

Letters to the Editor

Calcium and cardiovascular risks

Editor, – The recent article on calcium and cardiovascular risks (Aust Prescr 2013;36:5-8) deserves some comment. The largest meta-analysis on the antifracture efficacy of calcium and vitamin D showed that the benefit of this combination in 68 500 participants was very significant.¹ The original Women's Health Initiative study of 36 682 postmenopausal women showed no significant increase in the risk of myocardial infarction or death due to coronary heart disease in those taking calcium and vitamin D compared to those taking the placebo.² A recent review by the National Institutes of Health on 388 229 men and women aged 50–71 years concluded that a high intake of supplemental calcium is associated with an excess risk of cardiovascular death in men but not in women.³ Another relevant paper on the use of vitamin and mineral supplements in 38 772 older women showed that calcium supplementation, unlike other mineral supplements, was associated with decreased mortality.⁴

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REFERENCES

1. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ* 2010;340:b5463.
2. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007;115:846-54.
3. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality. The National Institutes of Health–AARP diet and health study. *JAMA Intern Med* 2013 Feb 4:1-8.
4. Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med* 2011;171:1625-33.

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

Our discussion of the evidence for fracture efficacy of calcium and/or vitamin D included the DIPART meta-analysis.¹ The claim of very significant antifracture efficacy of co-administered calcium and vitamin D in this meta-analysis is not supported by even superficial scrutiny. There was an 8% relative risk reduction in total fractures with

calcium and vitamin D, with a number needed to treat of 213 to prevent one fracture over three years. For hip fractures, the relative risk reduction was 16% and the number needed to treat was 255 to prevent one hip fracture over three years. However, the hip fracture results were heavily dependent on one cluster randomised controlled trial,² the results of which are problematic to interpret. When this trial was excluded the relative risk reduction was only 3%.¹ Thus, the DIPART meta-analysis does not provide compelling evidence for the antifracture efficacy of calcium and vitamin D.

The Women's Health Initiative study permitted widespread use of non-protocol vitamin D and calcium³ which obscured both adverse cardiovascular risks and potential benefits on cancer incidence.⁴ The Women's Health Initiative investigators have now repeated our analyses on the complete dataset and have produced very similar results to ours.⁵ Given this, we do not think it is credible to claim that the original analysis provides reassurance about cardiovascular risks for patients.

Observational studies are hypothesis-generating, not hypothesis-testing. There are numerous examples of discrepant results between observational studies and randomised clinical trials, when positive benefits of drugs observed in observational studies are not observed in clinical trials. Examples include hormone replacement treatment and cardiovascular risk, vitamin D and various outcomes, and folic acid and antioxidants and cardiovascular disease and cancer. It is therefore unwise to emphasise the results of observational studies when there is a large database of randomised controlled trials that shows clear, consistent evidence of modest increases in myocardial infarction and stroke from calcium supplement use.

However, we acknowledge the correspondents' point that the recent very large National Institutes of Health-sponsored observational study from the USA⁶ as well as similar large observational studies from Europe⁷⁻⁹ report increases in cardiovascular effects in association with calcium use.

Finally, our conclusion aligns with the recent recommendation of the US Preventive Services Task Force, whose members are free from both commercial and academic conflicts of interest, that vitamin D and calcium should not be administered for primary prevention of fractures in non-institutionalised postmenopausal women.¹⁰

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

REFERENCES

1. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ* 2010;340:b5463.
2. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res* 2004;19:370-8.
3. 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.
4. Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr* 2011;94:1144-9.
5. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. *Osteoporos Int* 2013;24:567-80.
6. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality. The National Institutes of Health-AARP diet and health study. *JAMA Intern Med* 2013 Feb 4:1-8.
7. Pentti K, Tuppurainen MT, Honkanen R, Sandini L, Kroger H, Alhava E, et al. Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. *Maturitas* 2009;63:73-8.
8. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* 2012;98:920-5.
9. Michaelsson K, Melhus H, Warensjo Lemming E, Wolk A, Byberg L. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. *BMJ* 2013;346:f228.
10. Moyer VA. Vitamin D and Calcium Supplementation to Prevent Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2013 Feb 26.

Editor, - I find information in the recent article on calcium and cardiovascular risks (*Aust Prescr* 2013;36:5-8) is opposite to the current recommendation from Osteoporosis Australia,¹ especially the section on implications for practice which says 'recommendations for the widespread use of calcium supplements are no longer appropriate' and 'dietary calcium intake does not require close scrutiny for most people'.

The current Osteoporosis Australia guidelines recommend that calcium intake for adults is 1000 mg/day. This increases to 1300 mg/day for women over 50 and men over 70. For people who do not obtain adequate calcium through their diet, a supplement of 500-600 mg may be required. There is no additional benefit of calcium intake being higher than recommended levels.

Should Osteoporosis Australia, Therapeutic Guidelines and the Australian Medicines Handbook update their recommendations for osteoporosis prevention and treatment?

