Calcium/Vitamin D Supplementation and Cardiovascular Events

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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. **(*Circulation*. 2007;115:846-854.)**

Key Words: calcium ■ cerebrovascular disorders ■ coronary disease ■ stroke ■ women

Vascular calcification and valvular calcification predict atherosclerotic risk[1,2] and are prevalent in chronic diseases such as diabetes,[3] systemic lupus erythematosus,[4] and chronic kidney disease,[5] in which the risk of coronary events is high. Arterial calcification and valvular calcification are organized, regulated processes similar in many respects to bone formation and remodeling.[6–9] Because of this relationship, bisphosphonates have been proposed as antiatherosclerotic agents,[10] and patients with coronary calcification commonly ask if they should reduce their calcium consumption.[11] The literature on this topic is scant and conflicting[12–16]; even less is known about the relationship between vitamin D and coronary risk.[17]

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We randomized 36 282 postmenopausal women to calcium plus vitamin D or to placebo in a fracture trial and report here the impact of 7 years of supplementation on cardiovascular outcomes, including time trends and analyses of subgroups.

Methods

Details of the study design have been published previously,[18] as have the baseline characteristics.[19–21] Eligible postmenopausal women 50 to 79 years of age joined the Women's Health Initiative hormone therapy and/or dietary modification trials between 1993 and 1998. One year later, they were invited to join the double-blinded calcium plus vitamin D trial; 91% joined the calcium/vitamin D trial at their first annual visit and 9% during the following year. Women provided written informed consent in a form approved by local institutional review boards and were randomly assigned to a calcium and vitamin D supplement (containing calcium carbonate, 500 mg as elemental calcium, with vitamin D_3 200 IU twice daily) (GlaxoSmithKline Consumer Healthcare, Parsippany, NJ) or matching placebo. Concurrent calcium supplementation was permitted, as was vitamin D, up to 400 IU daily.

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Clinical Outcomes

Weight, blood pressure, and waist circumference were recorded annually. Blood samples were collected at baseline, ie, at the time of enrollment into the hormone therapy and/or dietary modification trials, from all participants; in a random 6% sample, blood samples also were collected 1 and 3 years later.[22]

Participants reported emergency room visits, overnight hospital stays, and outpatient coronary revascularization procedures semiannually. Medical records for all overnight hospitalizations and outpatient coronary revascularization procedures were scrutinized for potential outcomes of interest. Centrally trained physician-adjudicators classified outcomes on the basis of medical record review. Myocardial infarction was categorized through the use of an algorithm that included symptoms, ECG findings, and cardiac enzymes.[23] Confirmed angina required hospitalization for angina with confirmatory stress test or obstructive coronary disease by angiography.[24] Stroke required rapid onset of a persistent neurological deficit not due to trauma, tumor, infection, or other cause[25]; strokes were coded as "other" if procedure related or if the adjudicator could not classify the event as hemorrhagic or ischemic. All deaths were centrally adjudicated; other outcomes were adjudicated on the basis of hospital record review by centrally trained, local adjudicators blinded to treatment assignment. Composite outcomes were defined during development of the analytical plan.

Statistical Methods

Statistical methods have been described.[20,21] In brief, hazard ratios with 95% confidence intervals (CIs) were calculated from Cox proportional-hazards models stratified by age, prevalent cardiovascular disease at baseline, and randomization status in the hormone and dietary modification trials. Subgroup analyses were planned a priori. Subgroup analyses were stratified by age, prevalent cardiovascular disease at baseline, and randomization status in the hormone and dietary modification trials. Consistency of treatment effects among subgroups was assessed by formal tests of interaction; tests for linear trend were used when appropriate. Nineteen subgroups were evaluated for coronary heart disease (CHD) and for stroke; subgroup results should be interpreted with caution because 1 significant finding would be expected by chance for each outcome based on a 0.05 nominal level of statistical significance. All reported probability values are 2 sided. Analyses were carried out by the coordinating center statistics unit using the SAS System for Windows, version 9 (SAS Institute, Cary, NC).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Between 1995 and 2000, 36 282 women were randomized at 40 clinical sites; when the trial closed in April 2005, the mean duration of follow-up was 7.0±1.4 years. Baseline characteristics were balanced between treatment groups (Table 1) except for hypertension ($P=0.03$). At baseline, mean calcium intake (diet plus supplements, exclusive of study medication) was 1148±654 mg/d in the active treatment group and 1154±658 mg/d in the placebo group, close to the recommended intake of 1200 mg daily.[26] Vitamin D consumption was 365±265 IU/d in the active treatment group and 368±266 IU/d in the placebo group. Sixty percent of study participants took at least 80% of their study medication through year 6.

