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Review Article

VITAMIN D, CALCIUM, AND CARDIOVASCULAR MORTALITY: A PERSPECTIVE FROM A PLENARY LECTURE GIVEN AT THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

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ABSTRACT

Objective: To examine data showing associations between serum 25-hydroxyvitamin D levels and calcium intake and cardiovascular mortality.

Methods: The articles reviewed include those published from 1992-2011 derived from search engines (PubMed, Scopus, Medscape) using the following search terms: vitamin D, calcium, cardiovascular events, cardiovascular mortality, all-cause mortality, vascular calcification, chronic kidney disease, renal stones, and hypercalciuria. Because these articles were not weighted (graded) on the level of evidence, this review reflects my own perspective on the data and how they should be applied to clinical management.

Results: For skeletal health, vitamin D and calcium are both needed to ensure proper skeletal growth (modeling) and repair (remodeling). Nutritional deficiencies of either vitamin D or calcium may lead to a spectrum of metabolic bone disorders. Excessive consumption of either nutrient has been linked to a variety of medical disorders, such as hypercalcemia or renal stones. There have also been associations between vitamin D or calcium intake and cardiovascular disease. However, neither of these associations have established evidence nor known causality for increasing cardiovascular risk or all-cause mortality in patients with creatinine clearances greater than 60 mL/min. In patients with more severe chronic kidney disease, stronger data link excess calcium (or phosphorus) intake and increase in vascular calcification, but not mortality. The safe upper limit for vitamin D intake is at least 4000 IU daily and probably 10 000 IU daily; for calcium, the safe upper limit is between 2000 to 3000 mg daily.

Conclusions: While no solid scientific evidence validates that serum vitamin D levels between 15 and 70 ng/mL are associated with increased cardiovascular disease risk, stronger but inconsistent evidence shows an association between calcium supplementation greater than 500 mg daily and an increase in cardiovascular disease risk. Most professional societies suggest that replacement levels of these nutrients be personalized with the goal of reaching a 25-hydroxyvitamin D concentration between 30 and 50 ng/mL and a calcium intake of 1200 mg daily. **(Endocr Pract. 2011;17:pp)**

Abbreviations:
25(OH)D = 25-hydroxyvitamin D; **DRI** = dietary reference intake; **IOM** = Institute of Medicine; **RDA** = recommended dietary allowance

INTRODUCTION

In the past few years, there has been a proliferation of publications on the effects of vitamin D and/or calcium on skeletal and nonskeletal health (1-2). While many of these articles have dealt with the nutritional requirements of vitamin D and calcium to define public policy (recommended dietary allowance [RDA] or dietary reference intake [DRI]) and population intake recommendations, many have examined the benefit–risk relationships of these 2 nutrients in altering the risk of cardiovascular disease

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(3-11). In doing so, many—and often divergent—views have been expressed concerning the safety of vitamin D and/or calcium (8-10).

This review will try to put these issues into a perspective based on the best available science published to date, as well as the author's perspective presented at an invited plenary lecture of the 2011 Annual Meeting and Clinical Congress of the American Association of Clinical Endocrinologists. This manuscript represents a systematic review of data from the search engines of PubMed, Medscape, and Scopus. The search words used were "vitamin D," "calcium," "cardiovascular events," "cardiovascular mortality," "all-cause mortality," "vascular calcification," "chronic kidney disease," "renal stones," and "hypercalciuria."

Most of the evidence is derived from case-control and cohort population studies. Minimal data are derived from prospective, double-blind, placebo-controlled studies. The evidence is, therefore, limited by the nature of the study designs.

One question that must be examined: Are serum levels of 25-hydroxyvitamin D (25[OH]D) associated with an increase in cardiovascular mortality?

In humans, vitamin D is predominately derived from sunlight (ultraviolet) exposure (12-14). In periods of evolution, when humans wore few clothes or sunblock, sunshine was the dominant, if not the only, natural source of vitamin D. By changing skin 7-dehydrocholesterol to cholecalciferol, ultraviolet light is responsible for regulating serum levels of vitamin D. In this regard, even with the most intense and prolonged sunlight exposure, the maximum level of vitamin D that can be achieved is approximately 60 ng/mL. Hence, an internal homeostatic regulatory mechanism within the skin prevents serum vitamin D levels from rising above this value, which suggests that in the course of human evolution, there may have been reasons related to survival to explain why levels do not rise above 60 ng/mL (15-17).

