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# Cardiovascular Complications of Calcium Supplements

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## ABSTRACT

There is longstanding concern that calcium supplements might increase cardiovascular risk in patients with renal impairment. The Auckland Calcium Study suggested that the same problem occurs in older people taking these supplements for prevention of osteoporosis. Our subsequent meta-analyses, (which followed protocols finalized before the data was available) confirmed that calcium supplements, with or without vitamin D, adversely affected risk of myocardial infarction and, possibly, stroke. Several groups have re-visited these data, consistently finding an adverse effect of calcium on myocardial infarction, not always statistically significant because some meta-analyses have been under-powered. Whether or not an adverse effect of calcium plus vitamin D on myocardial infarction is found depends on whether two specific groups of subjects are included—those in the Women's Health Initiative who were already taking calcium at the time of randomization, and subjects from an open, cluster-randomized study in which baseline cardiovascular risk was different between groups. Vitamin D alone does not affect vascular risk, so it is unlikely that differences between calcium alone and calcium plus vitamin D are real, and they are more likely to result from the inclusion of studies at high risk of bias. The mechanisms of the adverse cardiovascular effects are uncertain but may be mediated by the increase in serum calcium following supplement ingestion, and the effects of this on vascular function and coagulation. Available evidence suggests the risks of calcium supplements outweigh any small benefits on fracture incidence, so the case for their use is weak. J. Cell. Biochem. 116: 494–501, 2015. 

**KEY WORDS:** CALCIUM; OSTEOPOROSIS; MYOCARDIAL INFARCTION; STROKE

## INTRODUCTION

The current concern with the cardiovascular safety of calcium supplements has its origin in at least two different areas of the literature. The first is the use of calcium as a phosphate binder in patients with chronic renal failure. Vascular disease is the principal cause of death in these patients and extensive calcification of arteries is a prominent finding on their plain radiographs. More recently, the extent of coronary artery calcification was found to be predictive of cardiovascular risk, and calcium supplements were shown to increase coronary artery calcification, when compared with a calcium-free phosphate binder (sevelamer) [Russo et al., 2007]. Notably, an adverse effect of calcium supplements on mortality has been observed in pre-dialysis patients with mean glomerular filtration rates of 33 mL/minute [Di Iorio et al., 2012]. This level of renal function is comparable to that seen in many older patients at risk of osteoporosis [Lubwama et al., 2014], in whom use of calcium supplementation has been common.

The Auckland Calcium Study provided the second piece of evidence indicating that calcium supplements might have adverse cardiovascular effects [Bolland et al., 2008]. This was a randomized controlled trial in 1,471 healthy postmenopausal women who were randomized to receive calcium 1 g/day (as citrate) or placebo, over a period of five years. The primary endpoints were fracture and bone density change, but stroke and myocardial infarction were pre-specified as secondary endpoints on the basis of previous evidence that calcium supplementation produced small improvements in blood pressure and circulating cholesterol profiles. To our surprise, the changes in vascular event rates found in this study were adverse, contrary to our original hypothesis. The potential importance of this observation led to our searching a national hospital admissions database to ensure that no events had been overlooked, and then to a blinded adjudication of all events. This process resulted in small changes in the numbers of events in the calcium and placebo groups, but not to the significant adverse trend associated with randomization to calcium. The adverse finding was plausible in light of the

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pre-existing concerns regarding the cardiovascular safety of calcium supplements in the context of renal failure. However, it was not definitive, particularly considering that the issue had not surfaced in any of the previous studies of calcium supplementation for osteoporosis management. For both ethical and financial reasons there was no immediate prospect of undertaking a larger study which might have confirmed or refuted the findings of the Auckland Calcium Study, so the best way forward was to undertake meta-analyses of existing trials.

