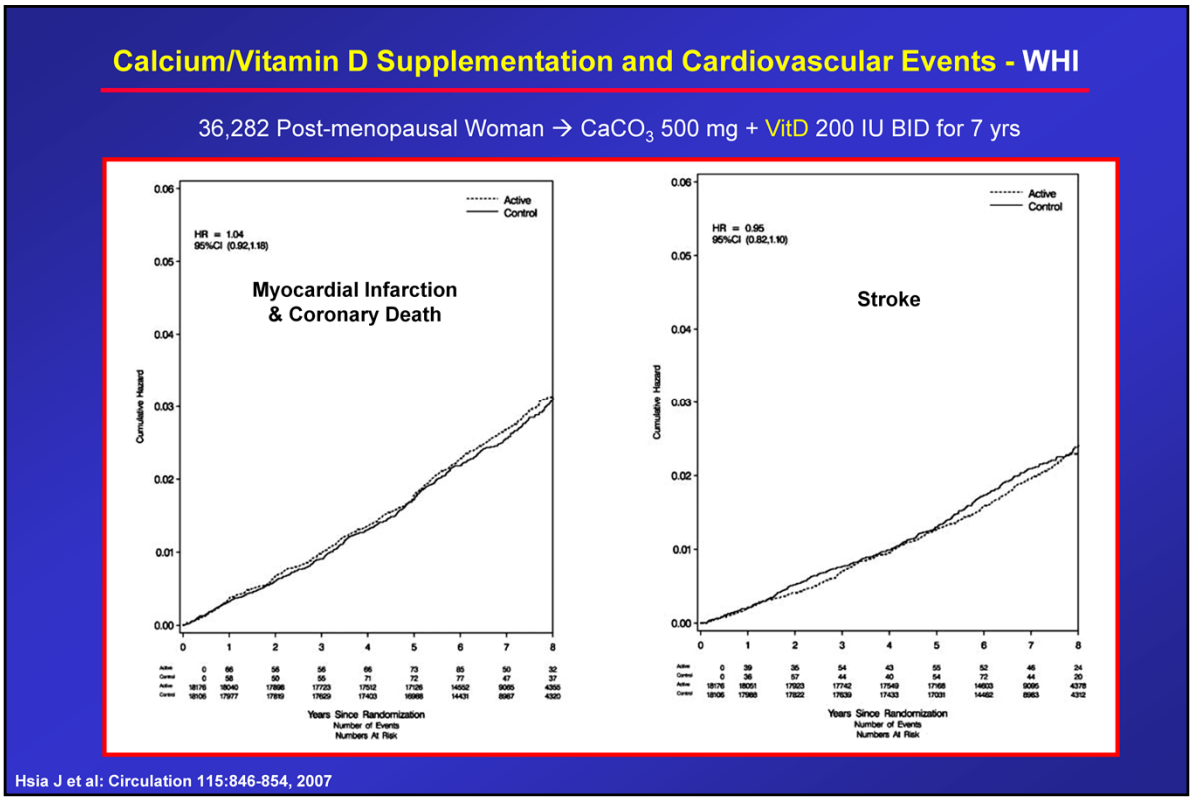


Figure 2. Kaplan-Meier estimates of cumulative hazard rates for CHD (myocardial infarction or coronary death; left) and for stroke (right). HR indicates hazard ratio.

Calcium/Vitamin D Supplementation and Cardiovascular Events - WHI

36,282 Post-menopausal Woman → $CaCO_3$ 500 mg + VitD 200 IU BID for 7 yrs

TABLE 2. Cardiovascular Events by Treatment Group Assignment

	Calcium/Vitamin D (N=18 176), n (Annualized %)	Placebo (N=18 106), n (Annualized %)	Hazard Ratio (95% CI)	*P*
Myocardial infarction or CHD death	499 (0.39)	475 (0.37)	1.04 (0.92–1.18)	0.50
Myocardial infarction	411 (0.32)	390 (0.31)	1.05 (0.91–1.20)	0.52
CHD death	130 (0.10)	128 (0.10)	1.01 (0.79–1.29)	0.92
CABG or PCI	674 (0.53)	607 (0.48)	1.09 (0.98–1.22)	0.12
Myocardial infarction/CHD death/CABG/PCI	920 (0.72)	841 (0.66)	1.08 (0.99–1.19)	0.10
Confirmed angina	404 (0.32)	377 (0.30)	1.08 (0.94–1.24)	0.30
Hospitalized heart failure	394 (0.31)	407 (0.32)	0.95 (0.83–1.10)	0.50
Stroke	362 (0.28)	377 (0.30)	0.95 (0.82–1.10)	0.51
Ischemic stroke	225 (0.18)	228 (0.18)	0.98 (0.82–1.18)	0.84
Hemorrhagic stroke	58 (0.05)	68 (0.05)	0.84 (0.59–1.19)	0.33
Other stroke	63 (0.05)	57 (0.04)	1.11 (0.77–1.59)	0.58
Transient ischemic attack	213 (0.17)	182 (0.14)	1.16 (0.95–1.42)	0.13
Stroke/transient ischemic attack	563 (0.44)	547 (0.43)	1.02 (0.91–1.15)	0.75

CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention. Numbers of events do not add up to the totals for categories because some women had >1 event.

Hsia J et al: Circulation 115:846-854, 2007

Objectives To investigate the effects of personal calcium supplement use on cardiovascular risk in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), using the WHI dataset, and to update the recent meta-analysis of calcium supplements and cardiovascular risk. Design Reanalysis of WHI CaD Study limited access dataset and incorporation in meta-analysis with eight other studies.

Data source WHI CaD Study, a seven year, randomised, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36 282 community dwelling postmenopausal women. Main outcome measures Incidence of four cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data.

Results In the WHI CaD Study there was an interaction between personal use of calcium supplements and allocated calcium and vitamin D for cardiovascular events. In the 16 718 women (46%) who were not taking personal calcium supplements at randomisation the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 (P=0.05 for clinical myocardial infarction or stroke, P=0.04 for clinical myocardial infarction or revascularisation), whereas in the women taking personal calcium supplements cardiovascular risk did not alter with allocation to calcium and vitamin D. In meta-analyses of three placebo controlled trials, calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21 (95% confidence interval 1.01 to 1.44),

P=0.04), stroke (1.20 (1.00 to 1.43), P=0.05), and the composite of myocardial infarction or stroke (1.16 (1.02 to 1.32), P=0.02). In metaanalyses of placebo controlled trials of calcium or calcium and vitamin D, complete trial-level data were available for 28 072 participants from eight trials of calcium supplements and the WHI CaD participants not taking

personal calcium supplements. In total 1384 individuals had an incident myocardial infarction or stroke. Calcium or calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.24 (1.07 to 1.45), P=0.004) and the composite of myocardial infarction or stroke (1.15 (1.03 to 1.27), P=0.009).

Conclusions Calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction, a finding obscured in the WHI CaD Study by the widespread use of personal calcium supplements. A reassessment of the role of calcium supplements in osteoporosis management is warranted.

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

Calcium Intake Fracture Outcome Study (CAIFOS): 1460 women, age 75.1 yo
Randomized to 600 mg $CaCO_3$ BID for 5 years; additional 4.5 yrs monitoring
Combined endpoint of atherosclerotic vascular mortality or first hospitalization

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) LDL 144 mg/dl	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

Lewis JR et al: J Bone Mineral Res 26(1), 35–41, 2011

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 post-trial 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±2.7 years at baseline (1998) recruited from the general population and randomized to receive 1200mg 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 pre-specified 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 1200mg daily does not significantly increase the risk of atherosclerotic vascular disease in elderly women.

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

Calcium Intake Fracture Outcome Study (CAIFOS): 1460 women, age 75.1 yo
Randomized to 600 mg $CaCO_3$ BID for 5 years; additional 4.5 yrs monitoring
Combined endpoint of atherosclerotic vascular mortality or first hospitalization

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.

Lewis JR et al: J Bone Mineral Res 26(1), 35–41, 2011

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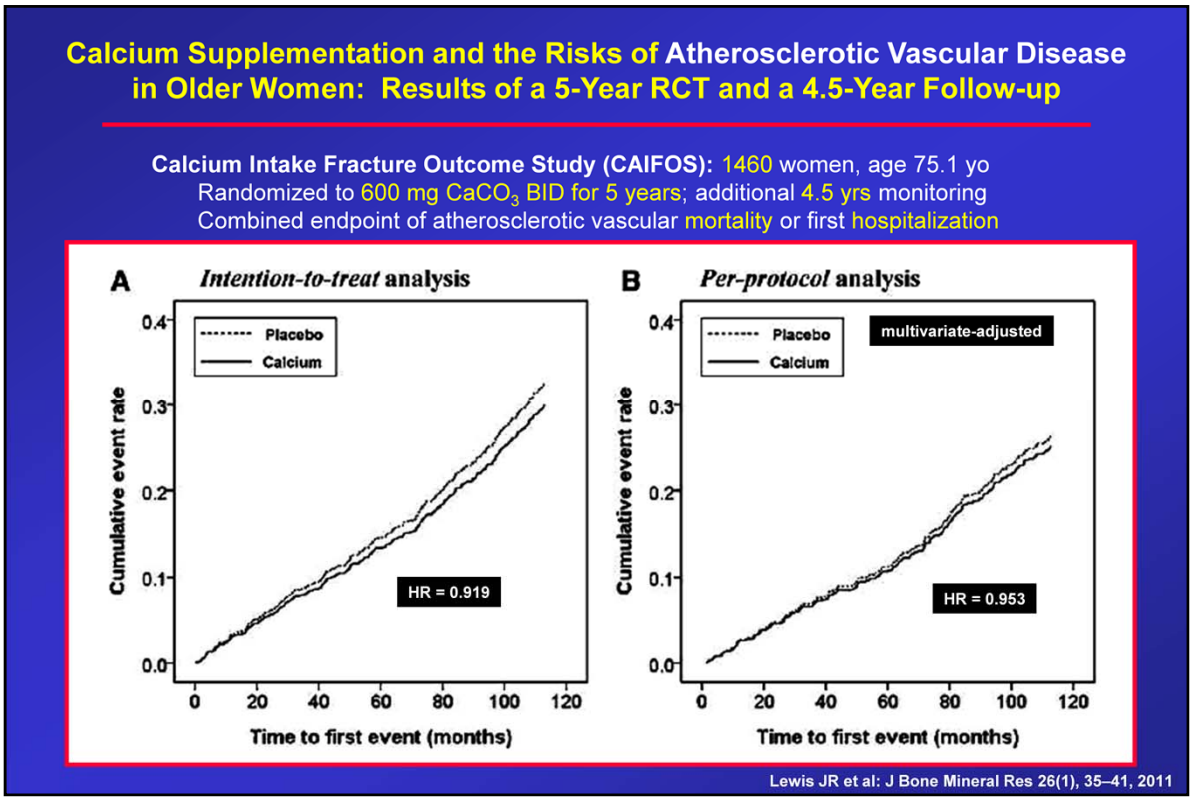


Fig. 2. Cox proportional hazards analysis for combined atherosclerotic vascular disease events (incident hospitalization or death) over 9.5 years adjusted for age, calcium intake at baseline, compliance, baseline atherosclerotic vascular disease, eGFR, diabetes, previous or current smoking, and cardiovascular 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.

