Calcium Supplements and the Risk of Myocardial Infarction

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Abstract

A consensus group composed of academic and industry experts in the fields of nutrition, cardiology, epidemiology, bone health, and integrative medicine convened on November 10–11, 2011 in Washington, DC, to examine the data on the relationship between calcium supplement use and risk for cardiovascular events, with an emphasis on four of the Bradford-Hill criteria for causal inference: strength, consistency, dose-response, and biological plausibility. Results from two RCTs, as well as 2 observational studies and meta-analyses of randomized controlled clinical trials, including a subgroup analysis from the Women's Health Initiative, have prompted concern about a potential association between calcium supplement use and a small increase in risk for adverse cardiovascular events. However, a number of issues with the studies—such as inadequate compliance with the intervention, use of non-trial calcium supplements, potential bias in event ascertainment events, and lack of information on, and adjustment for, known cardiovascular risk determinants—suggests bias and confounding cannot be excluded as explanations for the reported associations. There is little evidence to support a plausible biological mechanism linking calcium supplement use with adverse cardiovascular outcomes.

The expert group concluded the scientific literature does not support that calcium supplement use increases one's risk of adverse cardiovascular events. Individuals not obtaining recommended intake levels of calcium through dietary sources should continue to utilize supplements to achieve optimal bone health as recommended by the Institute of Medicine Food and Nutrition Board.

Background

No suggestions of serious adverse effects from supplemental calcium intake had been reported until a series of reports from Bolland, Reid, and colleagues raised the issue of a possible increase in risk for adverse cardiovascular events in men and women associated with the use of calcium or calcium plus vitamin D supplements [1-4]. The initial reports were from two clinical trials in which women and men had been randomly assigned to receive a calcium supplement or placebo and were followed for 2 (men) or 5 (women) y. The primary outcome measure was the change in bone mineral density in each of these studies; however, adverse cardiovascular events were pre-specified secondary outcomes. Bolland, Reid, and colleagues followed these articles with publication of a meta-analysis of data from other randomized controlled trials (RCTs) of calcium supplementation, as well as an article reporting a subgroup analysis of data from the Women's Health Initiative that included an update of their prior meta-analysis. The update of their prior meta-analysis to include these results produced pooled RR estimates of 1.24 for MI (95% CI, 1.07–1.45; p=0.004), 1.15 for stroke (95% CI, 1.00–1.32; p=0.06), and 1.15 for MI or stroke (95% CI, 1.03–1.27; p=0.009) [14]. On the basis of their results, Bolland et al. concluded that use of calcium supplements with or without vitamin D modestly increases cardiovascular risk and suggested that recommendations for the use of such supplements in older people should be reassessed. However, these conclusions have been questioned by a number of experts who have raised concerns about the methodology employed and the potential for bias and confounding that may account for the reported association. The above-described papers of Bolland, Reid, and colleagues have received wide publicity and have resulted in diminished use of calcium supplements by individuals who might otherwise benefit from their use. In addition, concerns among some health care professionals have prompted changes in the recommendations they provide regarding the use of calcium supplements by their patients.

Methods

Given the widespread use of calcium supplements in the population and the potential for harm as a result of decreased supplement use, the Council for Responsible Nutrition (CRN) Foundation judged that a critical examination of the reported association between calcium supplement use and increased cardiovascular disease (CVD) risk was warranted. To accomplish this goal, a consensus group composed of academic and industry experts in the fields of nutrition, cardiology, epidemiology, bone health, and integrative medicine convened on November 10–11, 2011 in Washington, DC, to examine the available data, with an emphasis on five of the Bradford-Hill criteria for causal inference: strength, consistency, dose-response, biologic plausibility, and results from experimentation. Data from RCTs, meta-analyses, and prospective cohort studies are discussed in the following poster presented on behalf of the authors and the CRN Foundation. The full consensus statement will publish in *Osteoporosis International*.