## META-ANALYSES OF CALCIUM SUPPLEMENT EFFECTS ON CARDIOVASCULAR EVENTS

In 2010 two such meta-analyses appeared. Wang et al [Wang et al., 2010] brought together results from three studies of calcium monotherapy which had already published cardiovascular data. This comprised 3861 subjects and showed a relative risk of cardiovascular events of 1.14 (95% CI 0.92–1.41). They concluded that this was not grounds for concern. Our own group, being aware that there were very little published data but a large number of clinical trials involving over 12,000 subjects, set out to obtain as much of the unpublished cardiovascular safety data from these trials as possible. We contacted all investigators of randomized, controlled trials of calcium supplementation which had involved >100 adult subjects. We received patient level data from five studies involving 8,151 subjects, and trial level data from a further six studies involving 3,770 subjects. Thus, we had data on 93% of subjects in qualifying trials. This analysis demonstrated a significant increase in risk of myocardial infarction in subjects randomized to calcium supplementation (relative risk of 1.27, 95%CI 1.01–1.59) and non-significant upward trends in relative risk of stroke (1.12) and death (1.07) [Bolland et al., 2010a]. These findings were not inconsistent with the Wang meta-analysis since the confidence intervals from both analyses overlapped considerably, but our own analysis had considerably more power through having data from more than three times as many study subjects, with a mean study duration of four years.

Within this analysis we have looked at subgroups that might be at increased risk from the adverse cardiovascular effects of calcium supplements. We have failed to find any interaction with age, gender, baseline 25-hydroxyvitamin D or type of supplement (carbonate versus citrate) [Reid et al., 2011a]. Within the Auckland Calcium Study, the only one with data on glomerular filtration rate, there was no interaction between this variable and the calcium effect [Bolland et al., 2008]. The possible interaction with dietary calcium is more complex: When the population is partitioned around the median calcium intake (805 mg/day) there does appear to be an interaction, with those with above median calcium intakes showing most of the adverse effect. However, when the population is broken down into quintiles, then all but the second quintile (500–699 mg/day) show similar adverse trends [Reid et al., 2011a].

It should be noted that this meta-analysis included the Caifos study from Perth, using the data provided to us by those investigators. Those investigators subsequently republished the data from this single study and concluded that it provided "compelling evidence" that there was no adverse cardiovascular effect from calcium supplements [Lewis et al., 2011]. Figure 1

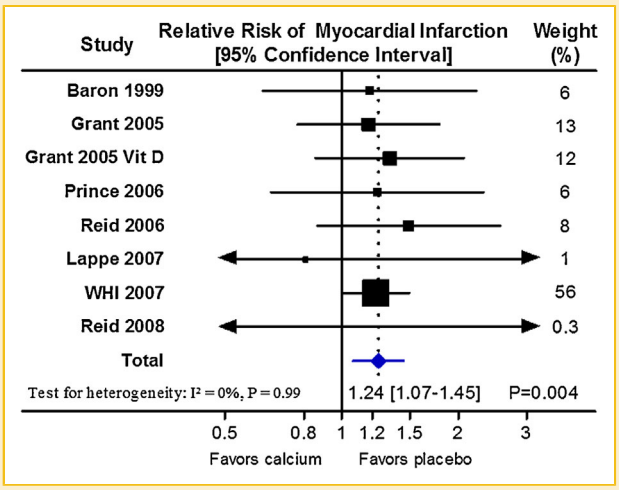


**Fig. 1.** Trial-level meta-analysis of the effect of calcium supplements with or without vitamin D on myocardial infarction. Analyses show data for 28,072 participants in 8 trials of calcium supplements where complete trial-level data were available, together with data for WHI participants not taking personal calcium supplements at randomization. One study randomized participants to calcium, calcium plus vitamin D, or placebo [Lappe et al., 2007]. For this analysis, we pooled the outcomes from both the calcium and calcium plus vitamin D arms. Abbreviations: Grant 2005 is the RECORD study calcium versus placebo arms, and Grant 2005 Vit D is the RECORD study calcium plus vitamin D versus vitamin D plus placebo arms [Grant et al., 2005]. From Bolland et al [Bolland et al., 2011a], used with permission.

demonstrates that this study (Prince et al) aligned very well with the adverse effects seen in all the other studies. Their later publication did not provide data on rates of myocardial infarction, but used a broader category of "atherosclerotic vascular disease", which included heart failure and arrhythmias in addition to endpoints related to cardiovascular disease. They eliminated self-reports of events and relied entirely on un-adjudicated hospital discharge diagnoses. They only included the first admission for a cardiovascular principal diagnosis. Thus, in an individual who was admitted to hospital with some other principal diagnosis but suffered a myocardial infarction during that admission, this was not included in the analysis. As a result of this restrictive approach to data inclusion the number of events was small, the power of the study low, and effects of the intervention on myocardial infarction potentially obscured by the many other cardiac diagnoses included in the omnibus endpoint assessed.