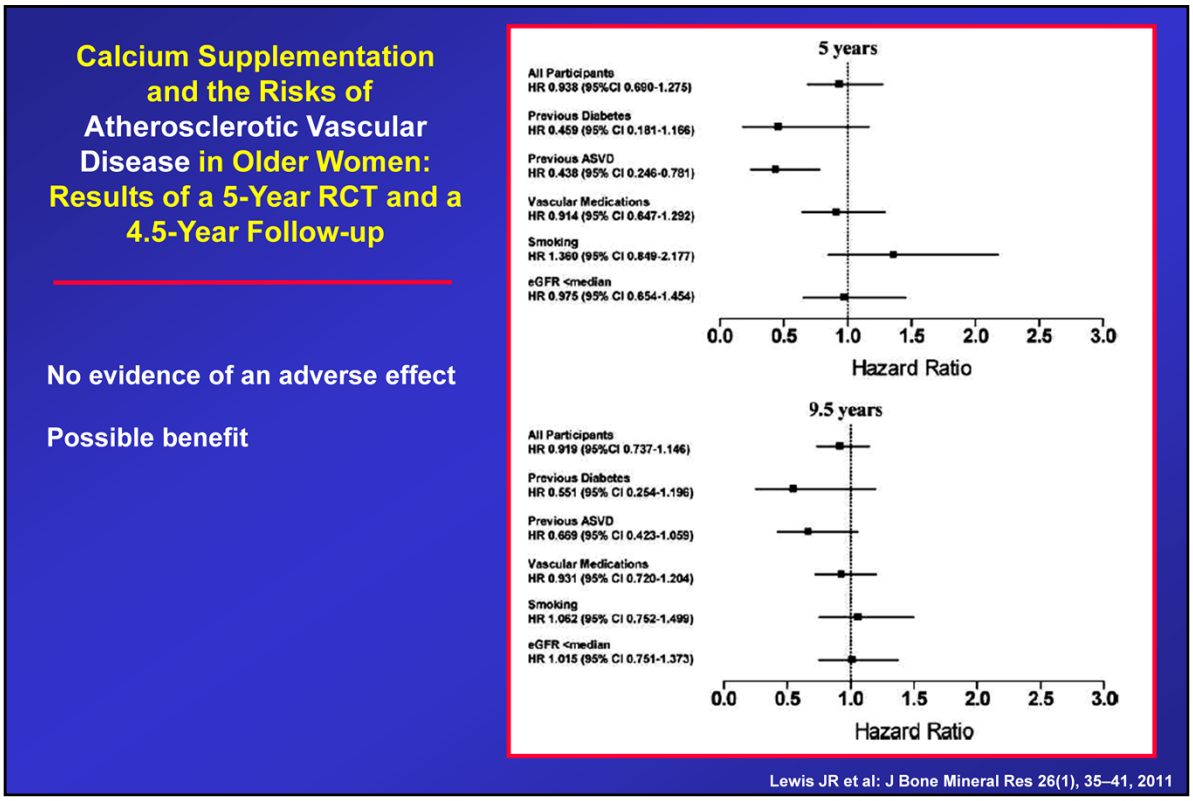


Fig. 3. The effect of calcium treatment compared with placebo on all atherosclerotic vascular disease hospitalizations and death outcomes over 5 and 9.5 years. The analyses used groups with the named baseline risk factor. Analyses adjusted for baseline age, calcium intake, compliance, cardiovascular 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.

Calcium Supplements for the Prevention of Colorectal Adenomas

930 Subjects with colon polyps: mean age 61, 72% men → 1,200 mg calcium for 4 yrs → scopes at 1 & 4 yrs

TABLE 4. OUTCOMES WITH RESPECT TO RECURRENCE OF ADENOMAS.

Polyps reduced by ~25% (p=0.02)

SUBJECTS*	PLACEBO		CALCIUM		ADJUSTED RELATIVE RISK OF ≥1 ADENOMA (95% CI)†	ADJUSTED RATIO OF MEAN NO. OF ADENOMAS (95% CI)†
	PERCENTAGE WITH ≥1 ADENOMA	MEAN NO. OF ADENOMAS	PERCENTAGE WITH ≥1 ADENOMA	MEAN NO. OF ADENOMAS		
Completed study						
First study interval	33	0.60	25	0.43	0.78 (0.63–0.96)	0.75 (0.58–0.96)
First study examination	33	0.59	24	0.40	0.75 (0.61–0.94)	0.70 (0.54–0.89)
Second study interval	38	0.73	31	0.55	0.81 (0.67–0.99)	0.76 (0.60–0.96)
Second study examination	36	0.62	30	0.51	0.83 (0.68–1.01)	0.83 (0.65–1.05)
First or second study interval	52	1.32	45	0.98	0.85 (0.74–0.98)	0.75 (0.62–0.90)
Had at least one endoscopy						
First or second study interval	51	1.26	43	0.92	0.85 (0.74–0.98)	0.75 (0.63–0.90)
Study examinations	50	1.15	42	0.86	0.84 (0.73–0.97)	0.77 (0.64–0.91)

*The first study interval was from randomization to the first follow-up colonoscopy; the second study interval (the main risk period) was after the first follow-up colonoscopy and up to and including the second follow-up colonoscopy. Four hundred twenty-three subjects in the placebo group and 409 in the calcium group completed the study; 459 and 454, respectively, had at least one endoscopy.

†The risk ratio for at least one adenoma and the ratio of the mean numbers of adenomas in the calcium group as compared with the placebo group are given. Both estimates have been adjusted for age, sex, clinical center, number of previous adenomas, and length of follow-up. CI denotes confidence interval.

Baron JA et al: NEJM 340:101-107, 1999

Background and Methods Laboratory, clinical, and epidemiologic evidence suggests that calcium may help prevent colorectal adenomas. We conducted a randomized, double-blind trial of the effect of supplementation with calcium carbonate on the recurrence of colorectal adenomas. We randomly assigned 930 subjects (mean age, 61 years; 72 percent men) with a recent history of colorectal adenomas to receive either calcium carbonate (3 g [1200 mg of elemental calcium] daily) or placebo, with follow-up colonoscopies one and four years after the qualifying examination. The primary end point was the proportion of subjects in whom at least one adenoma was detected after the first follow-up endoscopy but up to (and including) the second follow-up examination.

Risk ratios for the recurrence of adenomas were adjusted for age, sex, lifetime number of adenomas before the study, clinical center, and length of the surveillance period.

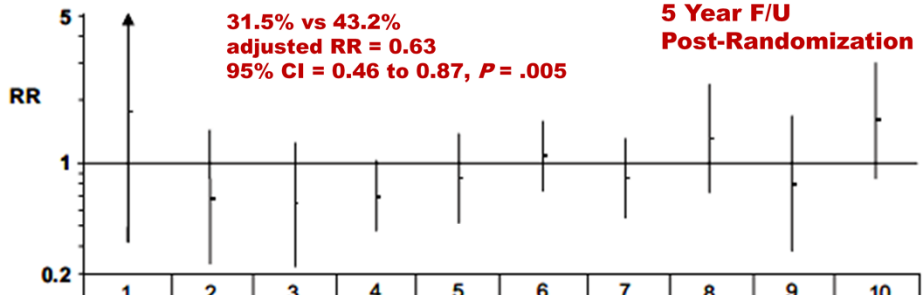
Results The subjects in the calcium group had a lower risk of recurrent adenomas. Among the 913 subjects who underwent at least one study colonoscopy, the adjusted risk ratio for any recurrence of adenoma with calcium as compared with placebo was 0.85 (95 percent confidence interval, 0.74 to 0.98; P=0.03). The main analysis was based on the 832 subjects (409 in the calcium group and 423 in the placebo group) who completed both follow-up examinations. At least one adenoma was diagnosed between the first and second follow-up endoscopies in 127 subjects in the calcium group (31 percent) and 159 subjects in the placebo group (38 percent); the adjusted risk ratio was 0.81 (95 percent confidence interval, 0.67 to 0.99; P=0.04).

The adjusted ratio of the average number of adenomas in the calcium group to that in the placebo group was 0.76 (95 percent confidence interval, 0.60 to 0.96; P=0.02). The effect of calcium was independent of initial dietary fat and calcium intake.

Conclusions Calcium supplementation is associated with a significant — though moderate — reduction in the risk of recurrent colorectal adenomas. (N Engl J Med 1999;340:101-7.)

Calcium Supplements for the Prevention of Colorectal Adenomas

930 Subjects: mean age 61, 72% men with colon polyps → 1,200 mg calcium for 4 yrs → scopes at 1 & 4 yrs



	1	2	3	4	5	6	7	8	9	10
RR for all adenomas	1.75	0.68	0.64	0.69	0.85	1.08	0.85	1.31	0.79	1.60
Upper limit 95% CI	7.23	1.43	1.25	1.03	1.37	1.57	1.30	2.36	1.67	3.01
Lower limit 95% CI	0.42	0.33	0.32	0.47	0.52	0.74	0.55	0.73	0.38	0.85

Years after end of study treatment

*The first study interval was from randomization to the first follow-up colonoscopy; the second study interval (the main risk period) was after the first follow-up colonoscopy and up to and including the second follow-up colonoscopy. Four hundred twenty-three subjects in the placebo group and 409 in the calcium group completed the study; 459 and 454, respectively, had at least one endoscopy.

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Conclusions Calcium supplementation is associated with a significant — though moderate — reduction in the risk of recurrent colorectal adenomas. (N Engl J Med 1999;340:101-7.)

Calcium Supplementation

“The Bad”

Vascular events in healthy older women receiving calcium supplementation: randomized controlled trial

1,471 Post-Meno Women
Mean Age 74 yrs
Overweight
High LDL
~40% prior smokers
Usual Ca intake ~800 mg

Excluded:
Women taking calcium
25VitD < 10 ng/ml
Latitude similar to
Memphis
(New Zealand)
HRT – probably excluded

Randomized to:
CaCitrate 200 mg in AM
300 mg in PM
No Vitamin D given
For 5 years

Table 1 | Descriptive and biochemical characteristics of healthy, postmenopausal women assigned to calcium supplementation or to placebo. Values are means (standard deviations) unless stated otherwise

Characteristics	Calcium group (n=732)		Placebo group (n=739)
Age (years)	74.2 (4.2)		74.3 (4.3)
Weight (kg)	66.8 (11.1)		67.0 (11.4)
Body mass index (kg/m^2)	26.5 (4.3)		26.4 (4.2)
Serum creatinine (mmol/l)	0.087 (0.015)		0.086 (0.014)
Glomerular filtration rate* (ml/min/1.73 m^2)	61 (10)		61 (11)
Adjusted calcium (mmol/l)	2.32 (0.071)		2.30 (0.065)
Glucose (mmol/l)	5.1 (0.7)		5.1 (0.7)
Total cholesterol (mmol/l)†	6.73 (1.20)		6.56 (1.04)
High density lipoprotein cholesterol (mmol/l)†	1.65 (0.45)		1.59 (0.40)
Low density lipoprotein cholesterol (mmol/l)†	4.39 (1.16)	~168 mg/dl	4.26 (0.98)
Ratio of high density lipoprotein to low density lipoprotein†	0.42 (0.19)		0.40 (0.17)
Triglycerides (mmol/l)†	1.55 (0.83)		1.57 (0.73)
Dietary calcium (mg/day)	861 (390)		853 (381)
Physical activity (METS)	33.6 (4.6)		33.5 (4.3)
No (%) current smokers	25 (3.4)		19 (2.6)
No (%) former smokers	295 (40.3)		275 (37.2)
Systolic blood pressure (mm Hg)	136 (23)		135 (23)
Diastolic blood pressure (mm Hg)	71 (11)		70 (10)
No (%) with previous hypertension	220 (30.1)		207 (28.0)
No (%) with previous ischaemic heart disease	59 (8.1)		54 (7.3)
No (%) with previous dyslipidaemia	67 (9.2)		56 (7.6)
No (%) with diabetes	19 (2.6)		20 (2.7)
No (%) with previous stroke or transient ischaemic attack	12 (1.6)		7 (1.0)

Bolland MJ et al: BMJ 2008: doi:10.1136/bmj.39440.525752.BE

Objective To determine the effect of calcium supplementation on myocardial infarction, stroke, and sudden death in healthy postmenopausal women.