Intermediate Biomarkers and Risk Factors for CHD

Although blood samples were collected on the entire cohort, bioassays were performed in only a 6% random sample. At baseline, total cholesterol was 5.64 mmol/L, low-density lipoprotein cholesterol was 3.28 mmol/L, high-density lipoprotein cholesterol was 1.54 mmol/L, triglycerides were 1.81 mmol/L, glucose was 5.49 mmol/L, and insulin was 11.4 μIU/mL. Differences between mean percent change in the intervention group and mean percent change in the control group are shown from baseline to year 2 after randomization (Figure 1). Percent change from baseline differed significantly between treatment groups for low-density lipoprotein cholesterol ($P=0.02$), waist circumference and weight ($P=0.03$ for both), systolic blood pressure ($P=0.01$), and diastolic blood pressure ($P<0.01$).

Clinical Cardiovascular Outcomes

Myocardial infarction or CHD death was confirmed in 499 women assigned to active calcium/vitamin D and 475 assigned to placebo (hazard ratio, 1.04; 95% CI, 0.92 to 1.18). Stroke was confirmed in 362 women assigned to calcium/vitamin D and 377 assigned to placebo (hazard ratio, 0.95; 95% CI, 0.82 to 1.10; Figure 2). Among women taking at least 80% of study medication, the hazard ratio for myocardial infarction/CHD death was 1.05 (95% CI, 0.88 to 1.25) and for stroke was 0.97 (95% CI, 0.79 to 1.20) (data not shown). Risks of coronary revascularization, confirmed angina, hospitalized heart failure, transient ischemic attack, and composite outcomes also were similar in the 2 treatment groups (Table 2).

Temporal Trends

Hazard ratios with nominal 95% CIs for myocardial infarction/CHD death at 1-year intervals of follow-up were as follows: year 1, 1.13 (95% CI, 0.79 to 1.61); year 2, 1.10 (95% CI, 0.75 to 1.61); year 3, 1.00 (95% CI, 0.69 to 1.46); year 4, 0.92 (95% CI, 0.66 to 1.28); year 5, 1.00 (95% CI, 0.72 to 1.39), year 6, 1.11 (95% CI, 0.81 to 1.51), and year ≥7, 1.07 (95% CI, 0.80 to 1.42). The z score for trend, based on Cox proportional-hazards modeling with time-dependent treatment effects, was 0.22 ($P=0.82$), indicating no significant trend in risk over time.

Hazard ratios with 95% CIs for stroke were as follows: year 1, 1.09 (95% CI, 0.69 to 1.72); year 2, 0.62 (95% CI, 0.41 to 0.94); year 3, 1.22 (95% CI, 0.82 to 1.82); year 4, 1.07 (95% CI, 0.70 to 1.65); year 5, 1.01 (95% CI, 0.69 to 1.47), year 6, 0.71(95% CI, 0.50 to 1.01), and year ≥7, 1.11 (95% CI, 0.81 to 1.52). The z score was 0.55 ($P=0.58$).

Trends by Age

Cumulative hazard ratios for myocardial infarction/CHD death and for stroke were evaluated by age decade. For women 50 to 59, 60 to 69, and 70 to 79 years of age at baseline, hazard ratios with 95% CIs for CHD were 0.94 (95% CI, 0.70 to 1.27), 1.08 (95% CI, 0.90 to 1.30), and 1.05 (95% CI, 0.85 to 1.30), respectively ($P=0.53$ for interaction). Hazard ratios with 95% CIs for stroke were 0.90 (95% CI, 0.62 to 1.32), 0.97 (95% CI, 0.78 to 1.20), and 0.96 (95% CI, 0.76 to 1.20), respectively ($P=0.72$ for interaction).

Additional Subgroup Analyses

We evaluated several demographic and clinical characteristics to determine whether other subgroups of women were at lower or higher risk for myocardial infarction/CHD death with calcium/

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/m^2	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)	
Hypertension			0.03
None	10 915 (66.7)	10 858 (66.5)	
Untreated	1260 (7.7)	1384 (8.5)	
Treated	4187 (25.6)	4092 (25.1)	
Diabetes mellitus	1055 (5.8)	1036 (5.7)	0.80
High cholesterol requiring pills	2008 (12.3)	1964 (12.1)	0.49
Cigarette smoking			0.31
Current	1405 (7.8)	1356 (7.6)	
Past	7255 (40.3)	7133 (39.8)	
Never	9325 (51.8)	9428 (52.6)	
CHD at baseline	487 (2.7)	456 (2.5)	0.34
Cardiovascular disease at baseline	881 (4.8)	860 (4.7)	0.66
Statin use	1178 (6.5)	1149 (6.3)	0.60
Aspirin use	3552 (19.5)	3517 (19.4)	0.78
NSAID use	5983 (32.9)	5891 (32.5)	0.44
Use of postmenopausal hormone therapy			
Assigned to active therapy in hormone trials	4039 (22.2)	4078 (22.5)	0.49
Current use, including exposure in hormone trials	9358 (51.5)	9484 (52.4)	0.09

NSAID indicates nonsteroidal antiinflammatory drug, including aspirin; CHD at baseline, self-reported myocardial infarction or coronary revascularization at baseline; cardiovascular disease at baseline, self-reported myocardial infarction, coronary revascularization, stroke, or transient cerebral ischemia at baseline; aspirin use, >80 mg taken at least twice weekly; and statin, 3′-hydroxy-3-methyglutaryl coenzyme A reductase inhibitor. Values are mean±SD or n (%).

vitamin D (Figure 3) or for stroke (Figure 4). The hazard ratios for CHD (P=0.91 for interaction) and stroke (P=0.14 for interaction) did not differ by total calcium intake (dietary plus supplemental) at baseline. Similarly, hazard ratios did not differ by vitamin D intake at baseline (P=0.45 for interaction for CHD and P=0.12 for stroke). Hazard ratios also did not differ by ethnicity, although numbers of events were small among Hispanic, American Indian, and Asian women (P=0.54 for interaction for CHD and P=0.63 for stroke).