Subsequent to the publication of this meta-analysis, the only new trial to provide relevant data is that of Sambrook et al. [2012]. In a study in institutionalized frail elderly who were randomized to act as controls, to have daily sunlight exposure, or to have daily sunlight exposure plus calcium supplements, the hazard ratio for death after almost three years follow-up was 1.47 (95% CI 1.05–2.06) in those randomized to sunlight plus calcium, in comparison with those randomized to sunlight alone [Reid et al., 2011b]. For deaths attributed to myocardial infarction, the hazard ratio was 5.39 (95% CI 1.18–24.7) and for cardiovascular death, the hazard ratio was 1.76 (95% CI 1.10–2.82). Thus, this was consistent with the adverse

finding in our meta-analysis, but through studying a very frail elderly population in which more than one-third of the subjects died during follow-up, a significant adverse effect on mortality emerged.

Our 2010 meta-analysis did not include trials in which the intervention was calcium plus vitamin D. It could be hypothesized that these studies might have different findings, since a cardio-protective effect of vitamin D has been suggested. This group of clinical trials is dominated by the Women's Health Initiative (WHI), a seven-year study of 36,000 women who were randomized to receive calcium (1 g as carbonate) plus 400 IU of vitamin D daily, or placebo. Cardiovascular outcomes from this study were first published by Hsia et al. [2007]. They showed a hazard ratio for myocardial infarction or coronary heart disease death of 1.04 (95%CI 0.92–1.18), and for these endpoints plus coronary revascularization it was 1.08 (95%CI 0.99–1.19). The authors concluded that there was no increase in cardiovascular risk from this intervention, though it should be noted that when the combined endpoint included coronary revascularization, the hazard ratio sat right on the cusp of statistical significance. These investigators noted an interaction between body mass index and the effect of the intervention on cardiovascular risk, such that in non-obese subjects (i.e. BMI $\leq$30) the hazard ratio for myocardial infarction or coronary heart disease death was 1.17. Thus, despite the investigators' conclusions, these findings were not entirely reassuring, and these confidence intervals overlap with those from our 2010 meta-analysis.

The apparent absence of an adverse effect within the WHI could be attributed to the co-administration of vitamin D, to the average age of this cohort being 10 years less than that in our 2010 meta-analysis, or, we hypothesized, to the high levels of self-administration of calcium within this study. At the time of randomization, 54% of study subjects were already taking calcium supplementation, and they continued this through the study, reaching a 69% rate of calcium self-administration by study-end. Allowing clinical trial participants free access to the intervention being studied is unusual, and has the potential to obscure both adverse and beneficial effects of the intervention. Therefore, we drafted a protocol for the re-analysis of the WHI database, seeking to determine whether there was an interaction between self-administration of calcium supplements and the cardiovascular effects of the intervention. As with our 2010 meta-analysis, this protocol was finalized and approved before the trial data were provided to us. The results of this re-analysis were published in 2011 and demonstrated significant interactions between self-administration of calcium and the cardiovascular effects of the intervention [Bolland et al., 2011a]. Thus, for clinical myocardial infarction there was a 22% increase in risk associated with randomization to calcium plus vitamin D ($P = 0.05$), and when trials using this combined intervention were meta-analyzed, an adverse effect on myocardial infarction was found which was comparable to that we had demonstrated for calcium monotherapy. A pooled meta-analysis of both groups of studies, but using only the WHI data from the calcium-naive women, is shown in Figure 1. Similar analyses for the endpoint of stroke showed more heterogeneity but a similar adverse trend. We have subsequently looked at the time-course of these treatment effects within our calcium monotherapy database and in the calcium-naïve subjects in the WHI. These completely independent databases both show the development of an adverse effect on myocardial infarction within a year of initiating supplements, whereas the effect on stroke takes three-to-four years to become apparent (Fig. 2). The similarity of findings in these two, independent populations suggests that the adverse effect itself is likely to be real, and its time-course likely to be significantly delayed for the endpoint of stroke.