Design Randomised, placebo controlled trial. Setting Academic medical centre in an urban setting in New Zealand. Participants 1471 postmenopausal women (mean age 74): 732 were randomised to calcium supplementation and 739 to placebo. Main outcome measures Adverse cardiovascular events over five years: death, sudden death, myocardial infarction, angina, other chest pain, stroke, transient ischaemic attack, and a composite end point of myocardial infarction, stroke, or sudden death.

Results Myocardial infarction was more commonly reported in the calcium group than in the placebo group (45 events in 31 women v 19 events in 14 women, P=0.01). The composite end point of myocardial infarction, stroke, or sudden death was also more common in the calcium group (101 events in 69 women v 54 events in 42 women, P=0.008). After adjudication myocardial infarction remained more common in the calcium group (24 events in 21 women v 10 events in 10 women, relative risk 2.12, 95% confidence interval 1.01 to 4.47). For the composite end point 61 events were verified in 51 women in the calcium group and 36 events in 35 women in the placebo group (relative risk 1.47, 0.97 to 2.23). When unreported events were added from the national database of hospital admissions in New Zealand the relative risk of myocardial infarction was 1.49 (0.86 to 2.57) and that of the composite end point was 1.21 (0.84 to 1.74). The respective rate ratios were 1.67 (95% confidence intervals 0.98 to 2.87) and 1.43 (1.01 to 2.04); event rates:

placebo 16.3/1000 person years, calcium 23.3/1000 person years. For stroke (including unreported events) the relative risk was 1.37 (0.83 to 2.28) and the rate ratio was 1.45 (0.88 to 2.49).

Conclusion Calcium supplementation in healthy postmenopausal women is associated with upward trends in cardiovascular event rates. This potentially detrimental effect should be balanced against the likely benefits of calcium on bone.

Vascular events in healthy older women receiving calcium supplementation: randomized controlled trial

Bolland MJ et al: BMJ 2008: doi:10.1136/bmj.39440.525752.BE

Table 2 | Potential vascular events self reported by healthy postmenopausal women assigned to calcium supplementation or to placebo or reported by family members. Values are numbers of women (numbers of events) unless stated otherwise

Vascular event	Calcium group (n=732)	Placebo group (n=739)	P value*	Relative risk (95% CI)
Angina	50 (88)	71 (99)	0.058	0.71 (0.50 to 1.01)
Myocardial infarction	31 (45)	14 (19)	0.0099	2.24 (1.20 to 4.17)
Other chest pain	16 (18)	15 (16)	0.86	1.08 (0.54 to 2.16)
Transient ischaemic attack	33 (42)	21 (27)	0.10	1.59 (0.93 to 2.72)
Stroke	40 (52)	28 (34)	0.14	1.44 (0.90 to 2.31)
Sudden death	4	1	0.22	4.04 (0.45 to 36.0)
Angina, chest pain, myocardial infarction, or sudden death	87 (155)	93 (135)	0.68	0.94 (0.72 to 1.24)
Myocardial infarction, stroke, or sudden death	69 (101)	42 (54)	0.0075	1.66 (1.15 to 2.40)
Death	34	29	0.52	1.18 (0.73 to 1.92)

Table 3 | Verified vascular events self reported by healthy postmenopausal women assigned to calcium supplementation or to placebo or reported by family members. Values are numbers of women (numbers of events) unless stated otherwise

Vascular event	Calcium group (n=732)	Placebo group (n=739)	P value*	Relative risk (95% CI)
Myocardial infarction	21 (24)	10 (10)	0.047	2.12 (1.01 to 4.47)
Stroke	31 (34)	22 (23)	0.21	1.42 (0.83 to 2.43)
Sudden death	3	3	1.0	1.01 (0.20 to 4.99)
Myocardial infarction, stroke, or sudden death	51 (61)	35 (36)	0.076	1.47 (0.97 to 2.23)

Objective To determine the effect of calcium supplementation on myocardial infarction, stroke, and sudden death in healthy postmenopausal women.

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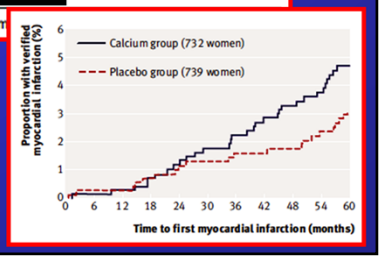
Vascular events in healthy older women receiving calcium supplementation: randomized controlled trial

Table 4 | Verified vascular events self reported by healthy postmenopausal women assigned to calcium supplementation or to placebo, reported by family members, and from the national database of hospital admissions in New Zealand.* Values are numbers of women (numbers of events) unless stated otherwise

Vascular event	Calcium group (n=732)	Placebo group (n=739)	P value†	Relative risk (95% CI)	Calcium event rate/1000 person years (95% CI)	Placebo event rate/1000 person years (95% CI)	Rate ratio (95% CI)	P value‡
Myocardial infarction	31 (36)	21 (22)	0.16	1.49 (0.86 to 2.57)	11.1 (7.7 to 15.3)	6.6 (4.2 to 10.0)	1.67 (0.98 to 2.87)	0.058
Stroke	34 (37)	25 (26)	0.23	1.37 (0.83 to 2.28)	11.4 (8.0 to 15.7)	7.8 (5.1 to 11.5)	1.45 (0.88 to 2.49)	0.15
Sudden death	3	6	0.51	0.51 (0.13 to 2.01)	0.9 (0.2 to 2.7)	1.8 (0.7 to 3.9)	0.51 (0.10 to 2.04)	0.36
Myocardial infarction, stroke, or sudden death	60 (76)	50 (54)	0.32	1.21 (0.84 to 1.74)	23.3 (18.4 to 29.2)	16.3 (12.2 to 21.3)	1.43 (1.01 to 2.04)	0.043

7 excess events / 1,000 Pt-Yrs

*Includes events not self reported by participants but found through the national database of hospital adm



Fully Verified: 1 event per year per 143 treated --> number needed to harm --> 143 / year

No effect for 1st 2 years

Bolland MJ et al: BMJ 2008; doi:10.1136/bmj.39440.525752.BE

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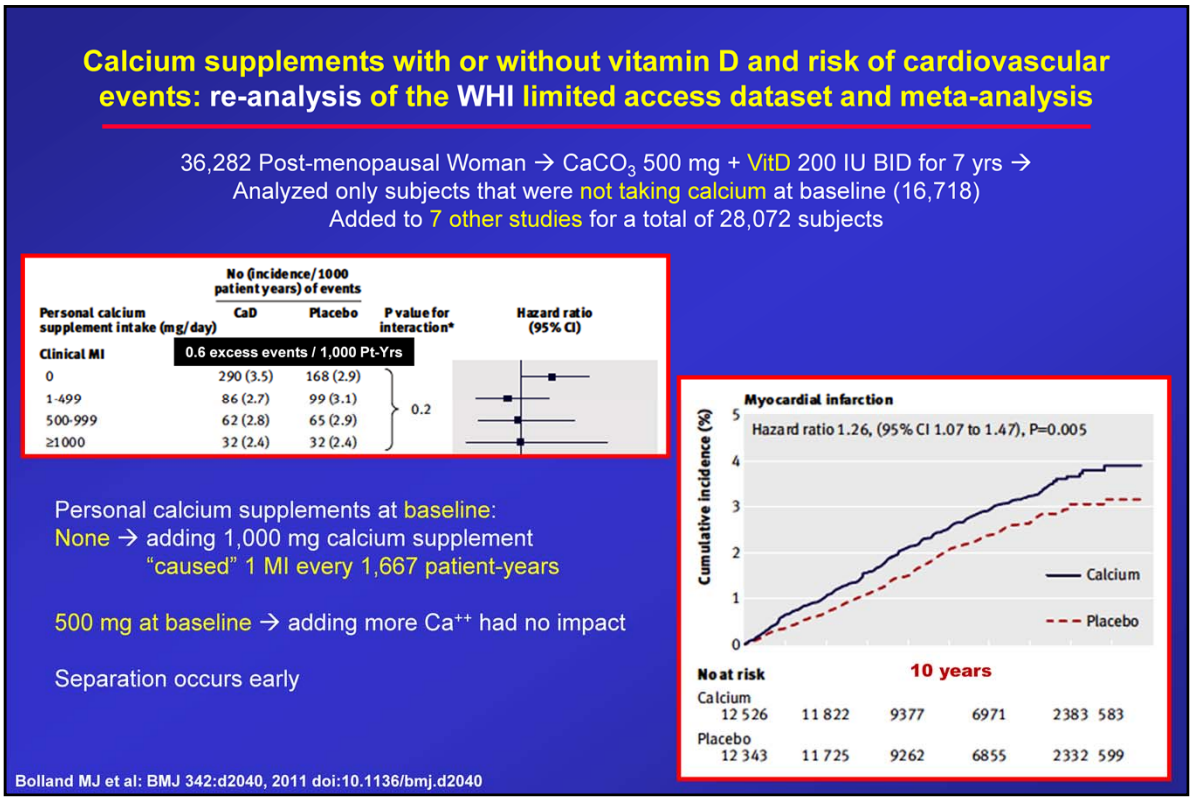