CHD risk with active calcium/vitamin D was inversely related to body mass index (P=0.04 for interaction); ie, women with higher body mass index were at lower CHD risk with active calcium/vitamin D supplementation, whereas those with lower body mass index were at higher CHD risk. Stroke risk with active calcium/vitamin D was lower among women with high cholesterol and those taking statins at baseline (P=0.04 for interaction for both). Stroke risk with active calcium/vitamin D was inversely related to the number of CHD risk factors; ie, women with fewer risk factors were at higher stroke risk with calcium/vitamin D supplementation (P=0.02 for interaction).

Discussion

Calcium/vitamin D supplementation neither increased nor decreased the risk for CHD or stroke in generally healthy

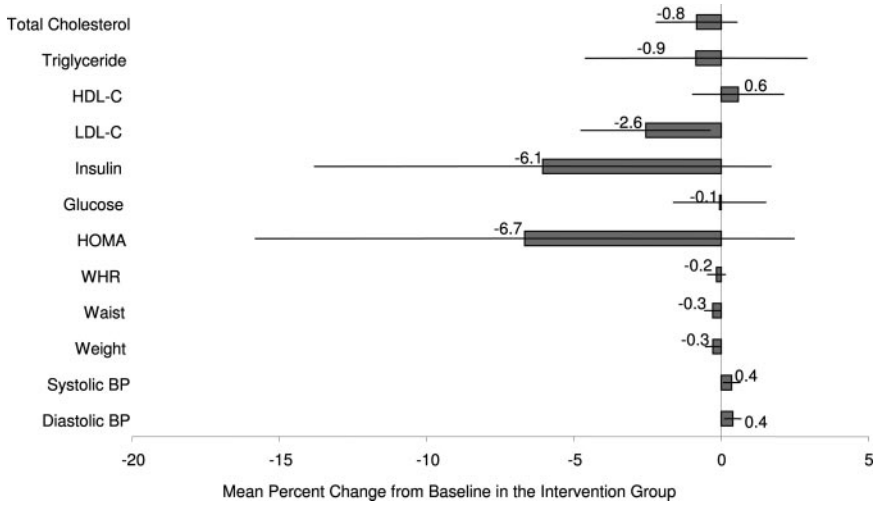

Figure 1. Differences in mean percent change from baseline to year 2 between women assigned to active calcium/vitamin D and those assigned to placebo for several intermediate outcomes. Horizontal lines represent 95% CIs. Physical measures were performed on the entire cohort; laboratory measures, in a 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.

postmenopausal women throughout the 7-year duration of this randomized trial. Neither total calcium intake (dietary plus supplemental) nor total vitamin D intake at baseline affected cardiovascular risk with calcium/vitamin D supplementation.

Possible explanations of this null finding include the following: (1) Background calcium use impaired our ability to identify a treatment effect; (2) the dose of vitamin D was inadequate; (3) poor adherence to study medication blunted any treatment effect; (4) concurrent postmenopausal hormone therapy interfered with treatment effects; (5) the trial was designed to evaluate the effects of calcium/vitamin D supplementation on fracture, not cardiovascular disease; or (6) calcium and vitamin D do not, in fact, affect cardiovascular risk.

A limitation of the trial was that women were allowed to continue their own calcium supplements because it would have been unethical to prohibit concurrent calcium use in a long-term, placebo-controlled trial. Baseline calcium consumption (diet plus supplements) was balanced between treatment groups, and no significant interaction between dietary or total calcium consumption at baseline and randomized treatment assignment was observed for either CHD or stroke.

Baseline vitamin D consumption (diet plus supplements) and regional solar irradiance[21] also were balanced between treatment groups. Parathyroid hormone levels are maximally suppressed at 25-hydroxy vitamin D blood levels >75 nmol/L (30 ng/mL).[27] In our trial, despite consuming 365 IU vitamin D daily (supplements plus dietary vitamin D) at