Because the analyses showed interactions between the self-administration of calcium and the cardiovascular effects of calcium plus vitamin D, we repeated these analyses for the other major endpoints of the WHI [Bolland et al., 2011b]. These hypothesis-generating analyses showed no interactions between personal calcium and vitamin D use, and the effects of calcium and vitamin D on total fracture, hip fracture, or mortality. However, there were significant interactions for cancer endpoints. Thus, the risk of breast cancer, colorectal cancer, and total cancer was lowered by treatment with calcium and vitamin D in women not taking personal calcium supplements. The analyses suggest that the widespread use of personal calcium and vitamin D in the WHI obscured both possible adverse and beneficial effects of these supplements.

More recently a further meta-analysis of these cardiovascular data has been published by Lewis et al. [2014]. The authors omitted data for men and for self-reported events. They also chose a much broader primary endpoint than myocardial infarction, even though all previous studies suggested that this is the event most affected by calcium supplements. In their analyses of calcium monotherapy and myocardial infarction, they omitted two studies from our previous meta-analysis, and added only one trial (with 4 MIs) published subsequently, explaining the similarity of their results: they include 5 trials ($N = 6333$) and find a relative risk of 1.37 (95%CI 0.98–1.92), whereas we included 6 trials with complete data ($N = 10210$), and found a relative risk of 1.27 (95%CI 1.01–1.59). When self-reports are excluded from our 2010 meta-analysis, the relative risk is 1.33 (95%CI 1.03–1.73) [Bolland et al., 2013] For their analysis of calcium plus vitamin D, Lewis added two substantial groups of women not included in our 2011 meta-analysis: 20,000 participants from the WHI who were already taking calcium at the time of randomization (most of whom continued to do so throughout the trial), and 6000 women in the study of Larsen [Larsen et al., 2004], which was not a randomized, controlled trial. Since we have shown that self-administration of calcium significantly influenced the cardiovascular outcomes of the WHI [Bolland et al., 2011a] the first of these additions is inappropriate. Recruitment for the Larsen study offered people living in different regions of the study city the opportunity to be involved, indicating to them whether they would be randomized to intervention or control before they made their decision to participate. There was only one "cluster" per intervention, and there was a higher uptake of the invitation in those offered calcium plus D. This group had lower use of cardiovascular medications, sedatives and analgesics than did those agreeing to act as controls, suggesting a difference in cardiovascular risk and other comorbidities at baseline, which would bias the study against finding an adverse effect of calcium supplements. Persistence with the calcium intervention is not reported, neither is the frequency of self-administration of calcium in those allocated to control. This design certainly does not qualify the Larsen study to be included in a meta-analysis of randomized, controlled trials. The Lewis analysis found

