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Risk of Heart Failure Among Postmenopausal Women

A Secondary Analysis of the Randomized Trial of Vitamin D Plus Calcium of the Women's Health Initiative

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Background—Vitamin D supplementation may be an inexpensive intervention to reduce heart failure (HF) incidence. However, there are insufficient data to support this hypothesis. This study evaluates whether vitamin D plus calcium (CaD) supplementation is associated with lower rates of HF in postmenopausal women and whether the effects differ between those at high versus low risk for HF.

Methods and Results—Analyses were restricted to 35 983 (of original 36 282) women aged 50 to 79 years old in the Women's Health Initiative randomized trial of CaD supplementation who were randomized 1:1 in a double-blinded fashion to receive 1000 mg/d of calcium plus 400 IU/d of vitamin D_3 or placebo. Overall, 744 adjudicated incident HF cases (intervention, 363; control, 381) occurred during a median follow-up of 7.1 (interquartile range, 1.6) years. CaD supplementation, compared with placebo, was not associated with reduced HF risk in the overall population, hazard ratio, 0.95; *P*=0.46. However, CaD supplementation had differential effects (*P* interaction=0.005) in subgroups stratified by baseline risk status of HF defined by the presence (high risk=17 449) or absence (low risk=18 534) of pre-existing HF precursors including coronary heart diseases, diabetes mellitus, or hypertension: 37% (hazard ratio, 0.63 [95% confidence interval, 0.46–0.87]) lower risk of HF in the low-risk versus hazard ratio, 1.06; *P*=0.51, in the high-risk subgroups.

Conclusions—CaD supplementation did not significantly reduce HF incidence in the overall cohort, however, it was beneficial among postmenopausal women without major HF precursors while of little value in high-risk subgroups. Additional studies are warranted to confirm these findings and investigate the underlying mechanism.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000611.

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Key Words: calcium ■ clinical trial ■ heart failure ■ vitamin D ■ women

Heart failure (HF) is a major public health problem with an enormous burden of morbidity, disability, and associated healthcare costs.[1] HF incidence rates are likely to remain high because of a rapidly aging population and a high prevalence of major precursors of HF, including hypertension, diabetes mellitus, and coronary heart disease (CHD). It is, therefore, imperative to identify effective interventions for prevention of HF.

Clinical Perspective on p 56

The role of vitamin D in HF pathogenesis in humans is not well established, partly owing to the lack of randomized controlled trial data on this relationship. However, it has been proposed that vitamin D can directly affect cardiac functioning through interaction with cardiomyocyte vitamin D receptors[2,3] or indirectly by modifying the incidence of hypertension, diabetes mellitus, CHD, or other major precursors of HF[4] Evidence for this relationship derives from trials in patients with HF and chronic kidney disease.[5–10] Among patients with chronic kidney disease, it has been suggested that insufficient vitamin D may lead to cardiac malfunction in the presence of excess parathyroid hormone levels precipitated by low vitamin D levels.[5,7–10] It has also been reported

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that supplementation with vitamin D has modest effects on ventricular function and N-terminal brain natriuretic peptide levels among patients with HF.[6]

The role of calcium in HF pathogeneses is not clear. There are no existing data on the direct effect of calcium supplementation on HF. However, results from 2 meta-analyses suggest that calcium may be associated with increased risk of some cardiovascular diseases (CVD). Bolland et al[11] reported calcium (alone) supplementation to be associated with a significant 27% increased risk of myocardial infarction in a pooled sample of 12 000 trial participants, while Wang et al[12] reported a 14% elevated risk of a composite of CVD associated with calcium (alone) supplementation. However, combined supplementation of calcium and vitamin D had a null effect on CVD incidence.[12]

Hsia et al[13] previously reported that vitamin D plus calcium (CaD) supplementation did not increase the risk of CVD, including HF, in the Women's Health Initiative CaD trial population. Their analyses involved participants with pre-existing HF at baseline; hence, it is not clear what the effect of the intervention was on women free of HF at baseline. The present analyses, therefore, evaluate the effect of randomized assignment to CaD supplementation in the prevention of HF among postmenopausal women free of HF and participating in the Women's Health Initiative CaD trial. Secondary prespecified goals for the present analyses were to examine the results in high-risk versus low-risk groups and according to baseline intake of personal vitamin D and calcium supplements. Hypertension, diabetes mellitus, and CVD, associated with HF population attributable risks of 59%, 12%, and 26%, respectively, among US women aged 40 to 80 years old[14] are also associated with low serum vitamin D levels.[6,12,14–17] Hence, vitamin D supplementation may have HF benefits in populations with these pre-existing chronic conditions. Prespecified sensitivity analysis included per-protocol analysis and estimation of CaD effects through inverse probability of censored weights methods.[18]

Methods

Design Overview: The CaD Trial

This is a secondary analysis of HF outcomes from a previously completed randomized control trial testing the effects of CaD on fractures and cancer outcomes as primary end points; however, CVD including HF were also ascertained. The CaD trial design and methodology have been published.[19,20] This study was approved by an institutional review committee and all subjects gave informed consent.