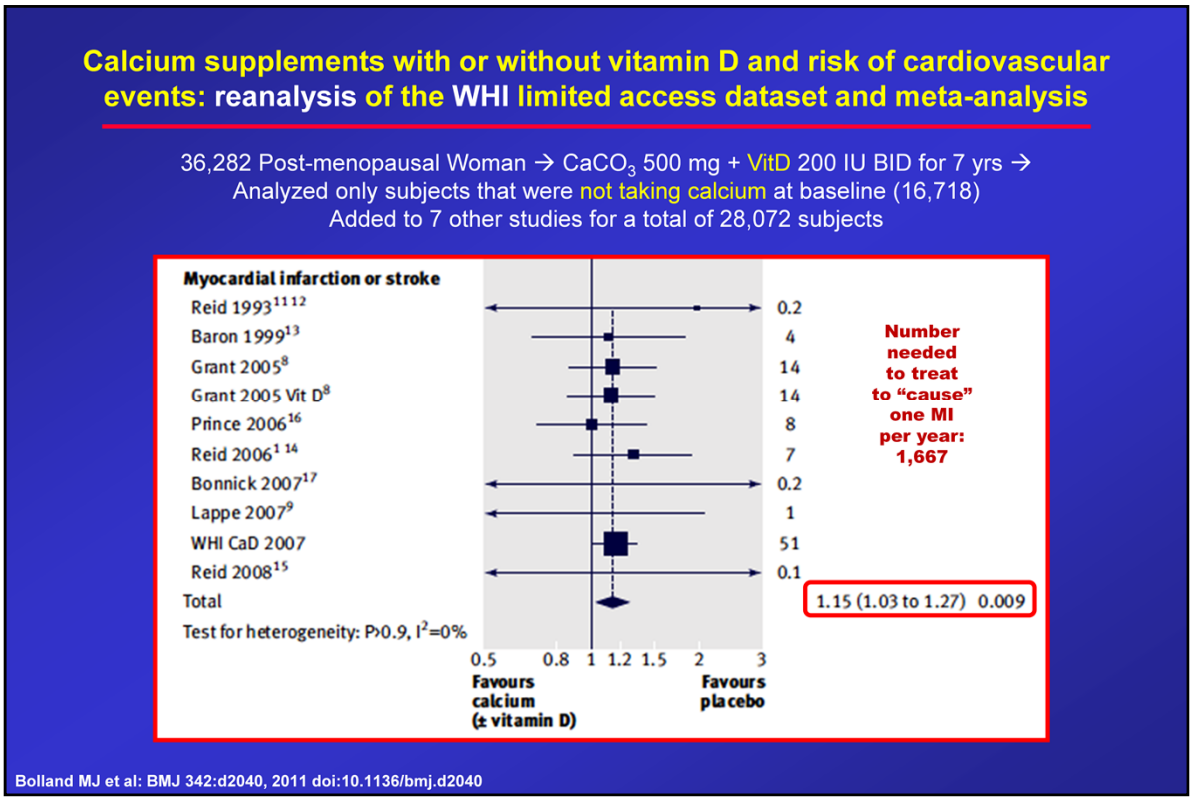
Objectives To investigate the effects of personal calcium supplement use on cardiovascular risk in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), using the WHI dataset, and to update the recent meta-analysis of calcium supplements and cardiovascular risk. Design Reanalysis of WHI CaD Study limited access dataset and incorporation in meta-analysis with eight other studies.

Data source WHI CaD Study, a seven year, randomised, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36,282 community dwelling postmenopausal women. Main outcome measures Incidence of four cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data.

Results In the WHI CaD Study there was an interaction between personal use of calcium supplements and allocated calcium and vitamin D for cardiovascular events. In the 16 718 women (46%) who were not taking personal calcium supplements at randomisation the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 (P=0.05 for clinical myocardial infarction or stroke, P=0.04 for clinical myocardial infarction or revascularisation), whereas in the women taking personal calcium supplements cardiovascular risk did not alter with allocation to calcium and vitamin D. In meta-analyses of three placebo controlled trials, calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21 (95% confidence interval 1.01 to 1.44), P=0.04), stroke

(1.20 (1.00 to 1.43), P=0.05), and the composite of myocardial infarction or stroke (1.16 (1.02 to 1.32), P=0.02). In meta-analyses of placebo controlled trials of calcium or calcium and vitamin D, complete trial-level data were available for 28 072 participants from eight trials of calcium supplements and the WHI CaD participants not taking personal calcium supplements. In total 1384 individuals had an incident myocardial infarction or stroke. Calcium or calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.24 (1.07 to 1.45), P=0.004) and the composite of myocardial infarction or stroke (1.15 (1.03 to 1.27), P=0.009).

Conclusions Calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction, a finding obscured in the WHI CaD Study by the widespread use of personal calcium supplements. A reassessment of the role of calcium supplements in osteoporosis management is warranted.



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Calcium Dietary and Supplemental Calcium Intake and Cardiovascular Disease Mortality: *The National Institutes of Health – AARP Diet and Health Study*

388,299 Men & Woman age 50-71 → Assessed dietary & supplemental calcium intake → National Death Index for median 12 years: CVD Deaths 7904 men, 3874 women
51% men & 70% women took supplements

Table 1. Selected Characteristics of Study Participants by Categories of Dietary and Supplemental Calcium Intakes[a]

	Dietary Calcium				Supplemental Calcium			
	Men		Women		Men		Women	
Variable	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Nonuser	User	Nonuser	User
Age at baseline, mean, y	61.3	62.0	61.2	62.1	61.6	61.8	61.6	61.6
Dietary calcium dose, mean, mg/d	463	1336	397	1170	782	815	681	719
Supplemental calcium dose, mean, mg/d	127	163	336	423	0	289	0	554
Alcohol consumption, mean, g/d	36.5	9.0	11.2	3.7	40.8	17.5	6.1	6.2

Higher calcium intake was associated with a lower alcohol intake in men

Conclusion: Adding >1,000 mg of supplemental calcium to 800 mg of dietary calcium Associated with a 20% increase in CVD Deaths only in men

Xiao Q et al: doi:10.1001/jamainternmed.2013.3283

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Design and Setting: Prospective study from 1995 through 1996 in California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania and the 2 metropolitan areas of Atlanta, Georgia, and Detroit, Michigan.

Participants: A total of 388 229 men and women aged 50 to 71 years from the National Institutes of Health–AARP Diet and Health Study.

Main Outcome Measures: Dietary and supplemental calcium intake was assessed at baseline (1995-1996). Supplemental calcium intake included calcium from multivitamins and individual calcium supplements. Cardiovascular disease deaths were ascertained using the National Death Index. Multivariate Cox proportional hazards regression models adjusted for demographic, lifestyle, and dietary variables were used to estimate relative risks (RRs) and 95% CIs.

Results: During a mean of 12 years of follow-up, 7904 and 3874 CVD deaths in men and women, respectively, were identified. Supplements containing calcium were used by 51% of men and 70% of women. In men, supplemental calcium intake

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Table 2. Relative Risks (95% CIs) for CVD Deaths for Quintiles of Dietary Calcium Intake in Men and Women

Variable	Dietary Calcium Intake					*P* Value for Trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Men						
Median intake, mg/d	478	616	739	898	1247	
No. of person-years	527 379	516 858	502 994	489 449	467 990	
All CVD deaths						
No. of cases	1879	1550	1519	1400	1556	
Age adjusted	Reference	0.81 (0.76-0.86)	0.79 (0.74-0.85)	0.75 (0.70-0.80)	0.86 (0.80-0.92)	.004
Multivariate[a]	Reference	0.91 (0.85-0.98)	0.96 (0.89-1.03)	0.92 (0.85-0.99)	1.04 (0.97-1.12)	.08
Women						
Median intake, mg/d	408	532	648	798	1101	
No. of person-years	397 388	397 012	394 567	392 622	386 100	
All CVD deaths						
No. of cases	918	785	700	708	763	
Age adjusted	Reference	0.83 (0.75-0.91)	0.73 (0.66-0.80)	0.72 (0.66-0.80)	0.76 (0.69-0.84)	<.001
Multivariate[b]	Reference	0.99 (0.90-1.09)	0.94 (0.85-1.04)	0.99 (0.89-1.10)	1.04 (0.94-1.15)	.37

Dietary Ca^{++} Beneficial

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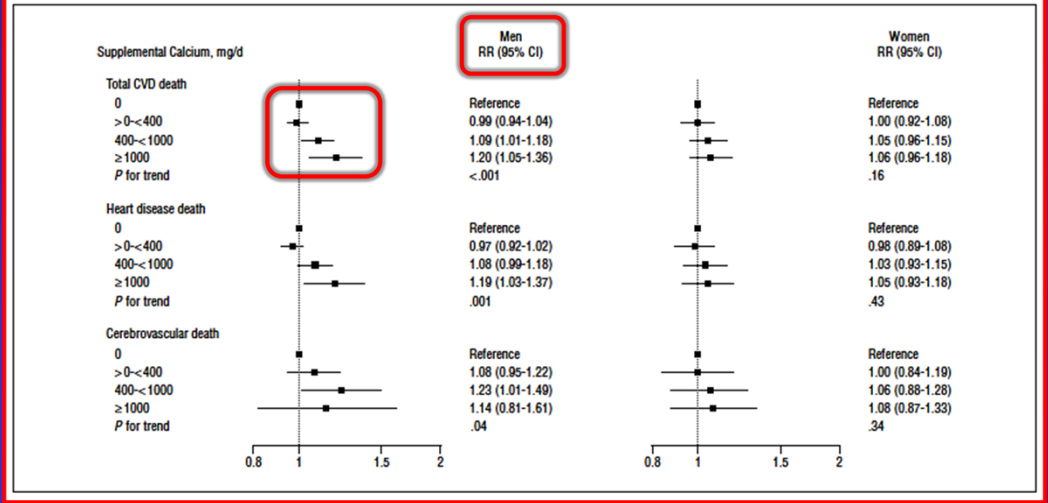

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Calcium Dietary and Supplemental Calcium Intake and Cardiovascular Disease Mortality: *The National Institutes of Health – AARP Diet and Health Study*

Table 3. Multivariate Relative Risks (95% CIs) for Total Cardiovascular Disease Deaths by Supplemental Calcium Intake, Stratified by Age, Smoking Status, Body Mass Index, and Hypertension

Variable	Supplemental Calcium Intake, mg/d				*P* Value for Trend
	0	>0-<400	>400-<1000	≥1000	
Men					
Age, y[a]					
<60	Reference	0.97 (0.87-1.09)	1.15 (0.96-1.38)	1.47 (1.09-2.00)	.01
≥60	Reference	0.99 (0.94-1.05)	1.08 (1.00-1.18)	1.15 (1.00-1.32)	.01
P value for interaction	.16				
Smoking status[b]					
Never	Reference	0.91 (0.82-1.00)	1.05 (0.90-1.23)	1.04 (0.79-1.36)	.62
Former	Reference	0.98 (0.92-1.05)	1.08 (0.97-1.20)	1.17 (0.98-1.38)	.04
Current	Reference	1.10 (0.99-1.21)	1.12 (0.93-1.34)	1.33 (0.94-1.89)	.04
P value for interaction	.01				
Body mass index[a]					
<25	Reference	0.93 (0.85-1.02)	1.08 (0.94-1.24)	1.03 (0.82-1.31)	.45
≥25 and <30	Reference	0.97 (0.90-1.04)	1.12 (1.00-1.25)	1.36 (1.14-1.63)	<.001
≥30	Reference	1.10 (1.00-1.21)	1.03 (0.87-1.22)	1.12 (0.83-1.50)	.36
P value for interaction	.19				
Hypertension[a]					
Yes	Reference	1.03 (0.94-1.13)	1.08 (0.93-1.25)	1.44 (1.16-1.80)	.002
No	Reference	1.02 (0.93-1.12)	1.15 (0.98-1.34)	1.18 (0.91-1.52)	.06
P value for interaction	.80				
Hypercholesterolemia[a]					
Yes	Reference	1.04 (0.95-1.15)	1.22 (1.05-1.41)	1.19 (0.93-1.51)	.01
No	Reference	0.99 (0.89-1.10)	1.05 (0.89-1.24)	1.39 (1.08-1.78)	.02
P value for interaction	.94				