The circulating vitamin D can enter the liver through the portal circulation to be taken up by hepatocytes, and the D is hydroxylated in the 25 position of the steroid backbone ring to produce 25(OH)D, the best measurement in clinical medicine of the adequacy of the nutritional replacement of vitamin D (18-20). Circulating D has its own direct effects on multiple tissues interacting with the vitamin D receptor alleles that are ubiquitous throughout human tissues. Here, 25(OH)D can increase the gastrointestinal absorption of calcium, influence mineralization of bone, and have effects on muscle cells—effects that are independent of its conversion in renal cells and macrophage-derived cells into 1,25-dihydroxyvitamin D (20-21). Circulating 25(OH)D also has an autocrine/paracrine pathway that is not as well understood as its endocrine function, but nevertheless, is also a very vital metabolic pathway for disposing 25(OH)D from the circulation. These latter 2 functions are related to the intracellular production of 1,25-dihydroxyvitamin D in many other cells that may regulate immune function and modulate cell survival in cancer cells (leukemia and breast and prostate cancer) within the cell in which 1,25-dihdroxyvitamin D is produced (autocrine) or in adjacent cells (paracrine) (20-22). The evidence supporting these autocrine/paracrine pathways effects of 1,25-dihydroxyvitamin D is stronger than the evidence for 25(OH)D per se on prevention of cancer (23). The remainder of the circulating 25(OH)D that is not stored in adipocytes or used intracellularly by way of 1,25-dihydroxyvitamin D pathways, is catabolized by 24-hydroxylase (20-22).

While there has been a great deal of recent controversy on the recommended intake of vitamin D, and it is not the purpose of this article to dive into this debate, a few points should be made concerning the recent publication of the Institute of Medicine (IOM) and how it might fit into the cardiovascular mortality story (1). The IOM recommends that persons aged 1 to 70 years receive 600 IU daily of vitamin D and persons older than 70 years receive 800 IU daily. While clinicians recognize that for individual patient management, the IOM vitamin D recommendations will fail to achieve a serum 25(OH)D level even above 20 ng/mL (the level suggested by the IOM), the good news is that the IOM recommendations do raise the RDA above the former RDA of 400 IU daily (24). In addition, to put the IOM work into perspective, this body of scientists was charged with making broad public policy (population) recommendations never intended to be applied to individual patient management. Individual patients often have other comorbid conditions (eg, gastrointestinal diseases, antiseizure medications) that increase their need for vitamin D, even to 5000 to 10 000 IU daily, to maintain their 25(OH)D level above 40 ng/mL, the level recommended by the American Association of Clinical Endocrinologists and other scientific professional groups (25-26). In fact, the IOM itself said that the upper "safety" intake limit of vitamin D was probably 4000 IU daily and could be as high as 10 000 IU daily. In addition, the large prospective placebo-controlled trial (Vitamin D and Omega-3 Trial [VITAL]) designed to examine the effect of vitamin D on the incidence of cancer and cardiovascular disease is using 2000 IU daily of vitamin D (27-28).

VITAMIN D AND CARDIOVASCULAR MORTALITY

The data on vitamin D and cardiovascular disease from a meta-analysis and a systematic review have been recently published (29-30) (Fig. 1). In addition, data have been published from additional systematic reviews: the Women's Health Initiative, as well as the National Health and Examination Survey III (31-32). The conclusions from these analyses are that within the ranges of serum 25(OH)D measured, there is no solid evidence that vitamin D directly causes an increase in cardiovascular mortality. Although

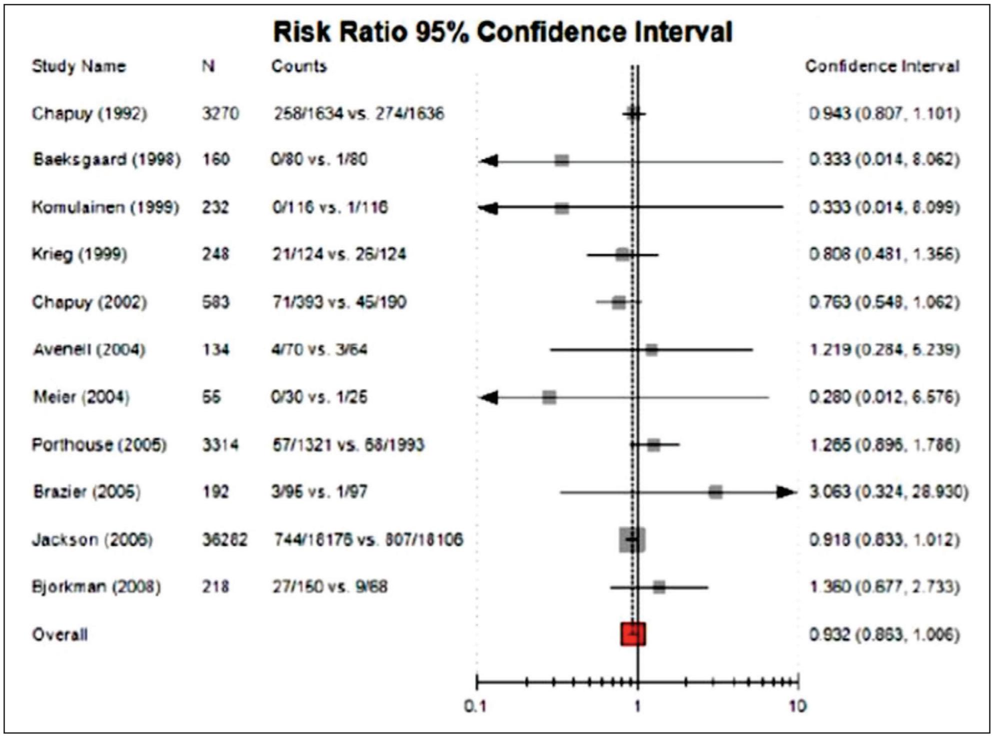

Fig. 1. The systematic review of the association of serum 25-hydroxyvitamin D and mortality, showing the point-estimate to be less than 1.0 in favor of no negative effect (29-30).