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Results

Table 1: **Summary of Prospective Observational Studies that Examine Calcium Supplement Use and CVD Events**

Study, Year (Reference)	Study Design	Participants	Supplement	Primary End Points	Follow up (y)	RR and 95% CI
Ascherio et al., 1998	Cohort	43,738 men age 40-75	Oral calcium supplement: 0 mg/d, ≥400 mg/d.	Incident stroke	8 y	RR of total stroke in participants who received ≥400 mg/d vs. non-recipients, 0.88 (95% CI, 0.60-1.27) RR of ischemic stroke in participants who received ≥400 mg/d vs. non-recipients, 0.83 (95% CI, 0.52-1.34).
Bostick et al., 1999	Cohort	34,486 postmenopausal women age 55-69 y	127-item food frequency questionnaire covering usual food intake and vitamin and mineral supplement use.	IHD mortality	8 y	Multivariate-adjusted RR for the highest vs. lowest quartiles of calcium intake, 0.67 (95% CI, 0.47-0.94) Multivariate-adjusted RR for high supplemental calcium vs. low dietary calcium intake, 0.66 (95% CI, 0.36-1.23).
Iso et al., 1999	Cohort	85,764 women aged 34-59	Oral calcium supplement: 0 mg/d, <400 mg/d, ≥400 mg/d.	Incident stroke	14 y	RR of stroke in recipients of ≥400 mg/d vs. non-recipients, 0.88 (95% CI, 0.66-1.18) .
Al-Delaimy et al., 2003	Cohort	39,800 men age 40-75 y	Quintiles of calcium supplement use: medians of 0, 57, 200, 325, 500, 1000 mg/d.	IHD	12 y	Highest vs. lowest quintiles of total calcium intake, 0.97 (95% CI, 0.81-1.16) Highest quintile of calcium supplement users vs. nonusers, 0.87 (95% CI, 0.64-1.19).
Pentti et al., 2009	Cohort	10,555 elderly women age 52-62 y	Self-reported questionnaires in 1989 and 1994.	CHD mortality	7 y	RR of CHD mortality of users versus nonusers, 1.26 (95% CI, 1.01-1.57)
LaCroix et al., 2009	Cohort	36,282 postmenopausal women age 51-82 y	Oral calcium / vitamin D supplement: 0 mg/d, 1000 mg and 400 IU/d	CHD and CVD mortality	7 y	RR of CHD mortality in recipients of 1000 mg and 400 IU/d vs. non-recipients, 1.01 (95% CI, 0.79-1.29). RR of CVD mortality in recipients of 1000 mg and 400 IU/d vs. non-recipients, 0.92 (95% CI, 0.77-1.10) .
Wolfe et al., 2011	Cohort	23,228 patients with rheumatic diseases.	Self-reported calcium supplement use with or without vitamin D.	MI	8 y	Those receiving calcium (with or without vitamin D), but no other bone active agents, had an OR for MI of 0.57 (95% CI, 0.42 – 0.77). In those taking bone active agents the OR for MI was 0.38 (95% CI, 0.22 – 0.66).