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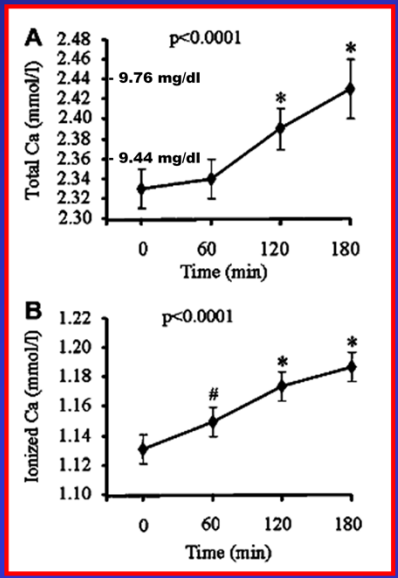
Calcium Supplementation

“The Ugly”

Possible Mechanisms

Acute Effect of Calcium Citrate on Serum Calcium and Cardiovascular Function

25 healthy subjects (16 women), mean age 60.3, BMI 25.7 were given 1,000 mg of Calcium Citrate



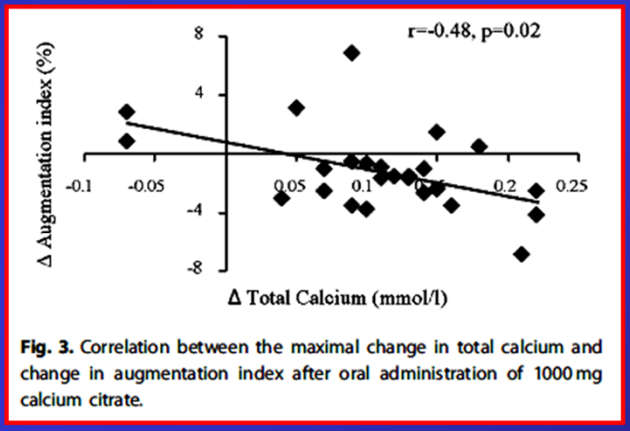


Fig. 3. Correlation between the maximal change in total calcium and change in augmentation index after oral administration of 1000 mg calcium citrate.

Augmentation Index (AIx): Increment in aortic pressure corrected for pulse. Correlates with left ventricular ejection volume.

A long-term 10% reduction in AIx would be expected to be associated with a 30% reduction in CV events.

Burt MG et al: J Bone Min Res 28(2): 412–418, 2013

Calcium supplements have been associated with an increased risk of cardiovascular events. However, the validity of these findings has been questioned. A major concern is that the mechanism underlying an increase in cardiovascular events has not been demonstrated. Calcium initiates cardiac and vascular contraction following influx of calcium into cardiac and smooth muscle from extracellular fluid. We have investigated whether the acute rise in serum calcium following calcium supplement administration is associated with adverse changes in cardiovascular function. In an open interventional study, we recruited 25 volunteers (16 female, age 60.3 ± 6.5 years, body mass index 25.7 ± 2.7 kg/m2) from the community who were not taking calcium supplements. Participants were studied before and 3 hours after a single oral dose of 1000 mg calcium citrate. We assessed well-validated markers of arterial stiffness (pulse wave velocity [PWV]), arterial wave reflection (augmentation index [AIx]), and myocardial perfusion (subendocardial viability ratio [SEVR]) by pulse wave analysis and endothelial function (reactive hyperemia index [RHI]) by peripheral arterial tonometry. Total and ionized serum calcium were acutely increased by 0.10 ± 0.07 and 0.06 ± 0.03 mmol/L, respectively, 3 hours after calcium citrate administration ($p < 0.0001$ for both comparisons). Following administration of calcium citrate there was a fall in AIx from a median of 29.7% (23.8% to 34.0%) to 26.4% (22.7% to 34.0%, $p = 0.03$) and an increase in SEVR from 163% (148% to 174%) to 170% (149% to 185%, $p = 0.007$). PWV and RHI were not significantly altered. The change in total calcium was negatively correlated with the change in AIx ($r = -0.48$, $p = 0.02$). In summary, the acute increase in serum calcium following calcium supplement administration is associated with reduced arterial wave

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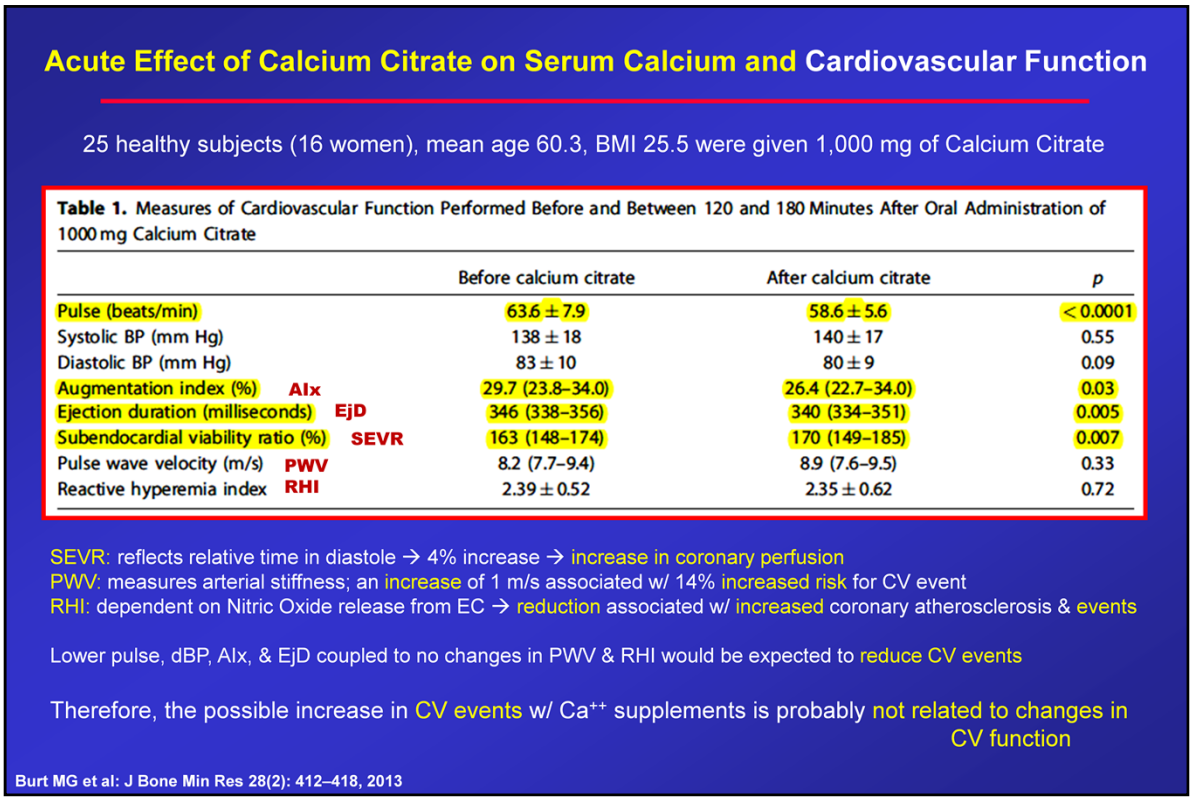

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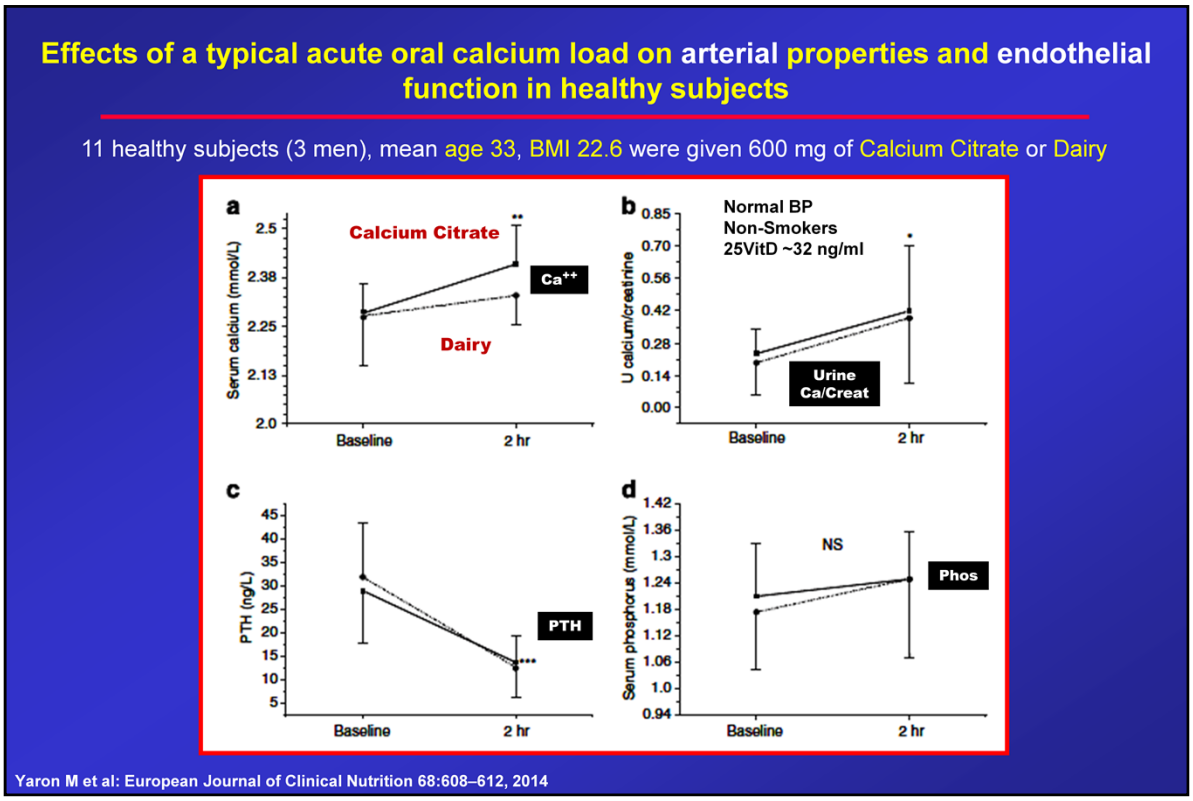

Figure 1. Blood and urine biochemistry at baseline and following the calcium challenges. The supplement challenge is indicated by solid lines and square symbols, the food challenge by dashed lines and closed circles. (a) serum calcium; (b) urinary calcium/creatinine; (c) plasma PTH; (d) serum phosphorus. Asterisks denote the differences between post-challenge and baseline values within each intervention. *P= 0.01, **P =0.002, ***P=0.001. There were no differences between the two challenges at either time point.

BACKGROUND/OBJECTIVES: Often recommended, calcium supplements have been incriminated as increasing the risk of cardiovascular events, whereas dietary calcium has generally been exonerated. As a first step to address the vascular safety of such dietary measures at the clinical nutritionist toolbox, we sought to determine and compare the acute effects of a typical oral calcium load, provided either as a supplement or as food, on vascular parameters assessed noninvasively in healthy subjects.