findings from the National Health and Examination Survey III suggest that there may be a U-shaped curve where all-cause mortality is higher at lower or higher levels of serum 25(OH)D, the 95% confidence intervals overlap so widely that there is uncertainty about the importance of these findings. Even the IOM report states that the systematic survey of Cheung et al showed that with serum 25(OH)D concentrations less than 17 ng/mL and greater than 32 ng/mL there was no increased risk for cardiovascular mortality: "The RR was 0.97 (95 percent CI 0.92, 1.02), with no evidence for between-study heterogeneity (P=0.39, $I^2 = 0$ percent)" (30).

The phrase "vitamin D toxicity" is a misnomer, because there is no evidence that vitamin D has any direct tissue toxicity. So-called vitamin D toxicity is expressed through hypercalcemia due to an increase in gastrointestinal calcium absorption that exceeds the kidney's capacity to excrete the extra calcium load or the bone's capacity to deposit calcium via mineralization (33-34). These 2 tissues (kidney and bone) have an enormous ability to prevent hypercalcemia unless their ability to do so is compromised. For the kidney, this refers to function generally below a creatinine clearance of 30 mL/min where the clearance of calcium may not increase as the filtered load increases. For bone, this refers to adynamic bone disease where the very low bone turnover may mitigate the bone uptake of calcium (35-38). In the absence of compromised renal or bone function, the serum 25(OH)D level in most datasets must be greater than 150 ng/mL to induce hypercalcemia (39-40). Since it may take an excess of 10 000 IU daily of vitamin D given for prolonged periods to induce a rise in the serum 25(OH)D concentration greater than 150 ng/mL, there is a wide safety margin in vitamin D administration. Likewise, hypercalciuria does not seem to appear with vitamin D replacement less than 10 000 IU daily (41-42). In non-calcium renal stone formers to begin with, there may be no increased risk for calcium stone formation with replacement of vitamin D less than 10 000 IU daily (26,42). The issue may differ in persons who have previously formed calcium renal stones in whom the exacerbation of hypercalciuria may increase the risk of calcium renal stone formation (43-44). The management suggestions for vitamin D pertain only to cholecalciferol and not to vitamin D metabolites (calcitriol, paracalcitriol) whose use is for different medical circumstances such as hypoparathyroidism, secondary hyperparathyroidism in chronic kidney disease, or specific oncology indications (45-49).

Hence, the American Association of Clinical Endocrinologists guidelines for vitamin D are clinically correct:

- To use 30 to 50 ng/mL for most patients as an optimal and safe range
- For many patients, 1000 to 2000 IU of vitamin D daily is required to maintain a 25(OH)D concentration at 30 ng/mL or above

- The common use of vitamin D in the range of 1000 to 2000 IU daily would be reasonable

For now, it is important to use the recommendations in conjunction with clinical judgment to determine the proper calcium and vitamin D requirements for any given patient.

Endocrinologists, like many specialists, see patients who often have comorbid diseases that have competing effects on different areas of human body metabolism. More complex therapy must be managed on an individual case-by-case basis and cannot be set into algorithms that might be proper strategies for public policy decisions.

CALCIUM AND CARDIOVASCULAR MORTALITY

The IOM recommends the following for public policy (RDA/DRI) calcium intake (1): (a) 1200 mg daily for women aged 51 years and older and 1000 mg daily for men aged 50 to 70 years; (b) a "safe" upper limit of calcium intake of 2000 to 3000 mg daily. The IOM emphasizes that this total intake should include the consistent daily food consumption and added "supplements" to reach the RDA/DRI amount. To obtain this balance between nutrition and supplement, it is, therefore, incumbent that physicians complete a nutritional history on the patient. In addition, the nutritional intake used to calculate the prescribed daily calcium intake should be representative of typical intake. In this way, the physician becomes a nutritionist. This strategy may avoid the recommendations to "take 1000 mg daily" of supplements and ignore the nutritional contribution to total calcium intake. If there is any concrete evidence that calcium supplementation contributes to an increased risk for cardiovascular mortality, it is in the arena of excess calcium supplementation.

In this regard, the history behind the theme that calcium may be harmful to vascular tissue is derived from theories that excess calcium might act passively, complexing with phosphorus to be deposited in or on the endothelial surface of vessels and inducing vascular calcification. The evidence for vascular calcification from exogenous calcium sources is best seen in the renal world of patients with chronic kidney disease. Evidence has shown that in the populations with stage 3 to 5 chronic kidney disease (glomerular filtration rate <60 mL/min to <15 mL/min), and especially stage 5 (<15 mL/min on dialysis), calcium given as a calcium-phosphate binder to control hyperphosphatemia leads to an increase in vascular calcification (50-52). Data on an increase in mortality associated with this are, however, lacking. Although interventions to reduce the serum calcium and/or phosphorus in the setting of chronic kidney disease have also been associated with a reduction in vascular calcification, these interventions have not reduced cardiovascular mortality (53-55). Nevertheless, research is very abundant in this area in the chronic kidney disease population where the most common cause of mortality is cardiovascular disease, and direct causality might be established among chronic kidney disease, calcium and phosphorus intake, and mortality.