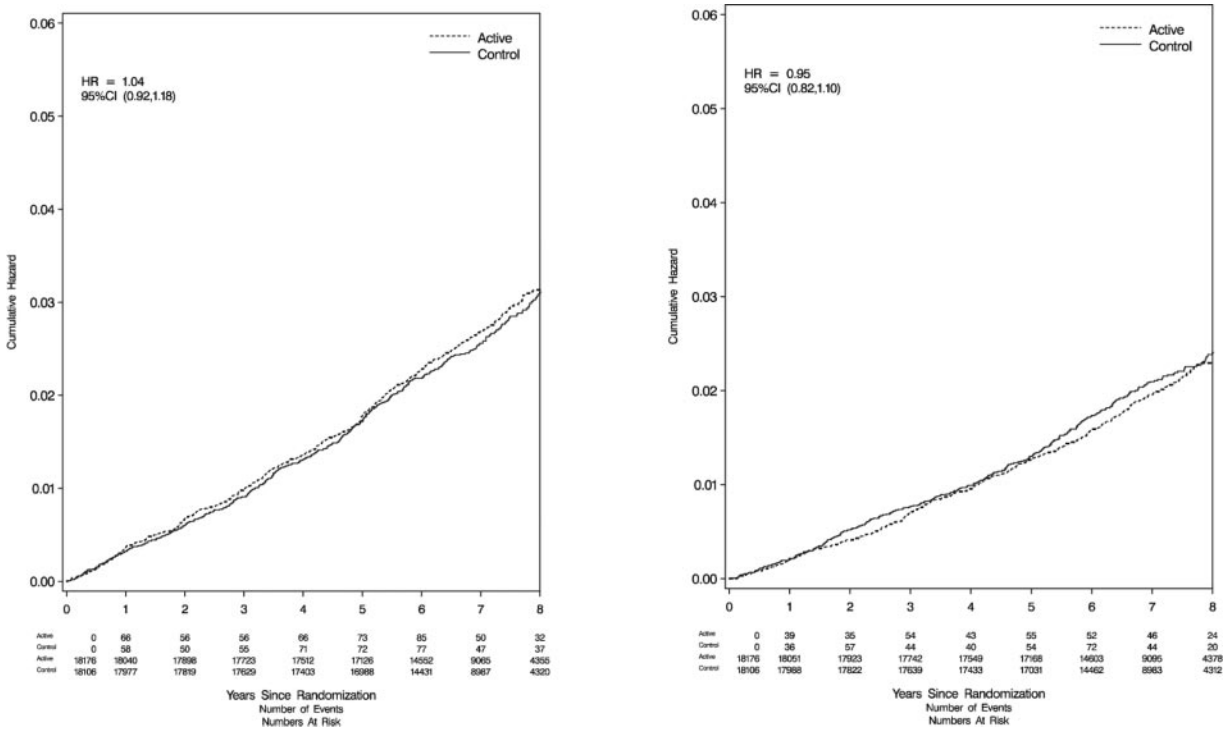

Figure 2. Kaplan-Meier estimates of cumulative hazard rates for CHD (myocardial infarction or coronary death; left) and for stroke (right). HR indicates hazard ratio.

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.

baseline, only 13% of women with incident fractures (n=1589) and 15% of matched controls had serum levels >75 nmol/L, consistent with the current view that 800 to 1000 IU daily may be needed to achieve optimal serum vitamin D levels.[28] Women assigned to active calcium/vitamin D supplementation would have been taking almost 800 IU daily, which may still have been insufficient. Nonetheless, women with higher vitamin D consumption at baseline were not at higher or lower risk for CHD or stroke if assigned to active calcium/vitamin D. Low vitamin D levels have been associated with acute stroke[29]; because we measured serum vitamin D levels in fracture cases and controls, not stroke cases, we are not able to confirm this association.

At the end of the trial (mean follow-up, 7 years), 76% of participants were taking some study pills, and 59% were taking ≥80% of their study medication. Calcium/vitamin D supplementation did not alter CHD or stroke risk in sensitivity analyses, in which women were censored when they became nonadherent, reducing the likelihood that adherence affected study results. Use of postmenopausal hormone therapy, which increases the risk of stroke[25] and CHD,[30] was balanced in the treatment groups. Neither CHD nor stroke risk differed with calcium/vitamin D supplementation among women assigned to active hormone therapy in the randomized hormone trials, making it unlikely that postmenopausal hormone use affected study results.

Another limitation of our analysis is that this trial was designed to evaluate the effect of intervention on fracture, not cardiovascular disease. In fact, the number of myocardial infarctions/CHD deaths (n=974) and strokes (n=739) was greater than the number of hip fractures (n=374), so a reasonable treatment effect should have been readily detectable. Overall, the most likely explanation for our findings is that calcium/vitamin D supplementation did not modulate CHD or stroke risk.

Calcium and vitamin D had a mixture of favorable and unfavorable effects on intermediate outcomes. Systolic pressure rose 1.1±12.4% among calcium/vitamin D recipients during the 2 years after randomization and 0.7±12.4% among placebo recipients ($P=0.01$ for the treatment group difference in percent change from baseline to year 2). Diastolic pressure fell 0.2±12.4% in the active treatment group and 0.6±12.4% in the placebo group ($P=0.007$). These findings contrast with the National Health and Nutrition Examination Survey, in which dietary calcium consumption was inversely associated with an age-related increase in systolic blood pressure.[31] Because of adjustments in concurrent medication dosage, we cannot be sure that the treatment group differences in our trial are due solely to calcium/vitamin D supplementation. Furthermore, in later years of the trial, the changes in blood pressure from baseline no longer differed between treatment groups.