Randomization and Intervention

The 36 282 postmenopausal women, aged 50 to 79 years old, who met the inclusion criteria and consented to participate in the CaD trial were randomized in a 1:1 ratio double-blinded fashion to receive either the intervention or placebo. The intervention group received a total dosage of 1000 mg elemental calcium and 400 IU vitamin D_3 per day.[19,20] This dose, according to the Institute of Medicine (IOM), was sufficient to meet the recommended dietary allowance of both vitamin D and calcium in postmenopausal women. Participants randomized to the placebo group were provided inactive tablets that looked exactly like the active tablets and instructed to take these tablets in the same format as those in the intervention group to preserve the blinding of the randomization to both study staff and participants.[19]

Participants who reported use of personal vitamin D (48.4%) and calcium (54.9%) supplements were allowed to continue taking them even after enrolling in the CaD trial. The personal vitamin D supplement consumption was later raised to an upper limit of 1000 IU/d after the IOM published new recommendations on vitamin D intake in 1999.[21] Details of participant selection for the CaD trial and the present analyses are reported in Figure 1.

Outcome: Ascertainment of HF Cases

Trained staff abstracted medical records annually for self-reported HF hospitalization and any 2-day hospitalization that reported a CVD outcome. The abstracted HF cases were then classified by an adjudication committee of physicians at local clinical sites; only a subset of HF cases were adjudicated by a central adjudication physician committee because HF was a secondary end point for the CaD trial. The local and central adjudication methods had an excellent 79% agreement rate (k).[22] The local physician committee used the following method: hospitalized HF (HF requiring and occurring during hospitalization) required physician diagnosis of new-onset or worsened congestive HF on the reported hospital admission and ≥1 of the following 4 criteria: (1) HF diagnosed by physician and receiving medical treatment for HF; (2) above plus documentation in the current medical record of a history of an imaging procedure showing impaired left ventricular systolic or diastolic function; (3) pulmonary edema/congestion on chest x-ray on the current admission; (4) dilated ventricle(s) or poor left ventricular or right ventricular function by echocardiogram, multigated acquisition, radionuclide ventriculogram, or other contrast ventriculography, or evidence of left ventricular diastolic dysfunction.

Covariates and Effect Modifiers

We stratified the study sample into 2 subgroups by baseline status of medical histories of major cardiovascular precursors of HF to estimate the effect of CaD intervention in these subgroups. For the prespecified subgroup analyses, we defined high risk using American College of Cardiology criteria, based on the presence of hypertension,

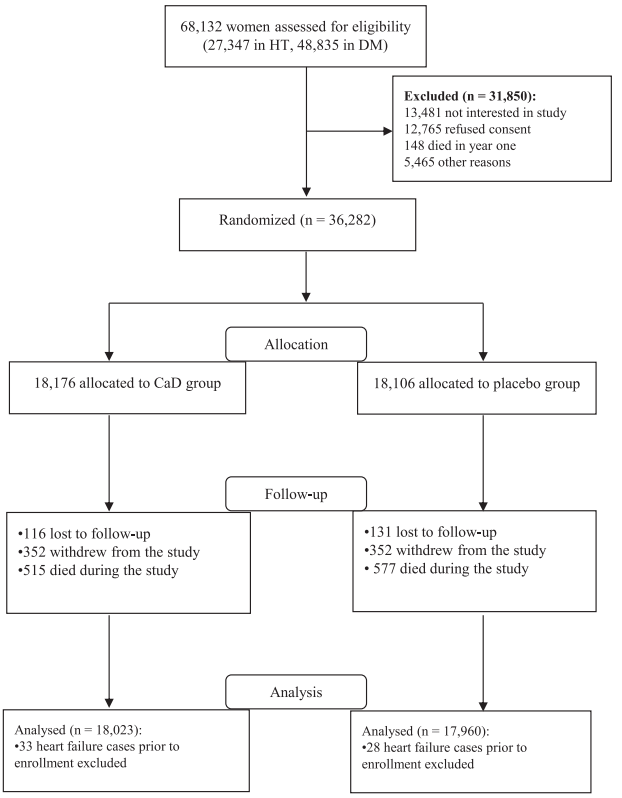

Figure 1. Participant recruitment and selection for the vitamin D plus calcium (CaD) trial and analyses. DM indicates diabetes mellitus; and HT, hypertension.

diabetes mellitus, CHD, or CVD.[23] Women who reported any histories of medically diagnosed hypertension, diabetes mellitus, CHD, or CVD before randomization were grouped as high risk of HF while those without any of these conditions were considered to be at low risk of HF.