SUBJECTS/METHODS: In this acute, cross-over, random-order intervention, 11 young and healthy vitamin D-sufficient volunteers (8 women/3 men, 33 ± 6.1 years, body mass index 22.6 ± 2.3 kg/m2), ingested 600 mg of calcium twice, once as calcium citrate and the other time from dairy products. Biochemical, vascular and hemodynamic parameters, before and 2 h after each challenge, were compared. Arterial stiffness was studied by measuring pulse wave velocity, augmentation index and large (C1) and

small (C2) arterial compliance. Endothelial function was assessed by flow-mediated dilation (FMD).

RESULTS: Despite effective calcium loading accompanied by a significant 60% parathyroid hormone level reduction on both occasions, there were no clinically significant changes in the vascular parameters neither in comparison with baseline, nor between the studies. A decrease in heart rate with no change in cardiac output was noticed after the supplement.

CONCLUSIONS: An effective calcium load has no clinically significant untoward effect on the vascular properties of young healthy subjects, regardless of its source. Additional studies should determine whether this holds true for chronic calcium supplementation, particularly in subjects with a priori vascular impairment.

Effects of a typical acute oral calcium load on arterial properties and endothelial function in healthy subjects

11 healthy subjects (3 men), mean age 33, BMI 22.6 were given 600 mg of Calcium Citrate or Dairy

Table 2. Vascular parameters before and after each calcium load **2 hours**

	Supplement		P[a]	*Food*		P[a]	*ANOVA*[b]
	Before	*After*		*Before*	*After*		
Central systolic BP (mm Hg)	100.5 (9)	104.9 (4)	NS	101.5 (7)	101.7 (6)	NS	NS
Central diastolic BP (mm Hg)	66 (7)	66 (7)	NS	66 (4)	67 (6)	NS	NS
Heart rate (b.p.m.)	63 (6)	58 (6)	0.02	59 (6)	61 (7)	NS	0.04
AIx (%) [< 40%]	10 (12)	12.8 (8)	NS	13.5 (8)	13.8 (8)	NS	NS
PWV (m/s) [< 12 m/s]	8.85 (1)	8.72 (1.3)	NS	8.54 (1.2)	8.21 (1.5)	NS	NS
FMD (%) [>2%]	7.9 (3.7)	7.0 (3.2)	NS	8.5 (4.2)	8.6 (3.7)	NS	NS
C1 (ml/mm Hgx10) [>15.5 ml/mm Hgx10]	17.8 (4.7)	18.6 (4.5)	NS	19.2 (5.5)	17.2 (3.8)	NS	NS
C2 (ml/mm Hgx100) [>6.6 ml/mm Hgx100]	7.8 (0.9)	7.4 (1.7)	NS	8.3 (1.7)	9.1 (2.7)	NS	0.03
CO (l/min) [4–8 l/min]	6.03 (0.88)	5.86 (0.91)	NS	5.85 (0.97)	5.75 (0.99)	NS	NS
Stroke volume (ml/beat) [55–100 ml/beat]	93.6 (10.7)	97.5 (16.4)	NS	93.4 (14.0)	94.9 (13.5)	NS	NS

Abbreviations: AIx, augmentation index; ANOVA, analysis of variance; BP, blood pressure; C1, large artery elasticity index; C2, small artery elasticity index; CO, cardiac output; FMD, flow-mediated dilation; PWV, pulse wave velocity. Normal values stratified by gender and age are given in square brackets. [a]Refers to the comparison by paired *t*-test between baseline and post-challenge values within each intervention. [b]Indicates repeated measures ANOVA between all values measured for any given parameter. Data are mean ± (s.d).

Challenges had a different impact on pulse rate & small artery elasticity
No impact on Augmentation Index, Pulse Wave Velocity, or Flow-Mediated Dilation

Yaron M et al: European Journal of Clinical Nutrition 68:608–612, 2014

BACKGROUND/OBJECTIVES: Often recommended, calcium supplements have been incriminated as increasing the risk of cardiovascular events, whereas dietary calcium has generally been exonerated. As a first step to address the vascular safety of such dietary measures at the clinical nutritionist toolbox, we sought to determine and compare the acute effects of a typical oral calcium load, provided either as a supplement or as food, on vascular parameters assessed noninvasively in healthy subjects.

SUBJECTS/METHODS: In this acute, cross-over, random-order intervention, 11 young and healthy vitamin D-sufficient volunteers (8 women/3 men, 33 ± 6.1 years, body mass index 22.6 ± 2.3 kg/m2), ingested 600 mg of calcium twice, once as calcium citrate and the other time from dairy products. Biochemical, vascular and hemodynamic parameters, before and 2 h after each challenge, were compared. Arterial stiffness was studied by measuring pulse wave velocity, augmentation index and large (C1) and small (C2) arterial compliance. Endothelial function was assessed by flow-mediated dilation (FMD).

RESULTS: Despite effective calcium loading accompanied by a significant 60% parathyroid hormone level reduction on both occasions, there were no clinically significant changes in the vascular parameters neither in comparison with baseline, nor between the studies. A decrease in heart rate with no change in cardiac output was noticed after the supplement.

CONCLUSIONS: An effective calcium load has no clinically significant

untoward effect on the vascular properties of young healthy subjects, regardless of its source. Additional studies should determine whether this holds true for chronic calcium supplementation, particularly in subjects with a priori vascular impairment.

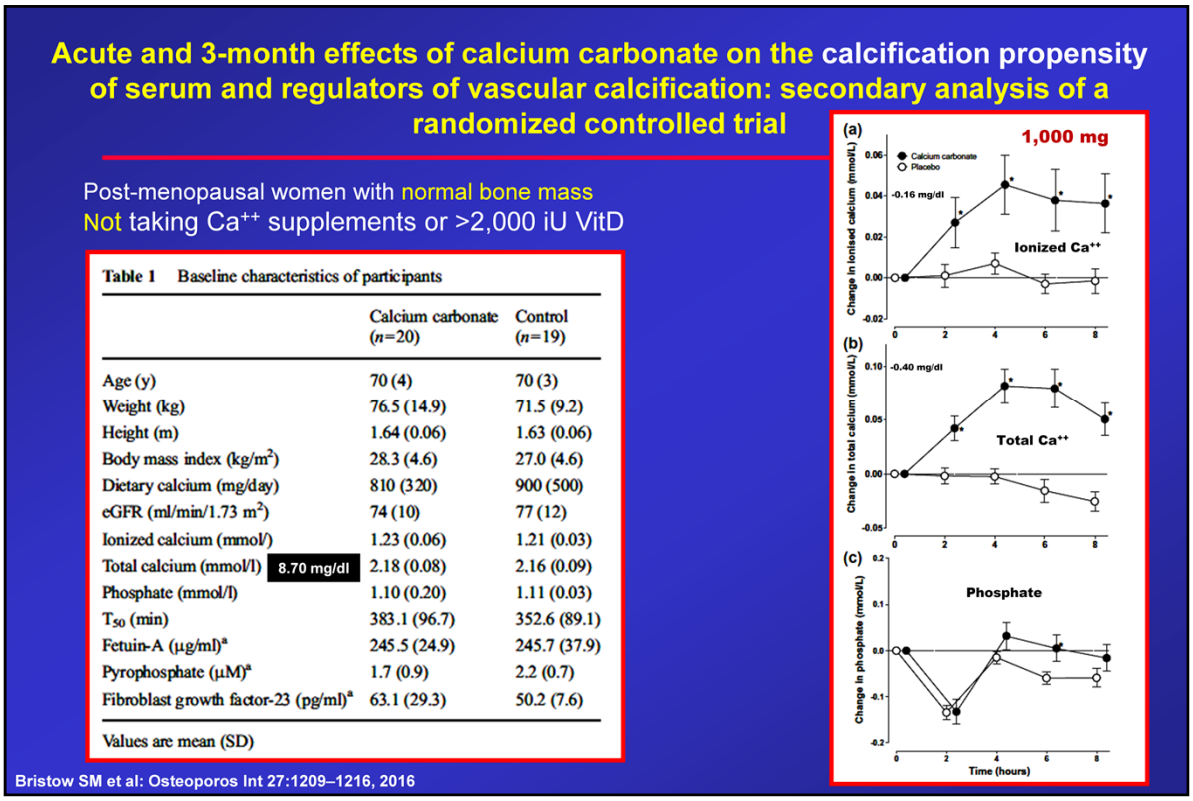

Fig. 2 Changes in serum. a Ionized calcium. b Total calcium. c Phosphate over 8 h in postmenopausal women after 1 g of calcium as carbonate (n=20) or a placebo containing no calcium (n=20). Asterisk indicates change from baseline significantly different from placebo group, $p<0.05$. Values are mean±SEM

Summary Calcium supplements have been associated with increased cardiovascular risk, but the mechanism is unknown. We investigated the effects of calcium supplements on the propensity of serum to calcify, based on the transition time of primary to secondary calciprotein particles (T50). Changes in serum calcium were related to changes in T50.

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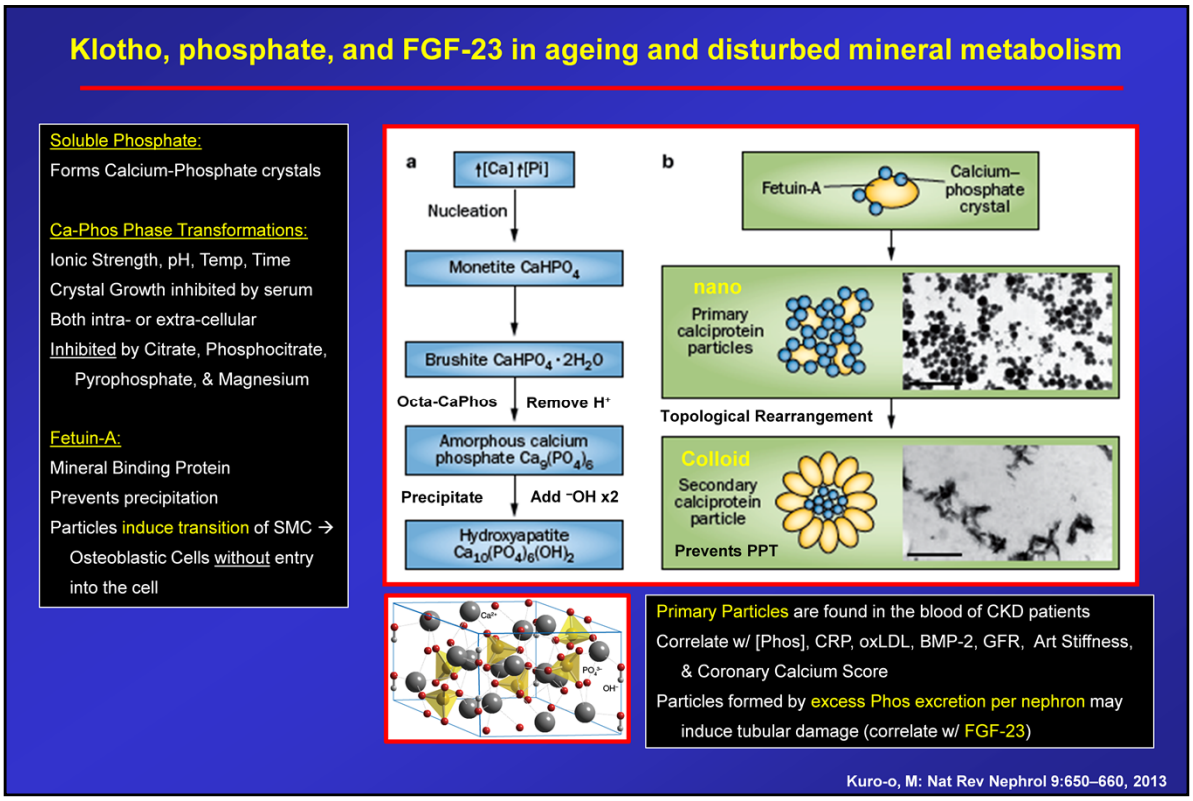