Weight increased in both treatment groups during the 2 years after randomization (1.4±10.5% versus 1.7±12.0%), as did waist circumference (1.5±7.6% versus 1.8±8.4%), but these increases were smaller among women assigned to active calcium/vitamin D ($P=0.03$ for both). The relationship between weight and calcium/vitamin D consumption in other reports has been inconsistent,[32,33] but women taking calcium supplements gained less weight than nonusers in a recent, large, 10-year epidemiological study.[34]

In both treatment groups, low-density lipoprotein cholesterol rose in the 6% of participants with measured biomarkers, but the increase was smaller among women assigned to active calcium/vitamin D (0.2±20.9% versus 2.6±20.7%; $P=0.02$). In a small 12-week trial, calcium/vitamin D supplementation had no effect on low-density lipoprotein cholesterol.[35] The modest difference seen in our trial may reflect changes in weight over the 2 years or adjustments in concomitant medications and cannot be definitively attributed to calcium/vitamin D supplementation.

We found several subgroups of women with lower hazard ratios for CHD or stroke with calcium/vitamin D supplementation. Women with higher body mass index appeared to be at

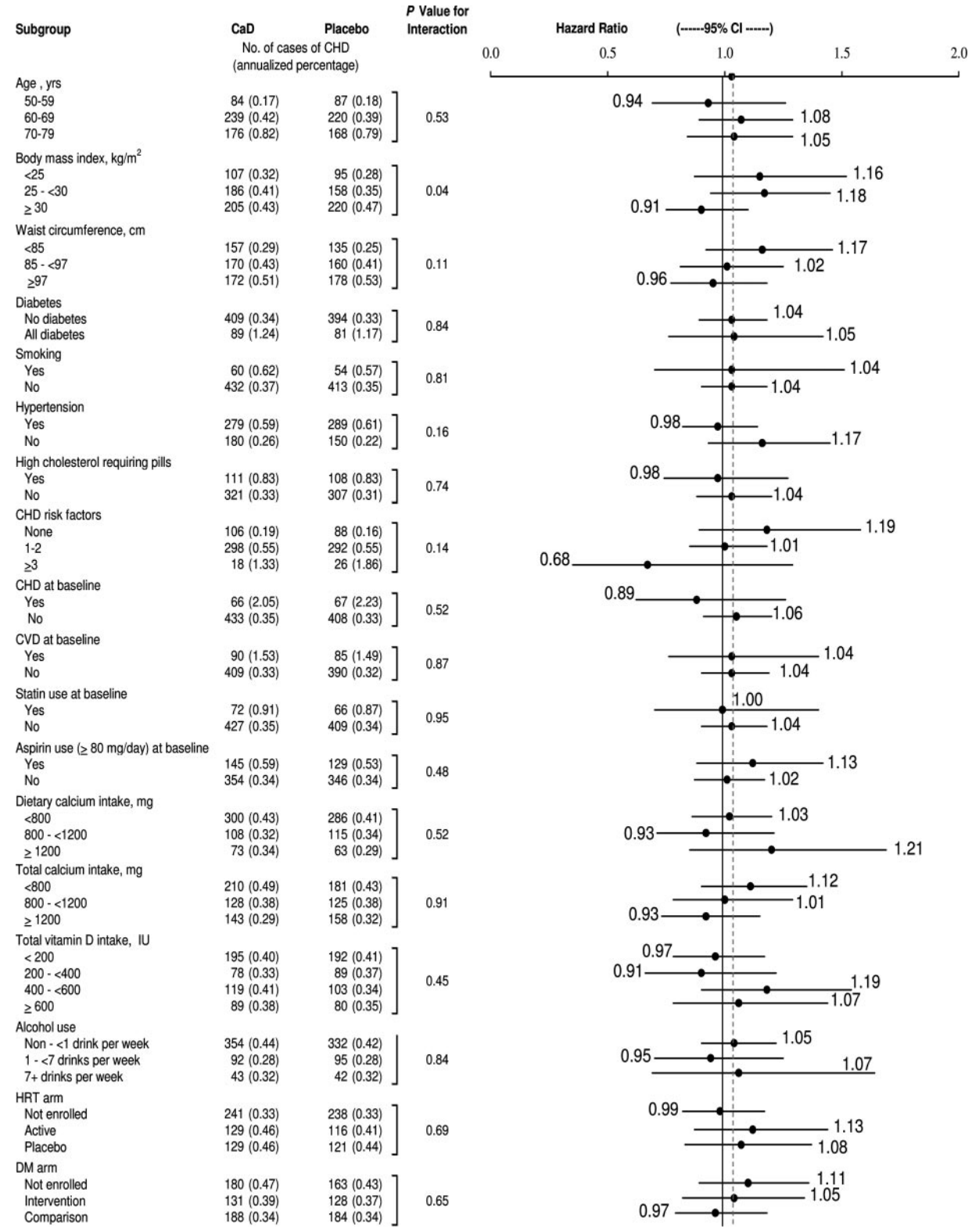