Associations have been reported between specific clinical disorders of calcium metabolism and an increased risk for cardiovascular mortality. Data have been published that suggest an association between hypercalcemia and increased mortality in healthy men and in patients with severe primary hyperparathyroidism (56-57). In the IOM report of data derived from their systematic analysis, the authors concluded that, "overall the majority of analyses showed no significant association between calcium intake and CV events" (1). However, the IOM found 1 cohort study (rated B for methodologic and reporting quality) that reported no significant associations between calcium intake and all-cause mortality in men or women aged 40 to 65 years. Only the Iowa Women's Health Study of postmenopausal women showed a significant increase in cardiovascular death in those women with a mean calcium intake lower than 696 mg daily (58-59). The IOM reported that there "are no randomized controlled trials of calcium intake evaluated all-cause mortality." The IOM may have undervalued recent systematic reviews, especially individual patient meta-analyses (7,9), which may have clinical and statistical advantages over trial-level meta-analyses (60-62).

New Zealand's original study was an individual randomized controlled trial of 1471 healthy postmenopausal women, of whom one-half received 1 g of calcium as the citrate and one-half received placebo over a period of 5 years (6,10). The events were adjusted for baseline levels of vitamin D, body mass index, blood pressure, and fasting serum lipid levels. Persons with baseline vitamin D levels less than 10 ng/mL were excluded, in part because of the National Health and Examination Survey III data suggesting a higher cardiovascular mortality in this population with lower vitamin D levels. The results of the individual trial are shown in Table 1 (6,10). Findings from the primary and secondary analyses suggested a higher risk of the listed cardiovascular events in the calcium-supplemented group than in the placebo group. The Kaplan-Meier curves suggested that calcium supplementation had a greater negative effect on cardiovascular outcome the longer the duration of follow-up (Fig. 2) (6).

These observations led to a large meta-analysis of effect of calcium supplementation on risk of myocardial infarction and cardiovascular events (8). This analysis included postmenopausal women in trials that had a basic consistent inclusion for summary statistics: randomized, placebo-controlled, calcium supplement of 500 or more mg daily, more than 100 patients, mean age older than 40 years, and trial duration longer than 1 year. In addition, trials were excluded if the patients received only calcium or only vitamin D—they had to have received both calcium and vitamin D such that the placebo group had to also have

Table 1
Individual Patient (Secondary) Analysis From the New Zealand Prospective Randomized Study of the Effects of Calcium Supplementation on Cardiovascular Outcomes (6,10)[a]

Outcomes	Calcium, No. patients (No. events)	Placebo No. patients (No. events)	Relative risk (95% confidence interval)	*P* value
Myocardial infarction	143 (164)	111 (125)	1.32 (1.02-1.71)	.032
Stroke	167 (190)	143 (156)	1.24 (0.99-1.56)	.07
Myocardial infarction, stroke, or sudden death	293 (361)	254 (287)	1.27 (1.07-1.51)	.006

[a] Kaplan-Meier survival plot for myocardial infarction showed the groups progressively diverged after about 2 years.

received vitamin D. Finally, trials were excluded if patients had received calcium only as dairy or as a complex nutritional supplement (eg, multivitamin). The breakdown of the nature of this meta-analysis is shown in Table 2 (8).

The analysis of all cardiovascular outcomes is shown in Figure 3. For all outcomes, the relative risk favored placebo with confidence intervals that did cross 1.0. However, the relative risk of myocardial infarction favored placebo

Table 2
Details of the Trials Included in the Meta-Analysis Examining the Effect of Vitamin D, Calcium, or Vitamin D and Calcium on Cardiovascular Outcomes[a]

Study	No. of patients	Duration, y	Primary endpoint
Studies with individual participant cardiovascular outcome data			
Reid et al	135	4	Bone mineral density
Baron et al	930	4	Colorectal adenoma
Grant et al	5292	4	Low-trauma fracture
Reid et al	1471	5	Clinical fracture
Reid et al	323	2	Spine bone mineral density
Subtotal	**8151**	**4.1**	
Studies with trial-level cardiovascular outcome data			
Dawson-Hughes et al	361	2	Spine bone mineral density
Riggs et al	236	4	Bone mineral density
Bonithon-Kopp et al	416	3	Colorectal adenoma
Prince et al	1460	5	Osteoporotic fracture
Bonnick et al	563	2	Spine bone mineral density
Lappe	734	4	Fracture incidence
Subtotal	**3770**	**3.8**	**93% of possible data**
Total	**11 921**	**4.0**	
Studies without cardiovascular outcome data			
Smith et al, Elder et al, Recker et al, Peacock et al			
Subtotal	**922**		

[a] Adapted with permission from BMJ Publishing Group Limited (Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691, Copyright 2010) (8).

with confidence intervals that did not cross 1.0 (Fig. 4). When looking at the Kaplan-Meier curves in this meta-analysis, the data look similar to those of the initial single randomized trial—a greater risk over time in the calcium-supplemented group than in the placebo group (Fig. 5). The authors concluded that "calcium supplements increase the risk of CV events" and that "these results are robust because they are based on pre-specified end-points of randomized, placebo-controlled trials."