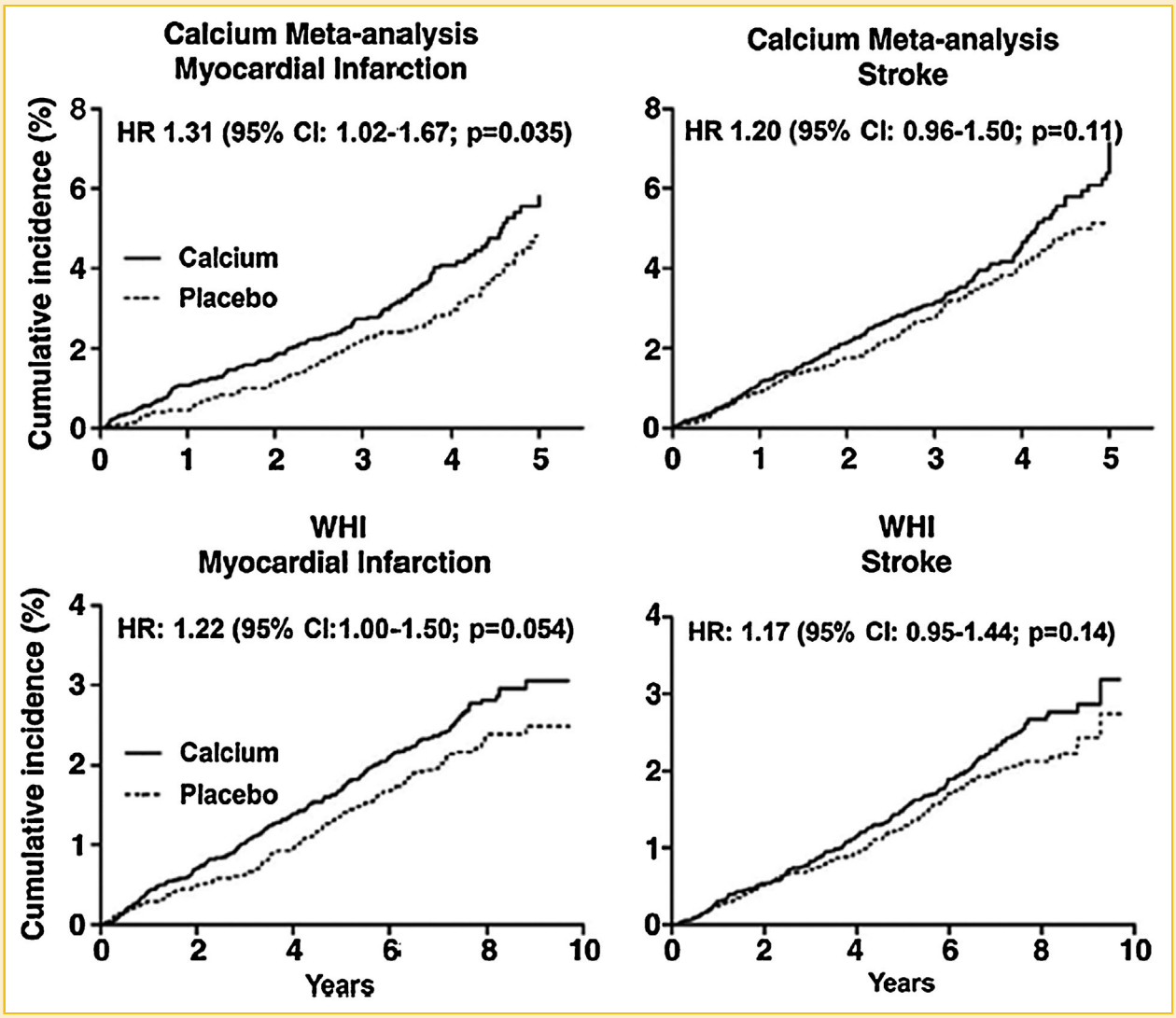


**Fig. 2.** Kaplan–Meier survival curves for time to incident myocardial infarction or stroke by treatment allocation in a meta-analysis of patient-level data from five trials of calcium supplements used as monotherapy (n = 8151) and in women in the Women's Health Initiative (WHI) calcium and vitamin D trial not using personal calcium supplements at randomization (n = 16 718). The magnitude and time-course of the effects of calcium supplements on the two groups of vascular events were very similar in these independent databases. From Radford et al, used with permission [Radford et al., 2013]. CI, confidence interval; HR, hazard ratio.

no effect of calcium and vitamin D supplements on total coronary heart disease, but 82% of the weight in this analysis comes from the WHI, so it is essentially a re-publication of that data.

Mao et al. [2013] have also recently meta-analyzed these data, finding that calcium monotherapy was associated with an adverse trend in myocardial infarction (OR 1.28, 95%CI, 0.–1.68). This confirms the Bolland meta-analysis, though when we calculate these confidence intervals we find they do not embrace 1.0. Thus, we have three meta-analyses that indicate a clinically significant increase in risk of myocardial infarction associated with randomization to calcium supplements. The addition of vitamin D is unlikely to modify this outcome, since vitamin D alone has no impact on cardiovascular risk [Bolland et al., 2014; Ford et al., 2014]. Therefore, the re-assurance which Lewis et al have taken from the addition of the WHI and Larsen studies to their meta-analysis of the combined intervention is likely to be misplaced.