Self-reported histories of physician-diagnosed cardiovascular conditions were obtained from all participants during trial enrollment. Details of the description of these baseline factors and other baseline potential confounders listed in Table 1 have been previously reported.[19] Hypertension was defined as a self-reported physician diagnosis of hypertension with or without current use of antihypertensive medications or high blood pressure (BP) (measured systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg) during enrollment into the CaD trial. CVD was defined as self-reported physician diagnosis of problems with the heart, blood circulation, or clots. CHD was defined as a composite of self-reported cardiac arrest, angina, coronary artery bypass graft surgery, and percutaneous transluminal coronary angioplasty. Diabetes mellitus was defined based on self-reported physician diagnosis of diabetes mellitus and current prescription of diabetic medications.

Table 1. Baseline Characteristics of Participants Stratified by Baseline Risk Status of Heart Failure and by Treatment Group—The Vitamin D and Calcium (CaD) Trial of the Women's Health Initiative (WHI) Study, 1995 to 2005

	Baseline Risk Status			
	Low-Risk Group (N=18 534)		High-Risk Group (N=17 449)	
Baseline Characteristics	CaD (n=9307)	Placebo (n=9227)	CaD (n=8716)	Placebo (n=8733)
No. (%) with data				
Age, y				
49–59	44	44	30	30
60–69	43	43	48	48
70–81	13	13	22	22
Race/ethnicity				
White	86	87	80	80
Black	6	6	12	12
Hispanic	5	4	4	4
Income ($)				
<25 000	18	18	24	25
25 000–50 000	43	44	47	46
50 000–70 000	21	20	17	18
75 000–100 000	10	10	6	7
>100 000	9	9	5	6
Physical activity level (total METs/wk)				
Low	37	37	40	40
Moderate	12	13	14	13
High	51	50	47	47
Smoking status				
None	52	53	53	54
Past	40	39	40	40
Current	8	8	7	7
Family history of CVD	62	62	70	70
Personal calcium (alone) supplements	50	50	50	50
Personal vitamin D (alone) supplements	50	50	50	50

CVD indicates cardiovascular disease; and MET, metabolic equivalent of task.

Sample Size and Power Calculations

Women (153 intervention; 146 placebo) with prior medical diagnosis of HF at trial enrollment were excluded from this analysis to create a primary prevention cohort of 35 983 (18 023 intervention; 17 960 control) postmenopausal women free of HF. When stratified by baseline risk status of HF, 17 449 (8716 intervention; 8733 control) were considered to be at high risk while 18 534 (9307 intervention; 9227 control) were considered to be at low risk. A total of 744 HF cases occurred (high-risk: 587 [302 intervention; 285 control] versus low-risk subgroup: 157 [61 intervention; 96 control]) during a total follow-up of ≈9.8 years. Based on these data and an α level of 0.05, this study had 80% statistical power to detect protective effects (hazard ratios [HR]) of CaD supplementation of ≥0.86, 0.64, and 0.78 in the overall CaD cohort, the low-risk, and high-risk subgroups, respectively.[24] Given a 2-tailed a priori hypothesis testing, the study was powered at 80%, type I error of 0.05, to detect interaction effect sizes of ≥1.52 when CaD effect is stronger in the high-risk compared with the low-risk group or ≤0.66 when CaD effect is stronger in the low-risk compared with the high-risk group.[25]

Statistical Analysis

All main analyses were performed based on an intention-to-treat approach. Chi-square and Student *t* test were performed to assess the balance of potential confounders between trial arms for the entire CaD cohort and by stratified subgroups. Cox proportional hazard regression models were used to estimate the effect (HR) of the intervention on HF. Both graphical, Kaplan–Meier curves (Figure 2) and Schoenfeld residuals plots (Figure I in the Data Supplement) and time-dependent proportionality tests (study cohort [*P* for interaction]; overall cohort (0.45), low risk [0.80], high risk [0.44]) were used to evaluate whether the proportionality assumption was violated by the intervention variable. Formal test of interaction between the randomization status and a binary indicator of baseline HF risk status was performed by including a product term between the 2 variables in the Cox proportional hazard models. All HRs were estimated from unadjusted Cox proportional hazard models because all potential covariates evaluated were balanced between the 2 arms of the study.

We also evaluated whether personal consumption of vitamin D or calcium supplements at baseline modified the effect of CaD on HF incidence because participants were allowed to continue consuming their personal calcium and vitamin D supplements after enrolling in the CaD trial. In addition, we tested whether total (diet plus supplements) vitamin D or calcium intake modified the effect of CaD on HF incidence. We also estimated a potential effect modification by self-reported postmenopausal hormone therapy and randomization to receive intervention in the hormone replacement therapy trial.

