Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis

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CRD summary
The review concluded that calcium supplements (without co-administered vitamin D) were associated with an increased risk of myocardial infarction. Overall, the authors’ conclusions reflected the evidence presented and appear likely to be reliable.

Authors’ objectives
To investigate whether calcium supplements increase the risk of cardiovascular events.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions. Search dates ranged from 1966 to March 2010. Search terms were reported. Reference lists of meta-analyses published between 1990 and 2007. Australian New Zealand Clinical Trials Registry and ClinicalTrials.gov were also searched.

Study selection
Randomised double-blind placebo-controlled trials where elemental calcium was administered at a dose of at least 500mg/day to participants of either gender whose mean age at baseline was more than 40 years were eligible for inclusion. Studies needed 100 or more participants. Study duration had to be more than one year. Time to first myocardial infarction, first stroke and death (and a composite of time to any of these three events) were the main outcomes of interest. Trials of calcium and vitamin D versus placebo, trials where calcium was given as a complex nutritional supplement or as dietary modification and trials in which most participants had a major systemic disease other than osteoporosis were excluded.

Mean ages in the included studies ranged from 51 to 77 years. Two-thirds of studies were of women only. Most studies did not report incidence of comorbidities. Supplement types included carbonate, citrate or lactogluconate-carbonate. Doses ranged from 0.6g/day to 2g/day. In studies that reported vascular outcomes, mean dietary calcium intake ranged from 406mg/day to 1,240mg/day.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Studies were evaluated for the reporting of method of randomisation, allocation concealment, withdrawals and losses to follow-up and compliance with study treatment. Two blinded reviewers independently adjudicated events from studies that provided individual patient data. Any disagreements were resolved by consensus (no further details about checking and verification methods used for other data were provided).

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Individual patient data on cardiovascular events was sought for each study (otherwise trial-level summary data were requested). One reviewer extracted the summary data in order to calculate relative risks (RR) and 95% confidence intervals (CI).

Methods of synthesis
A Cox proportional hazards model was used for trials with individual patient data; hazard ratios (HR) and 95% confidence intervals, and number needed to treat (NNT) were calculated. Where data were available for more than 80%
of participants, possible confounding by covariates was assessed. Subgroup analyses for dietary calcium, age, gender, vitamin D status and supplement type were performed. Poisson regression models were used to assess the relationship between the total number of events and treatment allocation. Meta-analyses of relative risks to produce pooled results were performed using a random-effects model. Cochran's Q and I² statistic were used to assess statistical heterogeneity. Publication bias was assessed with Funnel plots and Egger's regression model.

Results of the review
Fifteen trials (n=12,843) were included. Sample sizes ranged from 135 to 5,292 participants. Trial duration was from two to five years. Seven of the 11 trials that provided data on cardiovascular outcomes used suitable methods for randomisation; four explicitly described the allocation concealment method. Ten trials provided details of withdrawals and losses to follow-up. All 11 studies reported levels of compliance; generally studies reported compliance of more than 75% in participants who were taking tablets at study completion. No statistical heterogeneity was reported for any of the analyses.

Individual patient data analysis (five studies, n=8,151): Risk of myocardial infarction in patients allocated to calcium increased by 31% (HR 1.31, 95% CI 1.02 to 1.67, NNT=69). No statistically significant increases occurred in incidence of stroke (HR 1.20, 95% CI: 0.96 to 1.50) or the composite end point of myocardial infarction, stroke or sudden death (HR 1.18, 95% CI 1.00 to 1.39) or death (HR 1.09, 95% CI 0.96 to 1.23).

Subgroup analyses showed that a calcium intake above the median of 805mg/day was significantly associated with an increased risk of myocardial infarction. Further results were reported.

Trial summary data analysis: There was a statistically significant increase in incidence of myocardial infarction following treatment with calcium (RR 1.27, 95% CI 1.01 to 1.59, I²=0%; seven studies). No increased risk was found for stroke, death or the composite end point. There was no evidence of publication bias.

Authors’ conclusions
Calcium supplements (without co-administered vitamin D) were associated with an increased risk of myocardial infarction.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken using various methods. Independent duplicate study selections were made to reduce risks of reviewer error and bias, but only one reviewer extracted summary data and no methodological details were reported for the quality assessment. Inclusion was restricted to double-blind trials, but the authors reported only summary details of the quality assessment and this made it difficult to properly appraise the quality of individual studies. Sufficient study details were provided. Appropriate methods were used to pool both individual patient data and summary data and to assess heterogeneity. Despite the limited reporting of the study quality assessment, the authors’ conclusions reflected the evidence presented and appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that a reassessment of the role of calcium supplements in prevention and treatment of osteoporosis was warranted.

Research: The authors stated that the vascular effects of calcium supplements, especially without vitamin D, should be studied further.

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Bibliographic details
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.