Figure 3. Risk of CHD (myocardial infarction or CHD death) by treatment group assignment in various subgroups. Hazard ratios with nominal 95% CIs (horizontal bars) are adjusted for age and prevalent CHD at baseline. The red dotted vertical line represents the hazard ratio for CHD in the overall cohort. Probability values are for the interaction between the subgroup variable and treatment assignment. CHD includes nonfatal myocardial infarction and coronary death. Hypertension was defined as treated hypertension or a measured blood pressure of ≥140/90 mm Hg. Risk factors for CHD included current cigarette smoking, hypertension, self-reported diabetes, and high cholesterol. The presence of CHD at baseline was defined as self-reported myocardial infarction or coronary revascularization. The presence of cardiovascular disease (CVD) at baseline was defined as self-reported myocardial infarction, coronary revascularization, stroke, or transient cerebral ischemia. Because of missing data on some variables, the numbers of cases do not always add up to the total number of cases in the treatment group. Statin indicates 3′-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor; HRT, hormone replacement trial; DM, dietary modification trial; and CaD, calcium plus vitamin D.

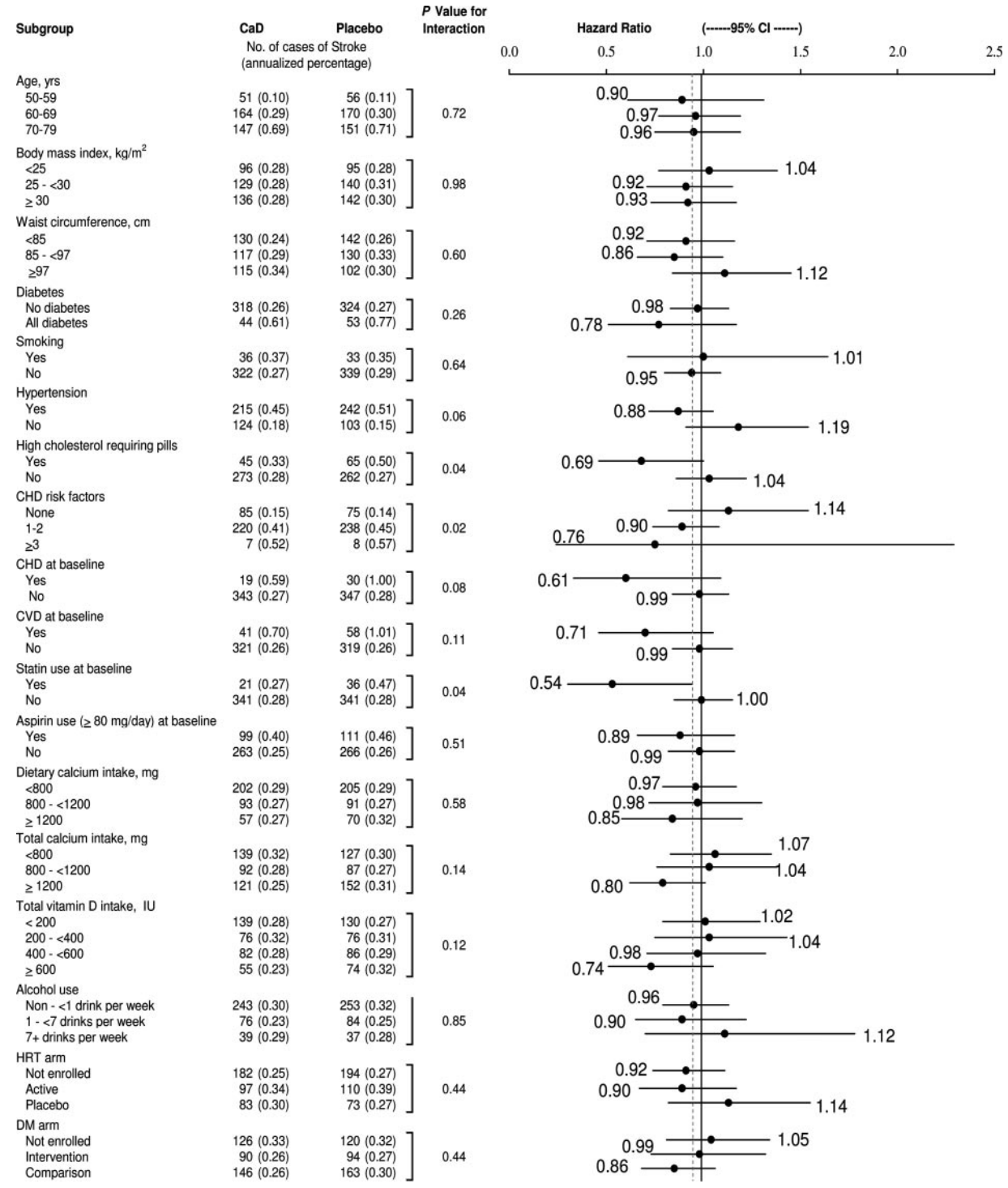

Figure 4. Risk of stroke by treatment group assignment in various subgroups. Hazard ratios with nominal 95% CIs (horizontal bars) are adjusted for age and prevalent cerebrovascular disease at baseline. Abbreviations as in Figure 3.

lower risk for CHD with calcium/vitamin D supplementation ($P=0.04$ for interaction), but in view of the number of subgroups examined, this finding may be due to chance.