Sensitivity analyses were performed by restricting the analyses to only participants who achieved ≥80% adherence rate to study medication (n=23 601, 65.6%). To estimate CaD effects (HRs) independent of censoring information, the inverse probability of censored weights method was implemented.[18,26] The inverse probability of censored weights model was adjusted for some of the factors previously reported as strong predictors of adherence to study medication in the CaD trial—age, education level, use of personal calcium, vitamin D or multivitamin supplements, history of HF risk factors, family history of CVD, and enrollment in other clinical trials.[27]

Results

Baseline sociodemographic, physical/lifestyle, and clinical factors were proportionally distributed between the 2 study arms for the entire CaD cohort (Table I in the Data Supplement) and in the 2 stratified subgroups of participants with and without major precursors of HF (Table II in the Data Supplement). Baseline known CVD risk factors were more

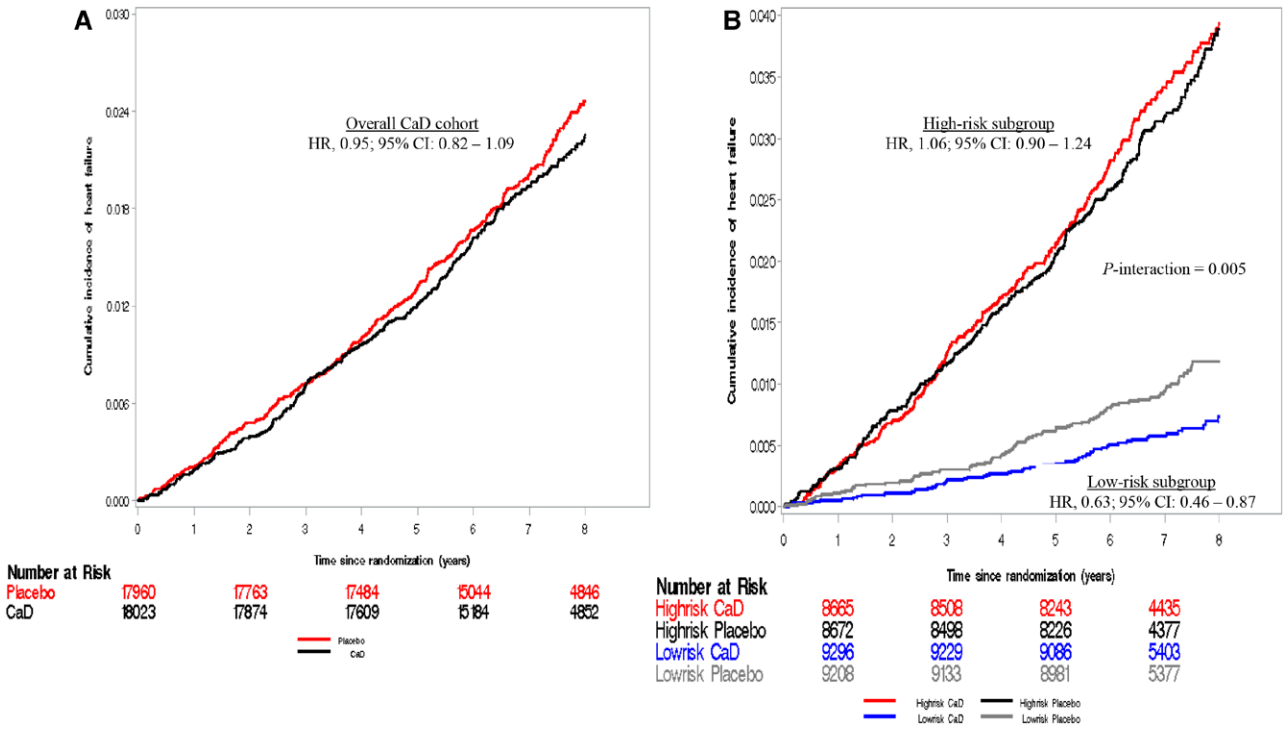

Figure 2. Kaplan–Meier curves comparing the cumulative incidence of heart failure between the vitamin D plus calcium (CaD) and placebo arms during follow-up period in the overall CaD cohort (**A**) and stratified baseline subgroups (**B**). CI indicates confidence interval; and HR, hazard ratio.

prevalent in the high-risk group compared with the low-risk group; however, personal calcium and vitamin D supplements consumption was proportional between these subgroups (Table 1). There were 744 HF cases (29.0/10 000 person-years) during a median follow-up of 7.06 years (interquartile range: 1.61); 363 (28.2/10 000 person-years) of these occurred in the intervention arm versus 381 (29.8/10 000 person-years) in the placebo arm. When stratified by baseline risk status, more HF cases occurred in the high-risk subgroup (587 [302 intervention; 285 control]) than in the low-risk subgroup of women (157 [61 intervention; 96 control]), *P* value of difference <0.001.