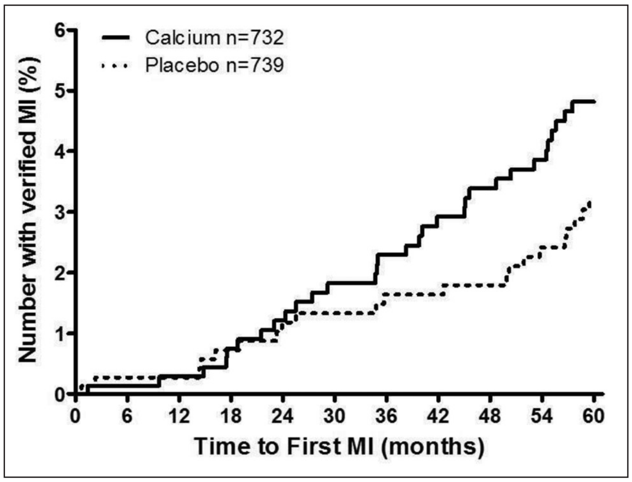

Fig. 2. Effect of calcium on myocardial infarction (MI). Data show the time to event analysis of the effect of calcium supplementation on myocardial infarction from the individual New Zealand study. Reprinted with permission from BMJ Publishing Group Limited (Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336:262-266, Copyright 2008) (6).

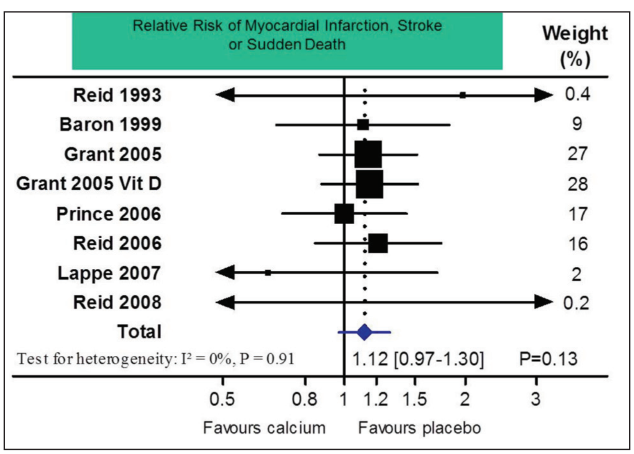

Fig. 3. The relative risk (point-estimates and 95% confidence intervals) of myocardial infarction, stroke, or sudden death from the meta-analysis of Bolland et al. Reprinted with permission from BMJ Publishing Group Limited (Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691, Copyright 2010) (8).

In a counterpoint to the just-cited meta-analysis, the group from Western Australia completed a prospective, placebo-controlled randomized study of 1460 women (age 75 years) randomly assigned to $CaCO^3$ (1200 mg daily) or placebo (7,9). The study was a 5-year follow-up with a prespecified endpoint, and the data were adjusted for 13 known separate risk factors for cardiovascular disease. In

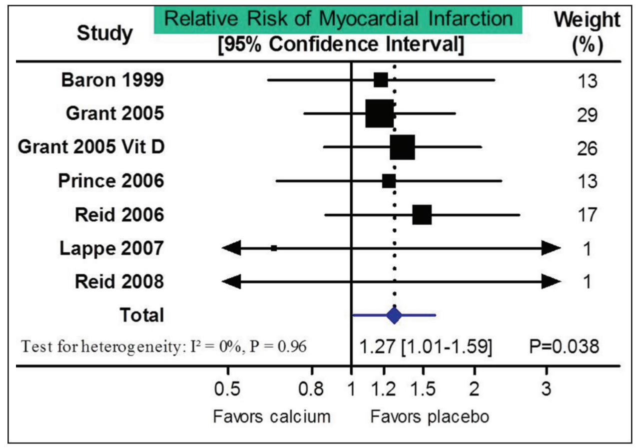

Fig. 4. The point-estimates and 95% confidence intervals describing the relative risks of myocardial infarction from the meta-analysis examining the effects of calcium supplementation vs placebo on myocardial infarction. Reprinted with permission from BMJ Publishing Group Limited (Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691, Copyright 2010) (8).