Table 2: **Summary of RCTs that Examine Calcium Supplement Use and CVD Events**

Study, Year (Reference)	Study Design	Participants	Supplement	End Points	Follow up (y)	RR and 95% CI
Baron et al., 1999	RCT (colorectal adenoma trial)	672 men and 258 women, mean age 61 y.	Oral calcium carbonate: 0 mg/d, 1200 mg/d.	CV events	4 y	The authors observed a hospitalized CV event rate of 11% (n=50) in the calcium group and 10% (n=46) in the placebo group.
Grant et al., 2005	RCT (low energy trauma fracture incidence trial)	5,292 men and women age ≥ 70 y.	Oral calcium carbonate and vitamin D_3: 0 mg/d and 0 IU/d 1000 mg/d and 800 IU/d, 1000 mg/d, and 1000 IU/d.	Death rates	2 y to 62 mo	No significant differences in death rates among the groups: calcium carbonate plus vitamin D_3 (16.9%), vitamin D_3 (16.2%), calcium carbonate (18.5%), placebo (16.3%), or in the combined calcium versus non-calcium groups (17.7% versus 16.2%).
Bazier et al., 2005	RCT (bone mineral density trial)	192 women age > 65 y	Oral calcium carbonate and vitamin D: 0 mg/d and 0 IU/d, 1000 mg/d and 800 IU/d.	CV events	1 y	Self-reported adverse cardiovascular events in 6.3% of the treatment group (n=6) versus compared with 5.2% (n=5) in the placebo group.
Prince et al., 2006	RCT (clinical fracture and vertebral deformity trial)	1460 women age > 70 y	Oral calcium carbonate : 0 mg/d, 1200 mg/d.	CHD	5 y	A 7.7% (n=56)self-reported diagnosis of CHD in the treatment group compared with 7.0% (n=51) in the placebo group. A RR of 1.12 (95% CI, 0.77 – 1.64) was observed for the diagnosis of CHD.
Jackson et al., 2006	RCT (Women's Health Initiative)	> 36,282 women aged 50-79 y	Oral calcium / vitamin D supplement: 0 mg/d, 1000 mg and 400 IU/d.	Deaths and CV events pre-specified variables, adjudicated.	7 y	In those individuals receiving calcium/vitamin D supplements, a RR of 0.91 (95% CI, 0.83 – 1.01) was observed for total mortality and no statistically significant risk were seen in regard to CV events.
Lappe et al., 2007	RCT (skeletal intervention trial)	1,179 postmenopausal women age > 55 y	Oral calcium carbonate or citrate: 0 mg/d, 1400 mg calcium citrate or 1500 mg calcium carbonate/d, 1400 mg calcium citrate or 1500 mg calcium carbonate/d and 1100 IU vitamin D/d.	CV events	4 y	An adjudicated CV event rate of 4.76/1000 person years in the calcium treatment groups compared with 6.94/1000 person years in the placebo group.
Hsia et al., 2007	RCT (Women's Health Initiative)	> 36,282 women aged 50-79 y	Oral calcium / vitamin D supplement: 0 mg/d, 1000 mg and 400 IU/d.	Deaths and CV events pre-specified variables, adjudicated.	7 y	Among individuals receiving calcium and vitamin D supplements in the treatment group versus the placebo a RR of 1.01 (95% CI, 0.79 – 1.29) for MI and a RR of 1.01 (95% CI, 0.79 – 1.29) was observed.
Lewis et al., 2011 [12]	RCT (Calcium Intake Fracture Outcome Study data)	1,460 women mean age 75.1 ± 2.7 y	Oral calcium carbonate supplement: 0 mg/d, 1,200 mg/d	Atherosclerotic vascular disease	5 y with 4.5 y additional observational follow up	Observed a 5-y RCT death and/or hospitalization multivariate-adjusted HR of 0.938 (95% CI, 0.69-1.275). Observed a 9.5-y observational study death and/or hospitalization multivariate-adjusted HR of 0.919 (95% CI, 0.737-1.146).

Conclusion

- After reviewing the available evidence, the authors conclude that a causal inference is not presently warranted between consumption of calcium from diet or supplements and increased risk for adverse cardiovascular events.
- The authors of this manuscript, the Institute of Medicine Food and Nutrition Board, and other cited experts in the field judge that these studies are not an appropriate basis upon which to change current recommendations, and that individuals who do not obtain sufficient intakes of calcium from diet should not be advised to avoid using calcium supplements due to concerns about a potential increase in cardiovascular event risk.
- It is recommended that future studies intended to evaluate risks and benefits of calcium or calcium and vitamin D supplementation be designed in a manner that allows reliable evaluation of cardiovascular outcomes, including proper ascertainment of events and comprehensive documentation of known cardiovascular risk determinants.

References

1. Bolland MJ et al. (2008). BMJ 336:232.
2. Reid IR et al. (2008). Arch Intern Med 168:2276.
3. Bolland MJ et al. (2008). BMJ 341:c3691.
4. Bolland MJ et al. (2008). Arch Intern Med 342:d2040.