Supplementation with CaD was not associated with risk of HF hospitalization in the overall cohort, HR, 0.95 (95% confidence interval [CI], 0.82–1.09); *P*=0.46. The effect of CaD, however, was modified (*P* for interaction=0.005) by baseline risk status of HF (defined by the presence or absence of CHD, other CVD, hypertension, or diabetes mellitus) at baseline. When stratified by baseline risk status, CaD was associated with a statistically significant 37% lower risk of HF, HR, 0.63 (95% CI, 0.46–0.87); *P*=0.005 (number needed-to-treat, 255 [95% CI, 174–723] in the low-risk subgroup), but not in the high-risk subgroup (HR, 1.06 [95% CI, 0.90–1.24]) (Figure 3). Consumption of personal vitamin D (*P* for interaction=0.33) or calcium (*P* for interaction=0.11) supplements did not modify the effect of CaD on HF incidence. The effects of CaD were also not modified by baseline self-reported total (diet plus supplements) consumption of vitamin D (*P* for interaction=0.26) or calcium (*P* for interaction=0.81; Table 2). Neither assignment to receive the intervention (estrogen alone or estrogen plus progestin) nor self-reported use of postmenopausal hormone therapy at baseline modified the effect of CaD on HF incidence (Table 2). Baseline covariates also did not confound these associations in multivariable-adjusted Cox proportional hazard regression models.

The intention-to-treat and per-protocol results were similar (Table 3). In the per-protocol analysis, CaD was not also associated with HF in the overall cohort or in the high-risk subgroup but was associated with a significantly reduced risk of HF in the low-risk subgroup (Table 3). Similar CaD effects were observed among women who did not report taking personal vitamin D and calcium supplements and were also independent of competing events when estimated with the inverse probability of censored weights methods (Table III in the Data Supplement). Regardless of baseline risk status of HF, mean total calcium and vitamin D intake and serum 25(OH)D levels (available for only 2012 women) were relatively lower in the incident HF cases compared with the noncases (Table IV in the Data Supplement).

Discussion

Vitamin D and calcium supplementation was associated with lower risk of HF in a subgroup of women without pre-existing HF precursors at baseline but had no effect in those with these conditions. These findings were independent of baseline total vitamin D and calcium intake and persisted in per-protocol analysis. Results from a recent meta-analysis of 17 trials (n=12 440), including the Medical Research Council Randomised Evaluation of Calcium Or vitamin D (RECORD) trial, showed that vitamin D alone (versus placebo) was associated with a 21% lower risk of cardiac failure (HR, 0.79 [95% CI: 0.60–0.98]; *P*=0.03) among men and women with a mean/median age >60 years old.[28] It is not clear whether the

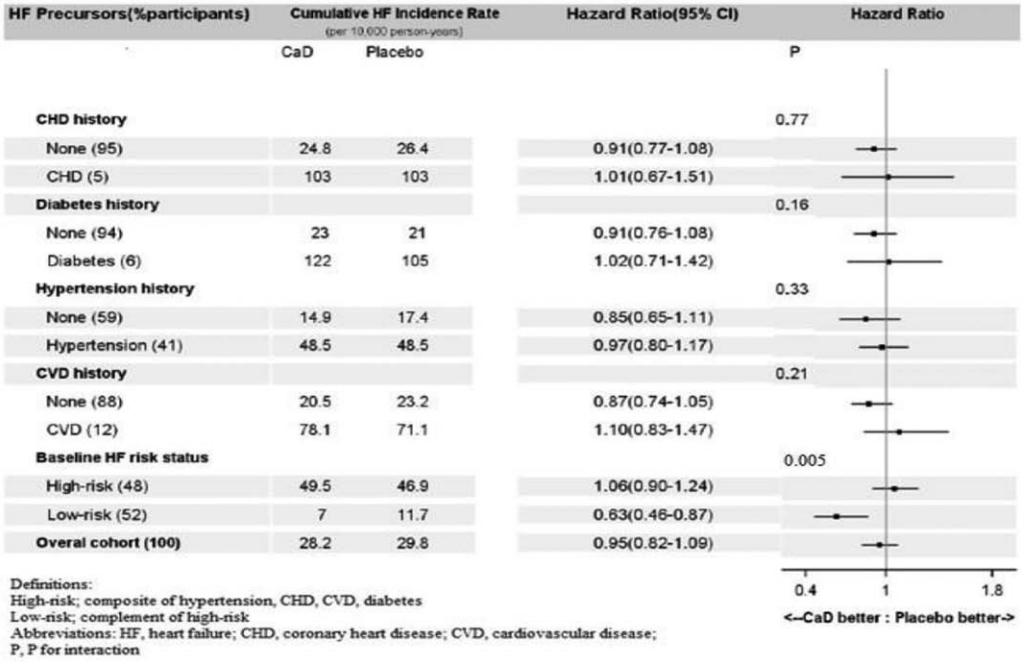

Figure 3. Forest plot of hazard ratios for effect of vitamin D plus calcium (CaD) supplementation on heart failure (HF). CHD indicates coronary heart disease; CI, confidence interval; and CVD, cardiovascular diseases.

observed effect of vitamin D supplementation might have differed between baseline populations stratified by pre-existing HF precursors in the meta-analysis population.

