Calcium and cardiovascular risks

SUMMARY
Co-administered calcium and vitamin D supplements prevent fractures in institutionalised elderly women, but there is little evidence that the supplements, administered as monotherapies or in combination, prevent fractures in other people in the community.

Calcium and vitamin D supplements are not always necessary for bisphosphonates to be effective. Individuals at high risk for vitamin D deficiency should be treated with vitamin D supplements before zoledronic acid is prescribed.

There is little evidence that dietary calcium intake is associated with risk of fracture or cardiovascular events, so dietary calcium generally does not require close scrutiny.

Calcium supplements increase the risk of myocardial infarction by about 25% and stroke by 15–20%. The co-administration of vitamin D does not mitigate these risks. Widespread use of calcium supplements to prevent fractures is therefore no longer appropriate.

Introduction
Calcium and vitamin D supplements are commonly recommended for the treatment or prevention of osteoporosis and for patients taking bisphosphonate treatment. These strategies need to be reconsidered as recent evidence suggests that calcium supplements are only marginally effective in preventing fractures, and increase cardiovascular risk.

Skeletal benefits of calcium with or without vitamin D
In 1992 a trial reported that co-administered calcium and vitamin D significantly reduced the risk of hip and non-vertebral fracture in institutionalised elderly women with low dietary calcium intake and a very high prevalence of vitamin D deficiency.1 However, for other people living in the community the evidence for the benefit of calcium or vitamin D supplements on fracture prevention is less clear. Meta-analyses of randomised controlled trials found that calcium supplements used as monotherapy marginally reduced the risk of total fracture,2 but increased the risk of hip fracture.3 Vitamin D supplements used as monotherapy had no effect on total fracture4 and had no effect5 or marginally increased6 the risk of hip fracture. The addition of vitamin D to calcium supplements did not change these findings. Calcium with vitamin D marginally reduced the risk of total fracture7 but did not prevent hip fractures8,9.

There are several explanations why calcium and vitamin D prevent fractures in vitamin D deficient, frail, elderly women, but not in other people. The benefits seen in elderly women may have arisen from correcting vitamin D deficiency and resulting osteomalacia, which is uncommon in younger people. Another possible explanation is that compliance with calcium supplements is poor (approximately 40–60% in randomised controlled trials6-8), which may reduce their effectiveness.

Are calcium and vitamin D supplements necessary when prescribing bisphosphonates?
In clinical trials of osteoporosis treatment, calcium and vitamin D supplements have routinely been co-administered. This has led to suggestions that bisphosphonates are only effective when co-prescribed with calcium and vitamin D, but other trials suggest this is incorrect.

The effects of alendronate on bone density were the same as alendronate plus calcium supplements in a two-year randomised controlled trial in women with dietary calcium intake of more than 800 mg/day.9 The decreases in bone turnover and improvements in bone density with zoledronate were similar regardless of whether calcium and vitamin D were co-prescribed10,11 or not12. Without calcium and vitamin D, clodronate decreased the risk of fractures by 20% in elderly women.13 This evidence shows that bisphosphonates used without calcium and vitamin D effectively decrease bone turnover, improve bone density, and prevent fractures.

Co-prescribing calcium and vitamin D to patients taking bisphosphonates is probably unnecessary for most people. An important caveat is that vitamin D deficiency is common in frail elderly patients (in whom osteoporosis is also common). Infusion of zoledronic acid into patients with vitamin D deficiency can provoke significant hypocalcaemia so the deficiency should be corrected before treatment.
Cardiovascular effects of calcium supplements

The first evidence for the adverse cardiovascular effects of calcium supplements in non-uraemic patients came from our five-year randomised controlled trial of calcium monotherapy in 1471 healthy postmenopausal women. There were increases in cardiovascular event rates in the women allocated to calcium (23.3 vs 16.3 events/1000 patient-years, p=0.043), but the size of the study and number of cardiovascular events meant that the results were not definitive.14

Further randomised controlled trials of calcium to address the concern were not practical as the primary endpoint would be one of harm. We therefore undertook a meta-analysis of unpublished cardiovascular data from randomised controlled trials. The lead authors of five trials provided patient-level data, and trial-level data on cardiovascular events were available for 11 trials. Meta-analyses showed that calcium supplements increased the risk of myocardial infarction by approximately 30%. There were also smaller, statistically non-significant, increases in mortality, the risk of stroke and in a composite cardiovascular endpoint.15

Co-administered calcium and vitamin D

The findings of our meta-analysis related to calcium supplements used as monotherapy, whereas the use of calcium with vitamin D is more common in clinical practice. The Women’s Health Initiative calcium and vitamin D trial, a seven-year randomised controlled trial in more than 36 000 postmenopausal women, had previously reported that calcium and vitamin D did not alter cardiovascular risk.16 An unusual feature of this trial was that personal, non-protocol use of the trial medications was permitted. The majority of the participants were taking their own calcium supplements at randomisation. Widespread personal use of calcium in the trial might have obscured an adverse effect of calcium supplements on cardiovascular risk.

We reanalysed the data from the trial comparing the effects of calcium and vitamin D in non-users and users of personal calcium. In women who were not taking their own calcium at baseline but were allocated to take calcium and vitamin D in the trial, there were increases in the risk of cardiovascular events of similar magnitude to those in the previous meta-analysis of calcium monotherapy. However, in women who were already taking personal calcium supplements, taking calcium with vitamin D in the trial had no effect on cardiovascular risk.17 The results suggested that the widespread use of personal calcium supplements in the Women’s Health Initiative trial had obscured the adverse cardiovascular effects of calcium with vitamin D.