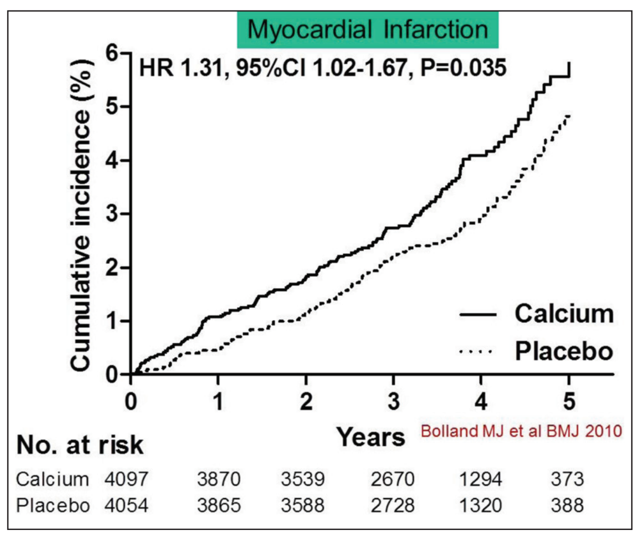

Fig. 5. The time to event analysis of the effect of calcium supplementation vs placebo on myocardial infarction from the meta-analysis. CI, confidence interval; HR, hazard ratio. Reprinted with permission from BMJ Publishing Group Limited (Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691, Copyright 2010) (8).

this study, there was no evidence that calcium supplementation increased the risk for cardiovascular disease. These authors believe that the New Zealand analysis included a substantial adjudication bias in that the myocardial infarctions were either self-reported or adjudicated, and they point out that when the Bolland et al individual trial data are reanalyzed, including only the adjudicated myocardial infarctions, the negative effect of calcium supplementation is less robust (Dr. Richard Prince, written communication, August 22, 2011). In addition, a forest plot (Fig. 6) shows the effect of using adjudicated data as opposed to the patient self-report data on risks of myocardial infarction from the studies reported by Bolland et al in their meta-analysis. The new data render the effect not significant (Dr. Richard Prince, written communication, August 22, 2011). These 2 opposing views are now hotly debated (63-65).

In addition, in a systematic review of literature published from 1996 to 2009 examining the effects of vitamin D and/or calcium on cardiovascular mortality from 17 randomized or cohort trials, there were no differences between calcium-supplemented and noncalcium-supplemented recipients (5). There is some concern over whether this latter study was underpowered to make the conclusions from the groups that only received calcium not combined with vitamin D.

The American Association of Clinical Endocrinologists osteoporosis guidelines suggest that the total calcium intake be 1200 mg daily and that this sum is achieved with diet and, when necessary, calcium supplementation. These guidelines have no comment on any association between calcium supplementation and cardiovascular risk.

CONCLUSION

Vitamin D measurements are important in skeletal health assessments. Persons may vary (because "it's biology") regarding the daily intake needed to achieve a 25(OH)D concentration of 40 ng/mL. No scientific data validate that a 25(OH)D concentration between 15 and 70 ng/mL has any increase in causality for cardiovascular mortality. Levels above the upper limit have not been adequately studied to make any conclusive statements. Scientific data suggest, but are inconsistent, that a specific calcium intake by supplements or serum calcium level has causality for an increase in cardiovascular mortality in the postmenopausal population. Public policy recommendations (RDA or DRI) differ from individual patient management recommendations, which must be accomplished on an individual patient level.

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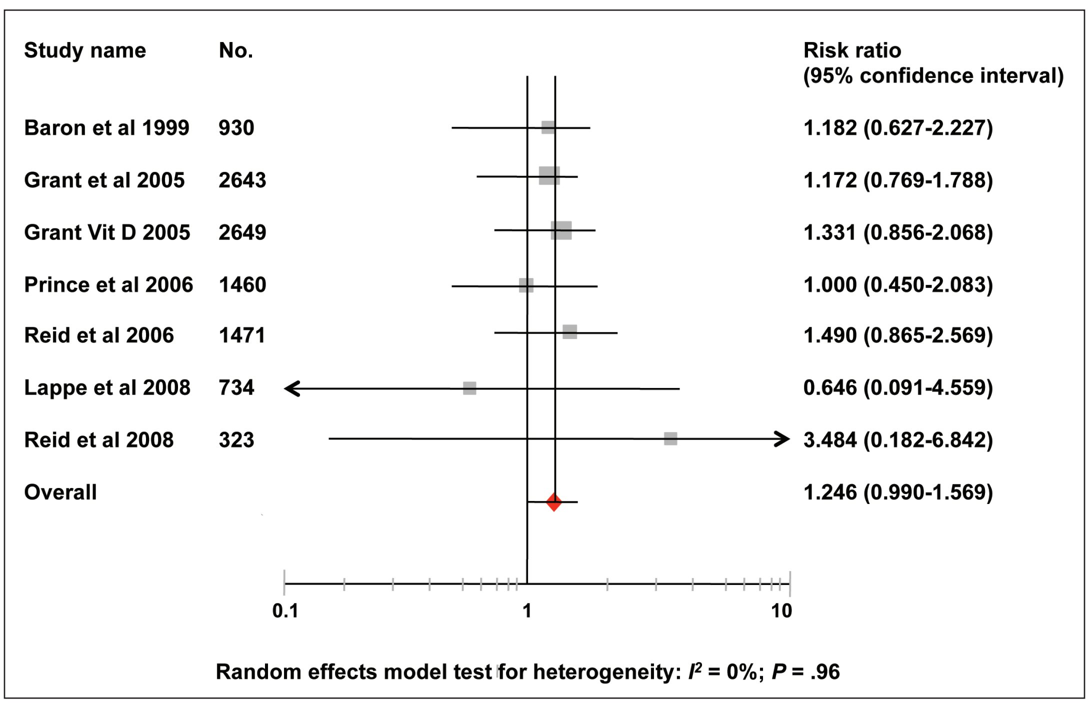

Fig. 6. The effect of using adjudicated data as opposed to the patient self-report data on risks of myocardial infarction with calcium supplementation from the studies reported by Bolland et al in their meta-analysis (8); the new data render the effect not significant (Dr. Richard Prince, written communication, August 21, 2011).