The basis for the differential effects of CaD intervention on HF incidence by baseline risk status is uncertain. Data from animal models suggest vitamin D may regulate cardiac functions, at least partially, via interaction with the vitamin D receptors in cardiaomyocytes.[2,3] Through a receptor-mediated mechanism, $1,25(OH)_2D$ regulates intracellular calcium homeostasis and calcium ion uptake in ventricular cardiac muscle cells to modify cardiac contractility.[29] An intermediate pathophysiological model involving the upregulation of the renin–angiotensin–aldosterone system has been observed in both human and animal studies. Renin–angiotensin–aldosterone system plays a major role in HF pathogenesis by regulating BP, cardiac contractility, electrolyte homeostasis, and eccentric hypertrophy of the myocardium.[30,31] It has been demonstrated that a knockout model of mice without the vitamin D receptors develop high BP, cardiac enlargement, and experience increased activation of the renin–angiotensin–aldosterone system.[32] The activation of renin–angiotensin–aldosterone system by low vitamin

Table 2. Effects of the Intervention Stratified by Baseline Supplements (Calcium and Vitamin D) and Postmenopausal Hormone Therapy Use

	Overall		Low Risk		High Risk		
Baseline Supplement Intake	95% CI	*P* Value	95% CI	*P* Value	95% CI	*P* Value	*P* Interaction
Nonprotocol calcium supplements							0.11
No (n=16 218)	1.07 (0.87–1.31)	0.54	0.73 (0.46–1.16)	0.18	1.19 (0.95–1.50)	0.14	
Yes (n=19 765)	0.85 (0.69–1.03)	0.102	0.55 (0.36–0.87)	0.01	0.94 (0.75–1.18)	0.58	
Nonprotocol vitamin D supplements							0.33
No (n=18 558)	1.01 (0.83–1.23)	0.91	0.74 (0.47–1.14)	0.17	1.12 (0.90–1.39)	0.33	
Yes (n=17 425)	0.88 (0.71–1.08)	0.22	0.53 (0.33–0.85)	0.01	0.99 (0.78–1.26)	0.93	
Hormone therapy trial assignment							0.83
Not randomized or randomized to receive placebo (n=27 929)	0.94 (0.80–1.11)	0.45	0.76 (0.52–1.09)	0.14	0.99 (0.82–1.19)	0.88	
Randomized to receive intervention (n=8054)	0.97 (0.73–1.30)	0.86	0.36 (0.18–0.71)	<0.01	1.32 (0.94–1.84)	0.11	
Self-reported postmenopausal hormone therapy use ever							0.36
No (n=17 252)	0.89 (0.74–1.08)	0.23	0.57 (0.37–0.89)	0.01	1.01 (0.81–1.25)	0.95	
Yes (n=18 731)	1.02 (0.82–1.27)	0.86	0.70 (0.44–1.13)	0.14	1.12 (0.88–1.44)	0.36	

CI indicates confidence interval; HR, hazard ratio; and *P*, interaction, *P* value for interaction with intervention.

Table 3. Results of Intention-to-Treat and Per-Protocol Analysis Estimating the Association Between CaD Supplementation and Heart Failure Incidence—The Vitamin D and Calcium (CaD) Trial of the Women's Health Initiative (WHI) Study, 1995 to 2005

	Intention-to-Treat Analysis (N=35 983)			*Per-Protocol Analysis (N=23 601)		
Study Population	Total	HF Cases, n (Rate/10 000 Person-Years)	HR (95% CI)	Total	HF Cases, n (Rate/10 000 Person-Years)	HR (95% CI)
Overall						
Control	17 960	381 (29.8)	1.00	11 993	190 (21.9)	1.00
CaD	18 023	363 (28.2)	0.95 (0.82–1.09)	11 608	188 (22.4)	1.02 (0.84–1.25)
Low risk						
Control	9227	96 (11.7)	1.00	6320	51 (11.0)	1.00
CaD	9307	61 (7.0)	0.63 (0.46–0.87)	6186	30 (6.6)	0.60 (0.38–0.94)
High risk						
Control	8733	285 (46.9)	1.0	5673	139 (34.4)	1.00
CaD	8716	302 (49.5)	1.06 (0.90–1.24)	5422	158 (40.9)	1.19 (0.95–1.49)

CaD indicates calcium plus vitamin D trial; CI, confidence interval; HF, heart failure; and HR, hazard ratio.

*Analysis is based on data from women with ≥80% adherence to study protocol.

D status has recently been suggested in humans based on observational studies.[33,34] However, a meta-analysis of 10 trials did not show an association between vitamin D (alone or with calcium) supplementation and reduction in either systolic or diastolic BPs.[16]

Hyperparathyroidism has also been postulated as an intermediate process in the vitamin D-HF pathophysiology. Data from patients with end-stage renal disease suggests secondary hyperparathyroidism, and elevated parathyroid hormone levels were associated with low vitamin D levels caused by failure of the kidneys to convert 25(OH)D to the metabolically active form of $1,25(OH)D_2$.[2,8–10] Chronic exposure to parathyroid hormone has been reported to be associated with poor myocardial structure and functioning, as well as elevated BP and accelerated atherosclerosis. It is, therefore, plausible the lower risk of HF observed in the low-risk subgroup is a result of the ability of the vitamin D supplements to prevent or mitigate the process of hyperparathyroidism.