We also found that women with more coronary risk factors were at lower risk for stroke with calcium/vitamin D supplementation ($P=0.02$ for interaction) but think this may be due to chance as well, particularly because the number of women with ≥3 risk factors was very small. On the other hand, women with self-reported hypercholesterolemia and those who used statins were at lower risk for stroke if assigned to active calcium/vitamin D ($P=0.04$ for interaction for both). The clinical link between high cholesterol and statin use and the proposed, albeit controversial, effect of statin use on bone enhance the plausibility of this interaction.

Statins increase new bone formation in vitro and enhance trabecular bone formation in rodents[36] through blockade of

the mevalonate pathway.[37] In women, as opposed to rodents, statins had no effect on markers of bone turnover,[38] bone density, fracture risk,[39] or progression of coronary calcification[40]; thus, the relationship between statin use and fracture risk remains controversial. Overall, the relationship between consumption of calcium/vitamin D supplements and statin use remains quite unclear with regard to cardiovascular disease risk. Another placebo-controlled trial the size and duration of the Women's Health Initiative is unlikely to be undertaken, although it is possible that trials of bisphosphonates or other agents may shed some light. Populations in those trials are not at particularly high risk for cardiovascular disease, however, so the number of atherosclerotic events may prove inadequate.

Calcium and vitamin D supplementation did not increase the risk for myocardial infarction, CHD death, stroke, coronary revascularization, hospitalized angina, heart failure, or transient ischemic attack. Thus, women taking these supplements need not fear adverse cardiovascular consequences while protecting their bone health.

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Disclosures

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References

1. Pletcher MJ, Tice JA, Pignone M. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med*. 2004;164:1285–1292.
2. Allison MA, Cheung P, Criqui MH, Langer Rd, Wright CM. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. *Circulation*. 2006;113:861–866.
3. Reaven PD, Sacks J, for the Investigators for the VADT. Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. *Diabetologia*. 2005;48:379–385.
4. Molad Y, Levin-Iaina N, Vaturi M, Sulkes J, Sagie A. Heart valve calcification in young patients with systemic lupus erythematosus: a window to premature atherosclerotic vascular morbidity and a risk factor for all-cause mortality. *Atherosclerosis*. 2006;185:406–412.
5. Jono S, Shioi A, Ikari Y, Nishizawa Y. Vascular calcification in chronic kidney disease. *J Bone Miner Metab*. 2006;24:176–181.
6. Anand DV, Lahiri A, Lim E, Hopkins D, Corder R. The relationship between plasma osteoprotegerin levels and coronary artery calcification in uncomplicated type 2 diabetic subjects. *J Am Coll Cardiol*. 2006;47:1850–1857.
7. Doherty TM, Asotra K, Fitapatrick LA, Qiao JH, Wilkin DJ, Detrano RC, Dunstan CR, Shah PK, Rajavashisth TB. Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. *Proc Natl Acad Sci U S A*. 2003;100:11201–11206.
8. Vattikuti R, Towler DA. Osteogenic regulation of vascular calcification: an early perspective. *Am J Physiol Endocrinol Metab*. 2004;286:E686–E696.
9. Caira FC, Stock SR, Gleason TG, McGee EC, Huang J, Bonow RO, Spelsberg TC, McCarthy PM, Rahimtoola SH, Rajamannan NM. Human degenerative valve disease is associated with up-regulation of low-density lipoprotein receptor-related protein 5 receptor-mediated bone formation. *J Am Coll Cardiol*. 2006;47:1707–1712.
10. Bevilacqua M, Dominguez LJ, Rosini S, Barbagallo M. Bisphosphonates and atherosclerosis: why? *Lupus*. 2005;14:773–779.
11. Davis W. Ask the doctor: calcium intake and vascular calcification. *Life Extension Magazine*. August 2005. Available at: www.lef.org/magazine/mag2005/aug2005_atd_01.htm. Accessed May 28, 2006.
12. Umesawa M, Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y, Kikuchi S, Koizumi A, Kondo T, Inaba Y, Tanabe N, Tamakoshi A. Dietary intake of calcium in relation to mortality from cardiovascular disease. *Stroke*. 2006;37:20–26.
13. Van der Vijver LP, van der Waal MA, Weterings KG, Dekker JM, Schouten EG, Kok FJ. Calcium intake and 28-year cardiovascular and coronary heart disease mortality in Dutch civil servants. *Int J Epidemiol*. 1992;21:36–39.
14. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and diary food intake to ischemic heart disease mortality among postmenopausal women. *Am J Epidemiol*. 1999;149:151–161.
15. Nerbrand C, Svardsudd K, Ek J, Tibblin G. Cardiovascular mortality and morbidity in seven counties in Sweden in relation to water hardness and geological settings: the project: myocardial infarction in mid-Sweden. *Eur Heart J*. 1992;13:721–727.
16. Rosenlund M, Berglind N, Hallqvist J, Bellander T, Bluhm G. Daily intake of magnesium and calcium from drinking water in relation to myocardial infarction. *Epidemiology*. 2005;16:570–576.
17. Kummerow FA. Nutrition imbalance and angiotoxins as dietary risk factors in coronary heart disease. *Am J Clin Nutr*. 1979;32:58–83.
18. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61–109.
19. Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13:S98–S106.
20. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL, Robbins J, Rohan TE, Sarto GE, Sharma S, Stefanick ML, Van Horn L, Wallace RB, Whitlock E, Bassford T, Beresford SA, Black HR, Bonds DE, Brzyski RG, Caan B, Chlebowski RT, Cochrane B, Garland C, Gass M, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Judd H, Kooperberg CL, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Lewis CE, Limacher MC, Manson JE, for the Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354:684–696.
21. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D, for the Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354:669–683.
22. Anderson GL, Manson JE, Wallace R, Lund B, Hall D, Davis S, Shumaker S, Wang CY, Stein E, Prentice RL. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13:S5–S17.
23. Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, Daugherty S, for the WHI Morbidity and Mortality Committee. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13:S122–S128.
24. Hsia J, Aragaki A, Bloch M, LaCroix AZ, Wallace R. Predictors of angina vs myocardial infarction from the Women's Health Initiative. *Am J Cardiol*. 2004;93:673–678.
25. Wassertheil-Smoller W, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, Kotchen T, Curb JD, Black H, Rossouw JE, Aragaki A, Safford M, Stein E, Laowattana S, Mysiw WJ, for the WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA*. 2003;289:2673–2584.
26. Office of Dietary Supplements, National Institutes of Health. Dietary supplement fact sheet: calcium. Available at: http://dietary-supplements.info.nih.gov/factsheets/calcium.asp. Accessed June 1, 2006.
27. Vieth R. What is the optimal vitamin D status for health? *Prog Biophys Mol Biol*. 2006;92:26–32.
28. Reginster JY, Zegels B, Lejeune E, Micheletti MC, Kvsaz A, Seidel L, Sarlet N. Influence of daily regimen calcium and vitamin D supplemen-