## OBSERVATIONAL STUDIES

A number of observational studies has now appeared addressing the effects of calcium supplements on myocardial infarction (Table I). Since there is already a substantial body of randomized trials, it is doubtful that observational analyses have much to offer since such studies are much more subject to bias, so should only have a role in hypothesis generation. These studies are roughly equally partitioned between those indicating an adverse effect of calcium supplementation and those not. The design of the Shah study is questionable since compliant and subjects are known to have different clinical characteristics and outcomes from those

TABLE I. Observational Studies of Calcium Supplement Use and Myocardial Infarction/IHD/CHD

| Reference | Study | N | Duration | Comparison | Endpoint | RR | Conclusion |
|---|---|---|---|---|---|---|---|
| Al-Delaimy 2003 | Health Professionals Follow-up Study | 39,800 | 12y | Ca 1 g/d | IHD Non-fatal MI | 0.87 (0.64–1.19)<br>1.02 (0.71– 1.46) | Neutral |
| Pentti 2009 | Kuopio Osteoporosis Study | 10,555 | 7y | Ca or CaD use | CHD | 1.24 (1.02–1.52) | Harm |
| Li 2012 | EPIC-Heidelberg | 23,980 | 11y | Ca use | MI | 1.81 (1.14–2.87) | Harm |
| Li 2013 | Harbin Peoples Health Study | 6712 | 2y | Ca use | MI | F: 1.70 (1.10–2.63)<br>M: 0.91 (0.48–1.71) | Harm |
| Wolfe 2013 | Rheumatoid arthritis cohort | 5689 | 4y | Ca use | MI | ~1.1 (0.8–1.8) | Neutral |
| Prentice 2013 | WHI Observational | 68,719 | 7y | CaD | MI CHD | 0.90 (0.75–1.09)<br>0.88 (0.74–1.04) | Neutral |
| Paik 2014 | Nurses' Health Study | 74,245 | 24y | Ca 1 g/d | CVD CHD | 0.82 (0.74–0.92)<br>0.71 (0.61–0.83) | Benefit |
| Shah 2009 | UK GP Database | 9910 | 2y | Compliant vs non-compliant | CHD MI | 0.71 (0.42–1.22)<br>0.73 (0.34–1.60) | Neutral |

IHD, ischemic heart disease; CHD, coronary heart disease; Ca, calcium; CaD, calcium + vitamin D, F, female; M, Male.

who are non-compliant [Curtis et al., 2011]. It is notable that only one observational study suggests a reduction in risk [Paik et al., 2014] and there were significant differences in baseline characteristics defining cardiovascular risk between calcium users and others in this study. In sum, these studies are consistent with a moderate adverse effect. There is a further group of studies which assess associations of calcium supplement use with death and, like the trial data for this endpoint, do not show a consistent association with calcium supplement use.

## MECHANISMS

The mechanism of the adverse effect of calcium on cardiovascular risk is unknown, but we have suggested that it might be related to the increases in circulating calcium concentration (1–3 standard deviations of its baseline distribution) that follow ingestion of these supplements. For example, Kruger et al. [2014] has recently shown a mean increase in serum calcium following a 1 g dose of calcium in fortified skim milk of 0.16 mmol/L, which is more than 3 standard deviations of the baseline calcium level in that population. An increase of 0.09 mmol/L (1.8 standard deviations of baseline) occurred with a calcium dose of 250 mg, indicating a non-linear dose-response. Values were well above baseline at the end of the 5-h observation period (Fig. 3). Guillemant has also reported that high and low doses of calcium supplements produce similar increases in serum calcium [Guillemant and Guillemant, 1993]. We have recently shown similar changes with calcium carbonate and calcium citrate and demonstrated that values do not return to normal 8 h following dosing [Bristow et al., 2014]. Since calcium supplements are often taken twice a day, supplement use may raise serum calcium levels throughout most of a 24-hour period, and Gallagher has recently documented hypercalcemia in 9% of women taking calcium and vitamin D [Gallagher et al., 2014]. Further, we have shown that these excursions in serum calcium are not diminished with long-term use of daily supplements [Bristow et al., 2014]. The fact that the calcemic effect of supplements does not demonstrate a linear dose-response might explain why increasing the supplement dose in those who are already taking these preparations does not affect cardiovascular risk, as was seen in the WHI [Bolland et al., 2011a].