We expected that the high-risk subgroup would benefit more from the intervention, based on evidence that vitamin D deficiency is relatively higher in this subgroup in the general population, but our data did not confirm this hypothesis. One plausible explanation for the lack of an association between CaD and HF incidence in the high-risk subgroup is that HF pathogenesis was already too advanced to be influenced by the CaD supplements. Thus, in this high-risk population, any potential benefit related to HF prevention may have been diminished. Our data suggest that the high-risk group may indeed have poorer health status compared with those free of these comorbidities; baseline factors associated with poor health and risk of HF, such as older age, obesity, and hypercholesterolemia, were predominantly prevalent in this high-risk subgroup (Table 1).

It is also plausible that medical therapy for management of the cardiovascular risk factors in the high-risk group may have modified the effect of CaD intervention on HF. We, therefore, evaluated whether the use of CVD medications such as angiotensin-converting enzymes inhibitors, angiotensin II receptor blockers, statins, β-blockers, or calcium channel blockers were effect modifiers. Individually and collectively (composite of CVD medications), CVD medications did not significantly interact with CaD in relation to HF except angiotensin II receptor blockers (*P* for interaction=0.04; Material in the Data Supplement). This supports the possibility that CaD supplementation may interact with medications used to treat comorbidities, thus making any direct effect of the intervention on HF outcome more difficult to detect. Additional studies on this topic are warranted.

This study contributes to the growing literature on the association between vitamin D and lower incidence of HF. This study is probably the first to demonstrate that CaD supplementation may be associated with lower risk of HF among postmenopausal women without pre-existing hypertension, diabetes mellitus, CHD, or other CVD but not in those with these conditions. The study had adequate statistical power to perform the prespecified subgroup analysis. The randomized trial design nature of the data minimized the effect of potential confounders.

Despite the strengths of this randomized trial, limitations of the study also warrant consideration. First, as a result of combining calcium with vitamin D as the intervention, it is unclear whether the observed associations are because of one or both of these dietary supplements. However, based on the meta-analysis[26] report that suggested an association between vitamin D (alone) supplementation and lower risk of HF and other reports that suggest calcium (alone) may be associated with increased risk of CVD events, it can be inferred that vitamin D was the active agent responsible for the prevention of HF in the Women's Health Initiative trial. Second, the CaD trial was limited to postmenopausal women, 50 to 79 years old, which may preclude generalizability of the findings to men or to younger women. Last, for ethical reasons, participants were allowed to continue consumption of both vitamin D and calcium supplements within the recommended dietary allowance guidelines put forth by the Institute of Medicine. However, consumption of personal vitamin D and calcium supplements did not modify the effect of CaD on HF incidence.

Our findings suggest that a low cost daily supplementation with vitamin D (400 IU) plus calcium (1000 mg) may be an

effective primary prevention strategy for HF in postmenopausal women free of pre-existing cardiovascular conditions. However, it seems to be of little value in preventing HF in the overall trial population and the subgroup of postmenopausal women who already have CVD conditions, including CHD, diabetes mellitus, and hypertension. These findings, if confirmed by other research, may have important public health and clinical implications.

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Disclosures

None.