DISCLOSURE

The author has no multiplicity of interest to disclose.

REFERENCES

1. **Committee to Review Dietary Reference Intakes for Vitamin D and Calcium**. Dietary Reference Intakes for Calcium and Vitamin D. Washington DC: Institute of Medicine of the National Academies; 2011. http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx. Accessed August 29, 2011.
2. **Chung M, Balk EM, Brendel M, et al; Tufts Evidence-Based Practice Center**. Vitamin D and Calcium: A Systematic Review of Health Outcomes. Evidence Report/Technology Assessment. Number 183. Rockville, MD: Agency for Healthcare Research and Quality, 2009.
3. **Wang TJ, Pencina MJ, Booth Dl, et al**. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117:503-511.
4. **Giovannucci E, Liu Y, Hollis BW, Rimm EB**. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*. 2008;168:1174-1180.
5. **Wang L, Manson JE, Sing Y, Sesso HD**. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med*. 2010;152:315-323.
6. **Bolland MJ, Barber PA, Doughty RN, et al**. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336:262-266.
7. **Prince RL, Devine A, Dhaliwal SS, Dick IM**. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med*. 2006;166:869-875.
8. **Bolland MJ, Avenell A, Baron JA, et al**. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691.
9. **Lewis JR, Calver J, Zhu K, Flicker L, Prince RL**. 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. *J Bone Miner Res*. 2011;26:35-41.
10. **Reid IR, Mason B, Horne A, et al**. Randomized controlled trial of calcium in healthy older women. *Am J Med*. 2006;119:777-85.
11. **Shapses SA, Manson JE**. Vitamin D and prevention of cardiovascular disease and diabetes: why the evidence falls short. *JAMA*. 2011;305:2565-2567.
12. **Holick MF**. Vitamin D requirements for humans of all ages: new increased requirements for women and men 50 years and older. *Osteoporos Int*. 1998;8(Suppl 2):S24-S29.
13. **Holick MF**. Vitamin D deficiency. *N Engl J Med*. 2007;357:266-281.
14. **Rosen C**. Clinical practice. Vitamin D insufficiency. *N Engl J Med*. 2011;364:248-254.
15. **Binkley N, Nonotny R, Krueger D, et al**. Low vitamin D status despite abundant sunlight exposure. *J Clin Endocrinol Metab*. 2007;92:2130-2135.
16. **Binkley N, Krueger D, Lensmeyer G**. 25-Hydroxyvitamin D measurement 2009: a review for clinicians. *J Clin Densitom*. 2009;12:417-427.
17. **Thacher TD, Clarke BL**. Vitamin D insufficiency. *Mayo Clin Proc*. 2011;86:50-60.
18. **Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA**. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. *Am J Clin Nutr*. 2008;88:1519-1527.
19. **Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R**. Estimates of optimal vitamin D status. *Osteoporos Int*. 2005;16:713-716.
20. **DeLuca HF**. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr*. 2004;80(Suppl 6):1689S-1696S.
21. **Heaney RP, Horst RL, Cullen DM, Armas LA**. Vitamin D3 distribution and status in the body. *J Am Coll Nutr*. 2009;28:252-256.
22. **Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW**. 25-hydroxylation of vitamin D3: relation of circulating vitamin D3 under various input conditions. *Am J Clin Nutr*. 2008;87:1738-1742.
23. **Manson JE, Mayne ST, Clinton SK**. Vitamin D and prevention of cancer--ready for prime time? *N Engl J Med*. 2011;364:1385-1387.
24. **Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board, Institute of Medicine**. DRI Dietary Reference Intakes for Calcium Phosphorus, Magnesium, Vitamin D and Fluoride. Washington, DC: The National Academies Press, 1997.
25. **Watts NB, Bilezikian JP, Camacho PM, et al; AACE Osteoporosis Task Force**. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract*. 2010;16(Suppl 3):1-37.
26. **Holick MF, Binkley NC, Bischoff-Ferrari HA, et al**. Evaluation, treatment, and prevention of vitamin d deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-1930.
27. **Manson JE, Buring JE**. Vitamin D and Omega-3 Trial (VITAL). In: ClinicalTrials.gov (Internet). Bethesda, MD: National Library of Medicine (US). 2010. Cited Dec 21. Available at: http://clinicaltrials.gov/show/NCT01169259. NLM Identifier: NCT01169259.
28. **Manson JE**. Vitamin D and the heart: why we need large-scale clinical trials. Cleve Clin J Med. 2011;77:903-910.
29. **Autier P, Gandini S**. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Int Med*. 2007;167:1730-1737.
30. **Chung M, Balk EM, Brendel M, et al**. Vitamin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess (Full Rep)*. 2009:1-420.
31. **LaCroix AZ, Kotchen J, Anderson G, et al**. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2009;64:559-567.
32. **Melamed ML, Michos ED, Post W, Astor B**. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med*. 2008;168:1629-1637.
33. **Heaney RP**. 25-Hydroxyvitamin D and calcium absorption. *Am J Clin Nutr*. 2011;93:220-221.
34. **Heaney RP, Vieth R, Hollis BW**. Vitamin D efficacy and safety. *Arch Intern Med*. 2011;171:266.
35. **Gal-Moscovici A, Sprague SM**. Use of vitamin D in chronic kidney disease patients. Kidney Int. 2010;78:146-151.
36. **Khosla N, Sprague SM**. When is vitamin D contraindicated in dialysis patients? *Semin Dial*. 2009;22:249-251.
37. **Andress DL**. Adynamic bone in patients with chronic kidney disease. *Kidney Int*. 2008;73:1345-1354.