The changes in serum calcium following supplement ingestion may be relevant to the pathogenesis of cardiovascular disease, since there is a body of observational evidence documenting associations between serum calcium levels and a number of cardiovascular endpoints. For example, individuals with serum calcium levels within the upper part of the normal range show increased carotid artery plaque thickness [Rubin et al., 2007], increased likelihood of having abdominal aortic calcification [Bolland et al., 2010b], increased extent of coronary artery calcification [Shin et al., 2012; Kwak et al., 2014], increased incidence of coronary heart disease or stroke in prospective studies [Lind et al., 1997; Slinin et al., 2011], increased risk of developing heart failure [Lutsey et al., 2014] and an increased risk of death [Leifsson and Ahren, 1996]. The acute changes in serum calcium following supplement ingestion would predict an increased likelihood of coronary artery calcification of 30–60% [Kwak et al., 2014], or an increased risk of cardiovascular events of 15–30% [Slinin et al., 2011], similar to what the clinical trials have found.

Of course, the demonstration of an association between serum calcium and cardiovascular disease, does not establish the direction

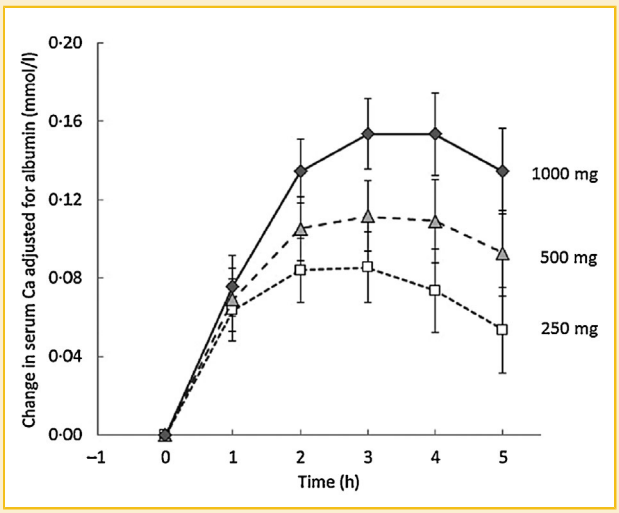


Fig. 3. Change from baseline in serum calcium (adjusted for albumin) for 3 doses of calcium-fortified milk (250 mg, 500 mg, and 1000 mg). Data are means and 95% confidence intervals. There was an effect of dose × time ($P = 0 \cdot 005$). From Kruger et al. [2014], used with permission.

of any causative relationship. Therefore, data from individuals with polymorphisms of the calcium sensing receptor are of interest, since these polymorphisms are associated with differences in serum calcium and it is clear in these individuals where the primary abnormality lies. An alanine to serine polymorphism at position 986 of the calcium sensing receptor is associated with an increase in total serum calcium level of 0.025 mmol/L, and also with an odds ratio for coronary heart disease of 1.25 (95% CI 1.02, 1.54), an odds ratio for mortality of 1.25 (95% CI 1.04–1.51) and an odds ratio for cardiovascular mortality of 1.48 (95% CI 1.18, 1.86) [Marz et al., 2007]. In this situation, the primary genetic abnormality is clearly the cause of the increase in serum calcium so the cardiovascular associations are likely to flow from this, rather than for causation to be in the reverse direction.

Two other pieces of evidence suggest that changes in serum calcium after supplement dosing might be mechanistically implicated in the adverse cardiovascular effects. Administration of strontium has been shown to increase risk of myocardial infarction by 60% in randomized, controlled trials of osteoporosis management [Bolland and Grey, 2014]. Strontium sits in the same column of the periodic table as calcium, so is chemically similar. It acts biologically as a calcium mimetic, binding to many of the same substrates, including the calcium sensing receptor, so it is possible that the same mechanisms are involved in the adverse effects of both of these ions on myocardial infarction. Second, repeated administration of calcium chelators, such as EDTA, produce repeated small diminutions in serum calcium and have now been suggested to be associated with reductions in cardiovascular events of roughly the same magnitude as the increases found with calcium supplements [Lamas et al., 2013]. The result of this randomized, controlled trial is consistent with the other evidence presented, suggesting that there is a direct causal relationship between circulating calcium levels and cardiovascular risk.