Klotho, phosphate and FGF-23 in ageing and disturbed mineral metabolism. Kuro-o, M. *Nat. Rev. Nephrol.* 9, 650–660 (2013)

Figure 2 | The formation of calciprotein particles. **a** | When the concentration of free calcium and phosphate exceed the concentration of the formation product, calcium–phosphate crystals are generated by nucleation. Calcium–phosphate crystals are transformed from monetite to hydroxyapatite through different phases and eventually precipitate. **b** | In the presence of serum, calcium–phosphate crystals bind to fetuin-A and form colloidal nanoparticles. The calcium–phosphate-crystal-laden fetuin-A molecules aggregate to form nanoparticles (50–100 nm diameter; scale bar 500 nm), which are called primary calciprotein particles. Primary calciprotein particles undergo topological rearrangement to form a stable structure, in which a densely packed fetuin-A monolayer covers a mineral core, thereby preventing further crystal growth.[83,84] These particles are referred to as secondary calciprotein particles and are 100–200 nm diameter. The image in panel b is republished with permission of the American Society of Nephrology, from © Nanoparticle-based test measures overall propensity for calcification in serum. Pasch, A. *J. Am. Soc. Nephrol.* 10, 1744–1752 (2012); permission conveyed through Copyright Clearance Center.

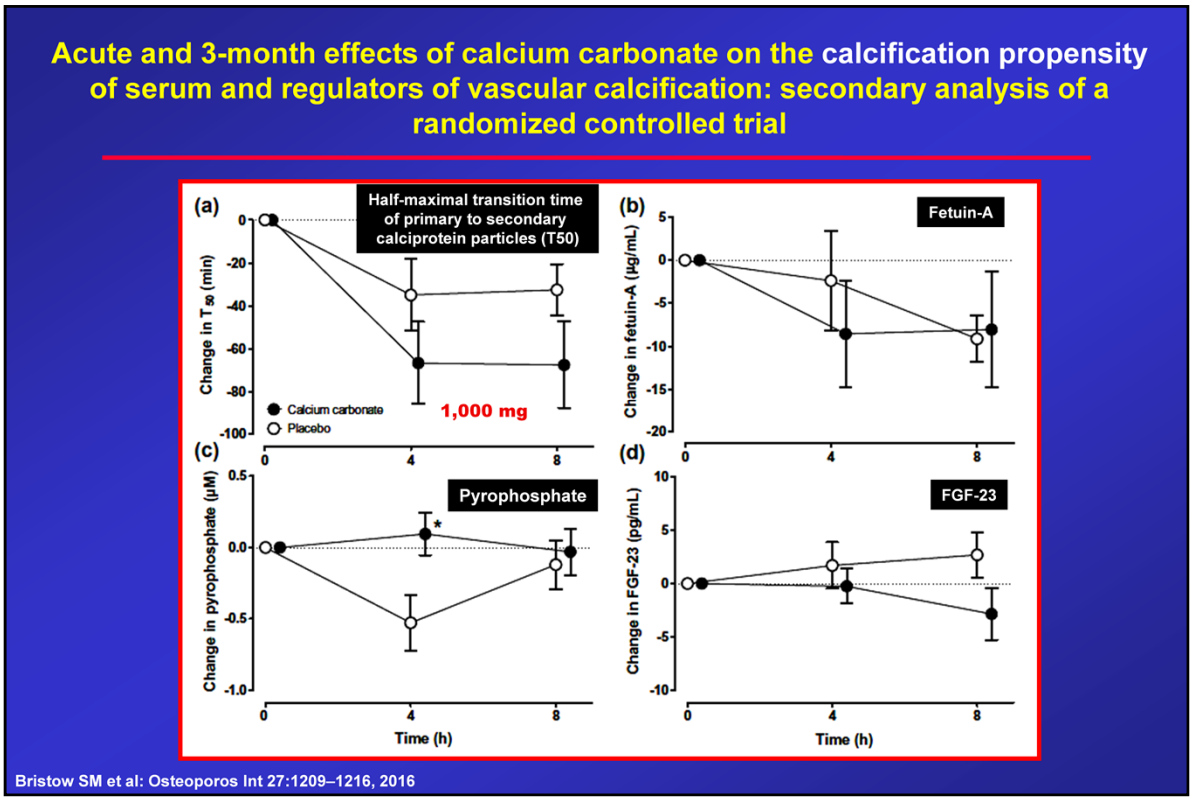

Fig. 3 Changes in a the half-maximal transition time of primary to secondary calciprotein particles (T50), b fetuin-A, c pyrophosphate and d fibroblast growth factor-23 (FGF23) over 8 h in postmenopausal women after 1 g of calcium as carbonate or a placebo containing no calcium. n=10/group, except for T50 where n=20/group. Asterisk indicates change from baseline significantly different from placebo group, p=0.04. Values are mean±SEM

Reduced T50, reflecting a reduced ability of serum to withstand calcification, is associated with progressive aortic stiffening and mortality in patients with chronic kidney disease (CKD), [20] and with mortality in renal transplant recipients [19]. Pasch et al. reported that T50 was positively associated with fetuin-A, albumin, and magnesium, and inversely associated with serum phosphate and calcium [18]. Similarly, in a cross-sectional analysis in patients with CKD, T50 was inversely associated with ionized calcium and phosphate and was lower among calcium supplement users versus non-users [20].

There have been other reports of an association between serum calcium and fetuin-A. Fetuin-A was positively correlated with serum calcium in 82 elderly women [20] and in 112 children with CKD [22]. Furthermore, in 40 end-stage renal disease patients, fetuin-A was higher after 12 months of peritoneal dialysis with a high versus low calcium dialysate [23]. It is possible that an increase in fetuin-A may

reflect a physiologic response to prevent calcification in the face of elevated serum calcium [24].

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Acute and 3-month effects of calcium carbonate on the calcification propensity of serum and regulators of vascular calcification: secondary analysis of a randomized controlled trial

Table 2 Correlations between changes in biochemical variables and changes in regulators of calcification measured at the same time points

	Change in ionized calcium		Change in total calcium		Change in phosphate		Change in calcium-phosphate product	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Change in T_{50}								
4 h	−0.14	0.38	**−0.32**	0.05	**−0.36**	0.03	**−0.39**	0.02
8 h	−0.19	0.25	**−0.39**	0.01	**−0.35**	0.03	**−0.41**	0.01
3 months	−0.04	0.87	0.01	0.97	−0.07	0.73	−0.07	0.74
Change in fetuin-A								
4 h	0.23	0.34	−0.03	0.91	0.13	0.60	0.13	0.62
8 h	0.37	0.12	0.31	0.20	0.12	0.63	0.20	0.42
3 months	0.18	0.46	**0.57**	0.01	−0.00	0.99	0.18	0.46
Change in pyrophosphate								
4 h	**0.51**	0.05	**0.61**	0.02	0.15	0.61	0.27	0.35
8 h	−0.24	0.41	0.31	0.26	−0.08	0.77	−0.01	0.97
3 months	0.38	0.17	0.11	0.69	0.28	0.31	0.30	0.28
Change in FGF23								
4 h	−0.14	0.56	−0.12	0.65	−0.15	0.56	−0.16	0.53
8 h	−0.20	0.43	−0.20	0.43	**−0.48**	0.04	**−0.49**	0.04
3 months	0.06	0.82	−0.01	0.96	0.26	0.30	0.21	0.40

Fasting

Bristow SM et al: Osteoporos Int 27:1209–1216, 2016

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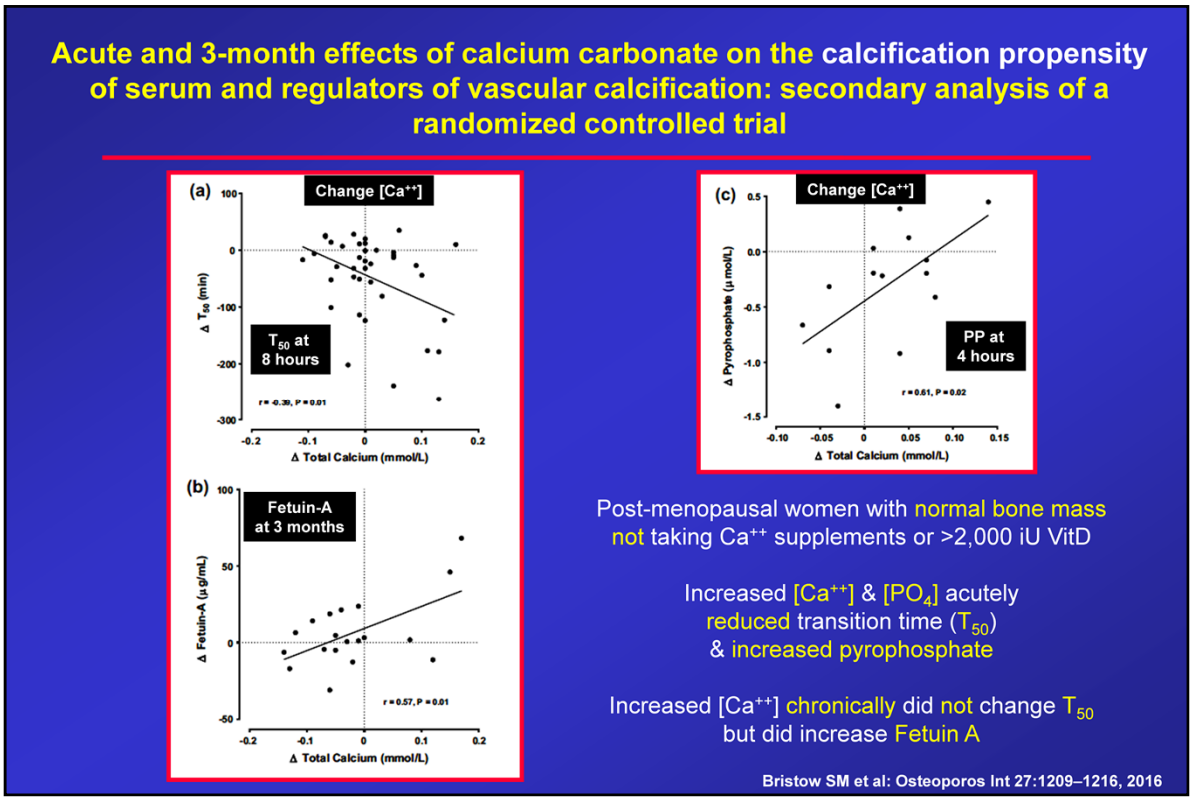

Fig. 4 Relationships between changes in serum total calcium from baseline and changes in a the half-maximal transition time of primary to secondary calciprotein particles (T50) at 8 h, b fetuin-A at 3 months and c pyrophosphate at 4 h. Data are from both the calcium carbonate and placebo groups.