We then pooled the data from the women not using personal calcium supplements in the Women’s Health Initiative trial with all other randomised controlled trials of calcium with vitamin D for which cardiovascular data were available. In this analysis, calcium with vitamin D increased the risk of myocardial infarction by 21% and stroke by 20%.17

Calcium with or without vitamin D

We pooled our two meta-analyses of calcium monotherapy and calcium with vitamin D, to determine the effect of calcium with or without vitamin D on cardiovascular risk. Calcium or calcium with vitamin D increased the risk of myocardial infarction by 25% and stroke by 15-19%. Based on these meta-analyses, in 1000 people treated for five years, calcium or calcium with vitamin D would cause six heart attacks or strokes and prevent three fractures.17

These findings are consistent with studies of patients with renal impairment, in whom calcium supplements accelerate vascular calcification and increase mortality, in both dialysis and pre-dialysis populations.18-20 A more recent randomised controlled trial of sunlight exposure to raise vitamin D concentrations in Australian nursing home residents also found that the addition of calcium supplements to sunlight exposure was associated with increases in all-cause and cardiovascular mortality.21,22

Given the widespread use of calcium and its presumed safety, it is unsurprising that these unexpected findings have not been universally accepted, although few substantive criticisms have been raised.23 Misclassification of other events as heart attacks was suggested as a possible explanation, but the increased risk is consistent whether events were self-reported, obtained from hospital discharges, death certificates or independently adjudicated. Others have suggested that the results are not valid because the trials were not primarily designed to assess cardiovascular events. This reasoning would make it impossible to ever detect unexpected adverse events. Others have suggested that more evidence is required before practice should be changed. However, there are no ongoing trials large enough to influence the results from the current meta-analyses, future trials are unlikely given the potential for harm from participating, and results of observational studies will not outweigh the Level 1 evidence from a systematic review of randomised controlled trials. Decisions about the use of calcium supplements must therefore be based on these current data.
Mechanisms
A cause for the increased cardiovascular risk remains unclear. The consistency of the results for calcium monotherapy and calcium and vitamin D suggests that the effect is caused by calcium supplements, and is not mitigated by the co-administration of vitamin D. One possible mechanism is that calcium supplements abruptly increase serum calcium. Higher serum calcium concentrations are associated with many measures of atherosclerosis such as carotid artery plaque thickness and aortic calcification. They are also associated with the incidence of myocardial infarction and mortality. It is possible that the rapid increases in serum calcium after taking a calcium supplement may alter vascular calcification and other pathophysiological processes occurring at the blood vessel surface.

Should dietary calcium be recommended in place of calcium supplements?
There are no randomised controlled trials that have evaluated the effect of increasing dietary calcium on either fracture incidence or cardiovascular outcomes. Several observational studies have addressed this topic, although the interpretation of observational studies is difficult. Causality cannot be inferred, confounding is difficult to assess and control for, and the total calcium intake of people taking calcium supplements is usually much greater than the intake achieved through diet alone. With these caveats in mind, there is little evidence that levels of dietary calcium intake are associated with cardiovascular risk. Similarly, meta-analyses of observational studies do not suggest that levels of calcium intake are associated with subsequent risk of fracture.

Implications for practice
For the majority of patients, the weak effects that calcium supplements have on fracture risk are outweighed by the increased cardiovascular risk. Recommendations for the widespread use of calcium supplements are no longer appropriate and should be reconsidered. The one population group in which there is clear evidence of fracture prevention with calcium and vitamin D is the institutionalised frail elderly with a high prevalence of vitamin D deficiency. In this population, however, there is also evidence that the addition of calcium supplements to sunlight exposure increases mortality, so the balance of harm and benefit currently remains uncertain. Routine vitamin D supplementation to prevent osteomalacia is reasonable in this group.

There is little evidence that levels of dietary calcium intake are associated with risk of fracture, and so dietary calcium intake does not require close scrutiny for most people. Patients at high risk of fracture should be encouraged to take drugs with proven efficacy in preventing vertebral and non-vertebral fractures. For bisphosphonates, calcium and vitamin D do not need to be routinely co-prescribed, although patients at high risk of vitamin D deficiency should be prescribed vitamin D supplements.

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Recommendations for the widespread use of calcium supplements are no longer appropriate and should be reconsidered

SELF-TEST QUESTIONS
True or false?
1. Calcium supplementation reduces cardiovascular risk.
2. Bisphosphonates do not work without calcium supplements.

Answers on page 35
Calcium and cardiovascular risks


Book review


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Melbourne: Therapeutic Guidelines Limited; 2012. 303 pages

These guidelines aim to present a comprehensive but succinct review based on current evidence and opinion. Topics are arranged by diagnostic entities and include explicit management recommendations. I found the book well organised. The expert group of authors are well regarded and the guidelines accurately reflect the most up-to-date information available. The use of key point boxes and lists of further readings give the reader the option of how much detail they want to read. However, these features were not present in all sections.

The book has some minor shortcomings. A toxicology topic on local anaesthetics would have been useful as they are widely used particularly in primary care. A discussion on the role of magnesium in Irukandji syndrome is also warranted, despite the controversy over the evidence, as it is still commonly used in certain situations.

This latest edition covers all the key topics in the field in an easily accessible reference format while still providing enough detail to guide specific therapeutic interventions. Clinicians should find it a useful portable guide.