### HOW MIGHT SERUM CALCIUM INFLUENCE CARDIOVASCULAR RISK?

The answer to this question is unknown, but there are a number of possibilities, including direct effects of calcium on arterial calcification, vascular tone, and coagulation.

**Arterial effects.** In cultures of vascular smooth muscle cells, increases in ambient calcium levels have been associated with increases in matrix vesicle formation [Reynolds et al., 2004] and matrix mineralization [Yang et al., 2004]. A randomized, controlled trial which compared calcium carbonate (as a phosphate binder) with sevelamer (a calcium-free phosphate binder), showed that there was less progression of coronary artery calcification with sevelamer in a population of pre-dialysis patients [Russo et al., 2007]. A randomized, controlled trial of a calcium-fortified milk over 2 years, similarly demonstrated an increase in aortic calcification in those randomized to the supplements [Daly et al., 2009]. More recently, Li et al have shown that calcium supplements increase carotid intima-media thickness in postmenopausal women randomized to calcium supplements [Li et al., 2013]. These in vitro and clinical studies all suggest that calcium can have deleterious effects on arteries. A further mechanism by which changes in serum calcium might influence vessel calcification and cardiovascular risk is through modulating free concentrations of pyrophosphate, an important inhibitor of soft tissue calcification. Simple physical chemistry considerations would suggest that higher calcium levels will be associated with increased calcium-pyrophosphate complexing, with lower levels of free pyrophosphate available to inhibit soft tissue calcification.

**Blood pressure.** Long-term use of calcium supplementation has been associated with small reductions in pre-dose blood pressure [Reid et al., 2005]. However, acute increases in serum calcium are associated with increased blood pressure. This has been demonstrated following calcium infusions [Nilsson et al., 2001; Kamycheva et al., 2005] and similar effects have been observed in patients dialyzed against a high-calcium dialysate [Locatelli et al., 2010]. We have recently shown similar changes following acute dosing with calcium supplements, systolic blood pressures being about 5 mmHg higher than control subjects following a 1 g calcium dose (Bristow, in preparation). In rats, acute dosing with the calcium sensing receptor agonist, cinacalcet, also produces similar effects on blood pressure, suggesting that a pressor effect of calcium might be mediated through calcium sensing receptor effects on peripheral resistance [Fryer et al., 2007].

**Coagulation.** Calcium is critical for several components of the coagulation cascade. There are calcium sensing receptors on platelets, so regulation of platelet function by calcium is possible. The acute induction of severe hypercalcemia in rats reduces whole blood clotting times by about one half [Hilgard, 1973], and in vitro manipulation of calcium concentrations across the physiological range, influences the clotting time of human blood [James and Roche, 2004]. We have recently demonstrated a 20% reduction in the time to clot initiation following ingestion of 1 g calcium supplement in healthy postmenopausal women (Bristow, in preparation). If each dose of calcium supplement produces such a hypercoaguable state, this could account for the comparatively rapid increase in the risk of myocardial infarction following initiation of calcium supplements.

## CONCLUSION

The balance of evidence suggests that calcium supplements increase the risk of myocardial infarction. While calcium plus vitamin D has been shown to reduce fracture risk in frail elderly in institutions [Chapuy et al., 1992], this is not the case for those living in the community (in whom vitamin D status and dietary calcium intake are less likely to be severely deficient) [Reid and Bolland, 2014]. Available evidence suggests that the adverse effects of calcium supplements, including cardiovascular risk, constipation [Reid et al., 2006], acute gastrointestinal symptoms [Lewis et al., 2012], kidney stones [Jackson et al., 2006], and hypercalcemia [Gallagher et al., 2014] outweigh any small effects on fractures. Therefore, a balanced diet should be the source of calcium nutrition, and appropriate pharmaceutical intervention is a safer and more effective way to reduce fracture risk in those in whom it is elevated.

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