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Acute effects of calcium supplements on blood pressure and blood coagulation: secondary analysis of a randomised controlled trial in post-menopausal women

100 post-menopausal women with normal bone mass, not taking Ca^{++} supplements or >2,000 iU VitD
Treatments: 1,000 mg Ca^{++} citrate, carbonate, or microcrystalline hydroxyapatite (MCH)

Table 1. Baseline characteristics of participants
(Mean values, standard deviations and ranges)

	Ca supplement			Control			
	Mean	SD	Range	Mean	SD	Range	*P*
		(*n* 77)			(*n* 20)		
Age (years)	69	5	59, 84	68	3	63, 74	0·23
Weight (kg)	74·4	13·3	50, 114	71·6	9·2	55, 88	0·38
Height (m)	1·62	0·06	1·47, 1·78	1·63	0·06	1·50, 1·70	0·41
BMI (kg/m^2)	28·4	4·8	19·2, 46·5	27·0	4·6	18·5, 33·9	0·25
Dietary Ca (mg/d)	860	380	240, 2140	900	500	340, 2220	0·72
25-Hydroxyvitamin D (nmol/l) ~28 ng/ml	72	21	29, 132	68	18	31, 112	0·46
Systolic blood pressure (mmHg)	132	19	94, 209	126	20	99, 167	0·2
Diastolic blood pressure (mmHg)	72	8	52, 90	72	8	55, 84	0·86
TEG variables		(*n* 18)			(*n* 20)		
Coagulation index*	−1·5	1·4	−4·2, 1·3	−1·8	1·4	−4·7, 0·3	0·52
R-time (min)†	17·6	5·3	7·9, 28·9	17·1	3·9	11·3, 24·8	0·78
K-time (min)‡	9·0	2·7	4·5, 13·7	9·3	3·2	4·6, 15·8	0·76
α-Angle (°)‡	24·6	6·4	16·8, 37·6	24·5	7·2	14·4, 42·5	0·97
Maximum amplitude (mm)§	50·0	5·7	38, 58·3	47·4	6·1	33·5, 54·9	0·21

TEG: thromboelastography → Index: Overall assessment of coagulability calculated from R-time, K-time, α-angle, & max amplitude

R-time: time to clot initiation
K-time & α-angle: rate of clot formation
Max Amplitude: strength of final clot

Bristow SM et al: Brit J Nutrition 114:1868–1874, 2015

Abstract: Recent evidence suggests that Ca supplements increase the risk of cardiovascular events, but the mechanism(s) by which this occurs is uncertain. In a study primarily assessing the effects of various Ca supplements on blood Ca levels, we also investigated the effects of Ca supplements on blood pressure and their acute effects on blood coagulation. We randomised 100 post-menopausal women to 1 g/d of Ca or a placebo containing no Ca. Blood pressure was measured at baseline and every 2 h up to 8 h after their first dose and after 3 months of supplementation. Blood coagulation was measured by thromboelastography (TEG) in a subgroup of participants (n 40) up to 8 h only. Blood pressure declined over 8 h in both the groups, consistent with its normal diurnal rhythm. The reduction in systolic blood pressure was smaller in the Ca group compared with the control group by >5 mmHg between 2 and 6 h ($P \leq 0{\cdot}02$), and the reduction in diastolic blood pressure was smaller at 2 h (between-groups difference 4·5 mmHg, $P = 0{\cdot}004$). Blood coagulability, assessed by TEG, increased from baseline over 8 h in the calcium citrate and control groups. At 4 h, the increase in the coagulation index was greater in the calcium citrate group compared with the control group ($P = 0{\cdot}03$), which appeared to be due to a greater reduction in the time to clot initiation. These data suggest that Ca supplements may acutely influence blood pressure and blood coagulation. Further investigation of this possibility is required.

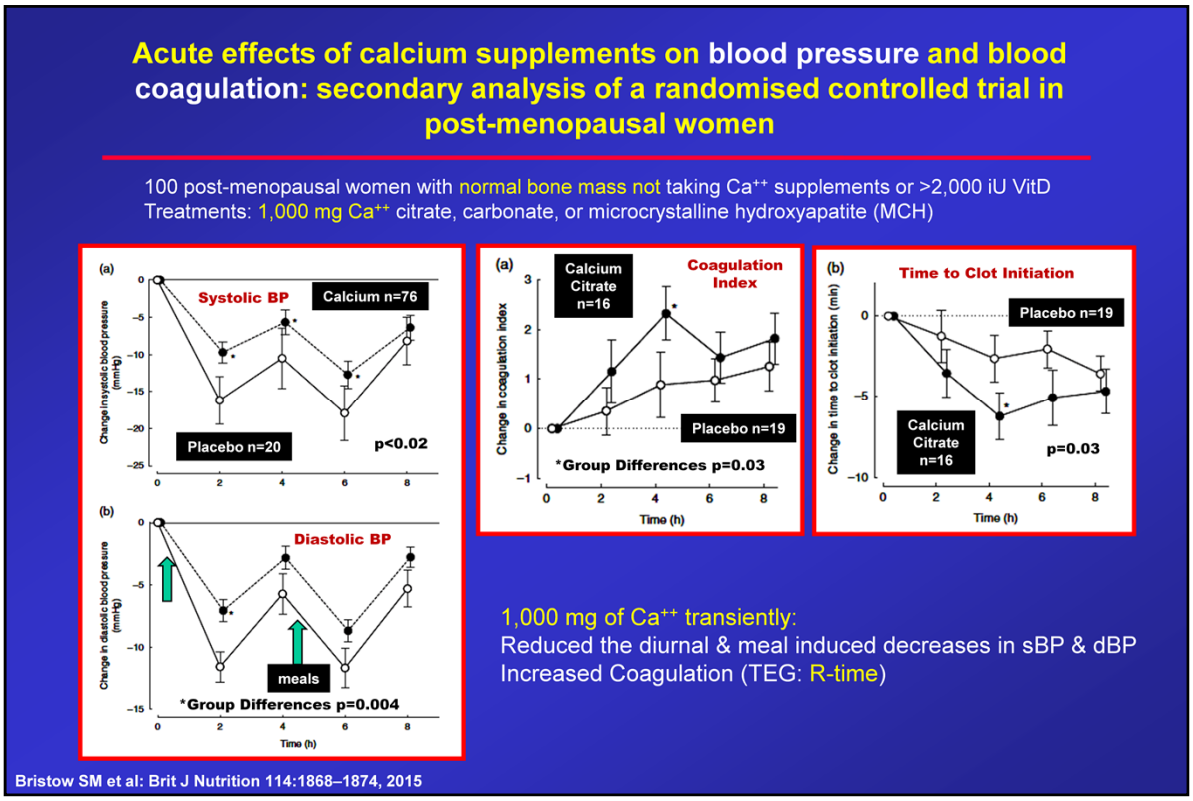


Fig. 2. Changes (a) systolic and (b) diastolic blood pressures in postmenopausal women over 8 h after the ingestion of 1000 mg of Ca (n=76) or a placebo containing no Ca (n=20). Values are means with their standard errors. Changes from baseline in systolic blood pressure were significantly different between the Ca and placebo groups between 2 and 6 h (all P <0·02) and diastolic blood pressure at 2 h (P =0·004). *Significantly different from the control group (P <0·02).

Fig. 3. Changes in the thromboelastographic measures of blood coagulation (a) coagulation index and (b) time to clot initiation (R-time) in post-menopausal women over 8 h after the ingestion of 1000 mg of Ca as citrate (, n 16) or a placebo containing no Ca (, n 19). Changes from baseline in the coagulation index and time to clot initiation were significantly different between the calcium citrate and placebo groups at 4 h (both P =0·03). * Significantly different from the control group, P=0·03. Values are means with their standard errors.

Bone, Artery, & Renal Function in CKD

Supplementation of Calcium in Patients with Normal Renal Function

Calcium Supplementation - usually combined with low-dose Vitamin D:

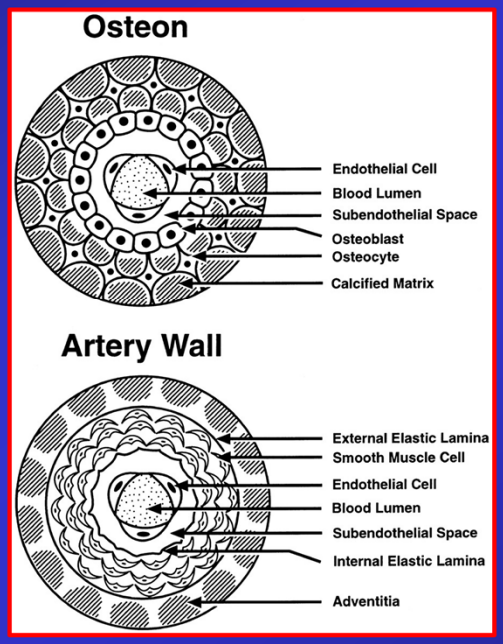
1. Absorption peaks at 4-5 hours; returns to baseline in ~12 hours
2. Calcium citrate absorbs slightly better than carbonate & suppresses PTH better
3. Has a small positive impact on spine & hip bone density, especially in secondary prevention
4. Reduces hip fractures in women on hormone replacement therapy but not if untreated
5. Reduces recurrent colon polyps by 25%
6. Lowers LDL (2.6%, p=0.02) & Insulin Resistance (6.7%, NS)
7. Reduces death from CHF; may reduce CV death & hospitalization in DM & CAD women

8. May increase MI & Stroke - very small impact [worst case: one event per 143 patient years]
   - Does not occur with dietary calcium
   - Evident with lowest dose (~500 mg daily) – more supplement has no additional impact
   - More likely in populations with higher LDL, hypertension, & smoking
9. Improves Cardiac Function
10. Reduces Time to Clot Initiation

Recommendations:

1. Increase Dairy if possible
2. Use small, frequent doses of oral calcium
3. Add aspirin or omega-3 in high-risk patients
4. Monitor PTH to determine adequacy

Diagram illustrating the similarity of the unit element of bone architecture, the osteon with artery wall, and particularly the presence of a subendothelial space.



Farhad Parhami et al. Arterioscler Thromb Vasc Biol 17:680-687, 1997

Atherosclerotic calcification and osteoporosis often coexist in patients, yielding formation of bone mineral in vascular walls and its simultaneous loss from bone. To assess the potential role of lipoproteins in both processes, we examined the effects of minimally oxidized low-density lipoprotein (MM-LDL) and several other lipid oxidation products on calcifying vascular cells (CVCs) and bone-derived preosteoblasts MC3T3-E1. In CVCs, MM-LDL but not native LDL inhibited proliferation, caused a dose-dependent increase in alkaline phosphatase activity, which is a marker of osteoblastic differentiation, and induced the formation of extensive areas of calcification. Similar to MM-LDL, oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (ox-PAPC) and the isoprostane 8-iso prostaglandin E2 but not PAPC or isoprostane 8-iso prostaglandin F2 alpha induced alkaline phosphatase activity and differentiation of CVCs. In contrast, MM-LDL and the above oxidized lipids inhibited differentiation of the MC3T3-E1 bone cells, as evidenced by their stimulatory effect on proliferation and their inhibitory effect on the induction of alkaline phosphatase and calcium uptake. These results suggest that specific oxidized lipids may be the common factors underlying the pathogenesis of both atherosclerotic calcification and osteoporosis.