tation on parathyroid hormone secretion. *Calcif Tissue Int*. 2002;70:78–82.
29. Poole KES, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, Warburton EA. Reduced vitamin D in acute stroke. *Stroke*. 2006;37:243–245.
30. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M, for the Women's Health Initiative Investigators. Estrogen plus progestin and risk of coronary heart disease. *N Engl J Med*. 2003;349:523–534.
31. Hajjar IM, Grim CE, Kotchen TA. Dietary calcium lowers the age-related rise in blood pressure in the United States: the NHANES III survey. *J Clin Hypertens*. 2003;5:122–126.
32. Shapses SA, Heshka S, Heymsfield SB. Effect of calcium supplementation on weight and fat loss in women. *J Clin Endocrinol Metab*. 2004;89:632–637.
33. Barr SI. Increased dairy product or calcium intake: is body weight or composition affected in humans? *J Nutr*. 2003;133:245S–248S.
34. Gonzalez AJ, White E, Kristal A, Littman AJ. Calcium intake and 10-year weight change in middle-aged adults. *J Am Diet Assoc*. 2006;106:1066–1073.
35. Gannage-Yared MH, Azoury M, Mansour I, Baddoura R, Halaby G, Naaman R. Effects of a short-term calcium and vitamin D treatment on serum cytokines, bone markers, insulin and lipid concentrations in healthy postmenopausal women. *J Endocrinol Invest*. 2003;26:748–753.
36. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G. Stimulation of bone formation in vitro and in rodents by HMG CoA reductase inhibitors. *Science*. 1999;286:1946–1949.
37. Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, Wesolowski G, Russell RG, Rodan GA, Reszka AA. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. *Proc Natl Acad Sci U S A*. 1999;96:133–138.
38. Hsia J, Morse M, Levin G. Effect of simvastatin on bone markers in osteopenic women: a placebo-controlled, dose-ranging trial. *BMC Musculoskeletal Disorders*. 2002;3:7.
39. LaCroix AZ, Cauley JA, Pettinger M, Hsia J, Bauer DC, McGowan J, Chen Z, Lewis CE, McNeeley SG, Passaro MD, Jackson RD. Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med*. 2003;139:97–104.
40. Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, Rumberger JA. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering With EBT Scanning (BELLES). *Circulation*. 2005;112:563–571.

CLINICAL PERSPECTIVE

Use of calcium and vitamin D supplements is widespread, particularly among older women. In observational studies, calcium has been associated with lower blood pressure and weight loss, which might be expected to lower risk for coronary heart disease and stroke. On the other hand, individuals with coronary artery calcification are at higher risk for coronary events, raising concern among patients that calcium supplementation may be deleterious. In the Women's Health Initiative placebo-controlled trial, calcium 1000 mg plus vitamin D 400 IU daily neither increased nor decreased the risk of coronary heart disease or stroke during a 7-year follow up of 36 282 postmenopausal women. Thus, women taking these supplements need not fear adverse cardiovascular consequences while protecting their bone health.