38. **Andress DL**. Vitamin D treatment in chronic kidney disease. *Semin Dial*. 2005;18:315-321.
39. **Vieth R**. Vitamin D toxicity, policy, and science. *J Bone Miner Res*. 2007;22(Suppl 2):V64-V68.
40. **Hathcock JN, Shao A, Vieth R, Heaney R**. Risk assessment for vitamin D. *Am J Clin Nutr*. 2007;85:6-18.
41. **Binkley N, Gemar D, Engelke J, et al**. Evaluation of ergocalciferol or cholecalciferol dosing, 1,600 IU daily or 50,000 IU monthly in older adults. *J Clin Endocrinol Metab*. 2011;96:981-988.
42. **Heaney RP**. Calcium supplementation and incident kidney stone risk: a systematic review. *J Am Coll Nutr*. 2008;27: 519-527.
43. **Liebman SE, Taylor JG, Bushinsky DA**. Idiopathic hypercalciuria. *Curr Rheumatol Rep*. 2008;8:70-75.
44. **Bushinsky DA**. Recurrent hypercalciuric nephrolithiasis: does diet help? *N Engl J Med*. 2002;346:124-125.
45. **Lund RJ, Andress DL, Amdahl M, Williams LA, Heaney RP**. Differential effects of paracalcitol and calcitriol on intestinal calcium absorption in hemodialysis patients. *Am J Nephrol*. 2010;3:165-170.
46. **Sprague SM, Coyne D**. Control of secondary hyperparathyroidism by vitamin D receptor agonists in chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5:512-518.
47. **Kriegel MA, Manson JE, Costenbader KH**. Does vitamin D affect risk of developing autoimmune disease? A systematic review. *Semin Arthritis Rheum*. 2011;40:512-531.
48. **Scragg R**. Vitamin D and public health: an overview of recent research on common diseases and mortality in adulthood. *Public Health Nutr*. 2011;14:1515-1532.
49. **Rubin MR, Bilezikian JP**. Hypoparathyroidism: clinical features, skeletal microstructure, and parathyroid hormone replacement. *Arq Bras Endocrinol Metab*. 2010;54: 220-226.
50. **Block GA**. Therapeutic interventions for chronic kidney disease-mineral and bone disorders: focus on mortality. *Curr Opin Nephrol-Hypertens*. 2011;20:376-381.
51. **Moe SM, Block GA, Langman CB**. Oral phosphate binders in patients with kidney failure. *N Engl J Med*. 2010; 363:990.
52. **Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group**. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2009:S1-S130.
53. **Palmer SC, Hayen A, Macaskill P, et al**. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA*. 2011;16;305:1119-1127.
54. **Langman CB, Cannata-Andía, JB**. Calcium and chronic kidney disease: myths and realities. Introduction. *Clin J Am Soc Nephrol*. 2010;5(Suppl 1):S1-S2.
55. **West SL, Swan VJ, Jamal SA**. Effects of calcium on cardiovascular events in patients with chronic kidney disease and in a healthy population. *Clin J Am Soc Nephrol*. 2010;5(Suppl 1):S41-S47.
56. **Leifsson BJ, Ahrén B**. Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab. 1996;81:2149-2153.
57. **Fitzpatrick L, Bilezikian JP, Silverberg SL**. Parathyroid hormone and the cardiovascular system. *Curr Osteoporos Rep*. 2008;6:77-83.
58. **Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR**. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. *Am J Epidemiol*. 1999;149:151-161.
59. **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.
60. **Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR**. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040.
61. **Reid IR, Avenell A**. Evidence-based policy on dietary calcium and vitamin D. *J Bone Miner Res*. 2011;26:452-454.
62. **Riley RD, Higgins JP, Deeks JJ**. Interpretation of random effects of meta-analysis. *BMJ*. 2011;342:d549.
63. **Nordin BE, Lewis JR, Daly RM, et al**. The calcium scare-what would Austin Bradford Hill have thought? *Osteoporosis Int*. 2011 [Epub ahead of print]
64. **Prince RL, Zhu K, Lewis JR**. Evidence of harm is unconvincing. *BMJ*. 2011;342:d3541.
65. **Bolland MJ, Grey A, Reid IR**. Authors' response to editorial. *BMJ*. 2011;342:d3520.