References

1. Ramani GV, Uber PA, Mehra MR. Chronic heart failure: contemporary diagnosis and management. *Mayo Clin Proc*. 2010;85:180–195. doi: 10.4065/mcp.2009.0494.
2. Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE. Vitamin D and cardiovascular disease. *Pharmacotherapy*. 2009;29:691–708. doi: 10.1592/phco.29.6.691.
3. Witham MD. Vitamin D in chronic heart failure. *Curr Heart Fail Rep*. 2011;8:123–130. doi: 10.1007/s11897-011-0048-6.
4. Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease will it live up to its hype? *J Am Coll Cardiol*. 2011;58:1547–1556. doi: 10.1016/j.jacc.2011.07.008.
5. Achinger SG, Ayus JC. The role of vitamin D in left ventricular hypertrophy and cardiac function. *Kidney Int Suppl*. 2005:S37–S42.
6. Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, Terasawa T, Trikalinos TA. Vitamin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess (Full Rep)*. 2009;183:1–420.
7. Drüeke TB, McCarron DA. Paricalcitol as compared with calcitriol in patients undergoing hemodialysis. *N Engl J Med*. 2003;349:496–499. doi: 10.1056/NEJMe038104.
8. Rostand SG, Drüeke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int*. 1999;56:383–392. doi: 10.1046/j.1523-1755.1999.00575.x.
9. Shoji T, Shinohara K, Kimoto E, Emoto M, Tahara H, Koyama H, Inaba M, Fukumoto S, Ishimura E, Miki T, Tabata T, Nishizawa Y. Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant*. 2004;19:179–184.
10. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernán MA, Camargo CA Jr, Thadhani R. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol*. 2005;16:1115–1125. doi: 10.1681/ASN.2004070573.
11. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691. doi: 10.1136/bmj.c3691.
12. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med*.2010;152:315–323. doi: 10.7326/0003-4819-152-5-201003020-00010.
13. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events. *Circulation*. 2007;115:846–854. doi: 10.1161/CIRCULATIONAHA.106.673491.
14. Kannel WB. Incidence and epidemiology of heart failure. *Heart Fail Rev*. 2000;5:167–173. doi: 10.1023/A:1009884820941.
15. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Krstic G, Wetterslev J, Gluud C. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev*. 2011: CD007470.
16. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM. Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med*. 2010;152:307–314. doi: 10.7326/0003-4819-152-5-201003020-00009.
17. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med*. 2010;51:228–233. doi: 10.1016/j.ypmed.2010.06.013.
18. Xu R, O'Quigley J. Estimating average regression effect under non-proportional hazards. *Biostatistics*. 2000;1:423–439. doi: 10.1093/biostatistics/1.4.423.
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(9 suppl):S98–S106.
20. Anderson GL, Manson J, 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(9 suppl):S5–S17.
21. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes FaNB. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC, 1999.
22. Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, Gaziano JM, Frishman WH, Curb JD. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol*. 2004;160:1152–1158. doi: 10.1093/aje/.
23. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW; American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009;53:e1–e90. doi: 10.1016/j.jacc.2008.11.013.
24. Hintze J. *NCSS 9*. NCSS, LLC. Kaysville, UT. 2013. www.ncss.com. Accessed January 23, 2014.
25. Weiliang Q, Jorge C, Ross L, Bernard R, Jing M. *powerSurvEpi (v 0.06): Power and Sample Size Calculation for Survival Analysis of Epidemiological Studies*. Boston, MA. 2012. http://cran.r-project.org/web/packages/powerSurvEpi/. Accessed May 27, 2014.
26. Heinze MKaG. *PSHREG: A SAS Macro for Proportional and Nonproportional Subdistribution Hazards Regression With Competing Risk Data*. Vienna: Medical University of Vienna. 2012.
27. Brunner R, Dunbar-Jacob J, Leboff MS, Granek I, Bowen D, Snetselaar LG, Shumaker SA, Ockene J, Rosal M, Wactawski-Wende J, Cauley J, Cochrane B, Tinker L, Jackson R, Wang CY, Wu L. Predictors of adherence in the Women's Health Initiative Calcium and Vitamin D Trial. *Behav Med*. 2009;34:145–155. doi: 10.3200/BMED.34.4.145-155.
28. Ford JA, MacLennan GS, Avenell A, Bolland M, Grey A, Witham M; RECORD Trial Group. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. *Am J Clin Nutr*. 2014;100:746–755. doi: 10.3945/ajcn.113.082602.
29. Walters MR, Ilenchuk TT, Claycomb WC. 1,25-Dihydroxyvitamin D3 stimulates 45Ca2+ uptake by cultured adult rat ventricular cardiac muscle cells. *J Biol Chem*. 1987;262:2536–2541.
30. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart. A new era in the treatment of heart failure. *Circulation*. 1996;94:2285–2296.
31. Xiang W1, Kong J, Chen S, Cao LP, Qiao G, Zheng W, Liu W, Li X, Gardner DG, Li YC. Cardiac hypertrophy in vitamin D receptor knockout

mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Physiol Endocrinol Metab*. 2005; 288:E125–132.
32. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest*. 2002;110:229–238. doi: 10.1172/JCI15219.
33. Forman JP, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension*. 2010;55:1283–1288. doi: 10.1161/HYPERTENSIONAHA.109.148619.
34. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, März W. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Clin Chim Acta*. 2010;411:1354–1360. doi: 10.1016/j.cca.2010.05.037.

CLINICAL PERSPECTIVE

We analyzed data from the Women's Health Initiative's Calcium and Vitamin D trial, a large-scale randomized controlled trial of supplementation with 1000 mg/d calcium and 400 IU/d of vitamin D among postmenopausal women, to test whether vitamin D plus calcium supplementation is associated with lower rates of heart failure in postmenopausal women and whether the effects differ between those at high versus low risk for heart failure. Our findings suggest that a low cost daily supplementation with vitamin D plus calcium may reduce the incidence of heart failure among those without pre-existing major risk factors for heart failure (coronary heart disease, diabetes mellitus, or hypertension) but may be of little value among those who already have one or more of these heart failure precursors. There is currently strong interest in vitamin D deficiency as a heart failure risk factor and vitamin D supplementation as preventive therapy, but outcomes data from large randomized controlled trials are lacking. This study adds importantly to this sparse database. These findings, if confirmed by other research, may have important public health and clinical implications.