Tina Nguyen
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REFERENCE

1. Ebeling PR, Daly RM, Kerr DA, Kimlin MG. An evidence-informed strategy to prevent osteoporosis in Australia. *Med J Aust* 2013;198:90-1.

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:



We think that our article accurately summarises evidence from existing randomised controlled trials. In a recent meta-analysis of the effect of calcium supplements on fractures (with or without vitamin D),¹ 15 of the 16 studies with fracture as an endpoint administered at least 750 mg/day of calcium supplement, and the total calcium intake from diet and supplements ranged from 1230 to 2300 mg/day. Thus, the beneficial skeletal effects of calcium have only been demonstrated in trials evaluating the same doses of calcium that also increase risk of myocardial infarction. There is no robust evidence that calcium supplements in doses less than 1000 mg/day prevent fractures.

We agree that the role of calcium in osteoporosis management should be reconsidered by individual healthcare practitioners as well as organisations issuing guidelines on osteoporosis management.

REFERENCE

1. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007;370:657-66.

Editor, - I am writing to you on behalf of the Osteoporosis Australia Medical and Scientific Advisory Committee about the recent *Australian Prescriber* article (*Aust Prescr* 2013;36:5-8) strongly calling for the use of calcium supplementation to be reconsidered, under the heading 'Implications for practice'. This is one side of a highly debated issue and a view that is predominantly expounded by one New Zealand group of academics. It is certainly not the consensus amongst Australian experts. Furthermore, the publication of such an unbalanced article, with such a strong conclusion, is both misleading and potentially very confusing both to your readers and the general public.

Members of the Osteoporosis Australia Medical and Scientific Advisory Committee have reviewed all of the published literature on this topic, including the studies referred to in the article. While we acknowledge this is an area of ongoing research and debate, we do not believe the evidence is conclusive enough to make such strong recommendations.

Our current position statement on calcium supplementation remains unchanged. This recommends a total daily intake of 1000 mg to 1300 mg of calcium per day (recommended dietary intake or RDI), depending on age and sex. Ideally, the RDI should be achieved by consuming a diet rich in calcium. When the RDI cannot be achieved through diet alone, supplements may be required. In these circumstances, Osteoporosis Australia recommends a supplement of 500–600 mg of calcium.¹

A recently published extensive evidence-informed review of calcium, vitamin D and exercise to optimise bone health throughout life has similar conclusions.²

Instead of adding clarity, printing articles such as this creates confusion. We are disappointed that *Australian Prescriber* elected to publish this story without a broader review of the published literature and without seeking input from expert organisations, including Osteoporosis Australia.

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Osteoporosis Australia receives limited funding from Pfizer Consumer Healthcare and Swisse, both of which are manufacturers of calcium supplements.

REFERENCES

1. Osteoporosis Australia. Statement on calcium supplements. 2012 June. www.osteoporosis.org.au/images/stories/calcium_statement062012.pdf [cited 2013 May 3]
2. Ebeling PR, Daly RM, Kerr DA, Kimlin MG. An evidence-informed strategy to prevent osteoporosis in Australia. *Med J Aust* 2013;198:90-1.

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

 The claim that the view that the role of calcium supplementation should be reconsidered is only held by one New Zealand group is incorrect. Several publications in international medical journals written by authors from various countries, including Australia, reached similar conclusions.¹⁻⁶ Most recently, the US Preventive Services Task Force, whose members are free from both commercial and academic conflicts of interest, concluded that vitamin D and

calcium should not be administered for primary prevention of fractures in non-institutionalised postmenopausal women.⁷

We are surprised that our article is described as unbalanced as we reviewed the best available evidence on the efficacy and safety of calcium supplements. Six large randomised controlled trials with fracture as the primary endpoint have been undertaken. Their results have been incorporated into systematic reviews of the efficacy and safety of calcium supplements that include both trial-level and patient-level meta-analyses. The results of all these analyses were discussed in our article. The evidence is clear – calcium supplements reduce total fractures slightly, do not prevent hip fractures in community-dwelling individuals, and increase cardiovascular events. Within this large clinical trial dataset, the cardiovascular risks of calcium supplements outweigh the skeletal benefits.^{8,9}

The position statement of Osteoporosis Australia is not supported by the available evidence. There is substantial overlap in authorship of the position statement and the ‘white paper’ cited by Professor Ebeling, which explains the similar conclusions. In a recent meta-analysis of the effect of calcium supplements with or without vitamin D on fractures,¹⁰ 15 of the 16 studies with fracture as an endpoint gave at least 750 mg/day of calcium supplements, and the total calcium intake from diet and supplements ranged from 1230 to 2300 mg/day, well above the levels recommended by Osteoporosis Australia. There is no robust evidence that calcium supplements in doses less than 1000 mg/day or that increasing dietary calcium intake to 1000–1300 mg/day prevents fractures. In fact, observational studies of dietary calcium intake fail to generate a hypothesis of skeletal benefit from achieving dietary calcium intakes at the level recommended by Osteoporosis Australia.^{11,12}

REFERENCES

1. Jones G, Winzenberg T. Cardiovascular risks of calcium supplements in women. *BMJ* 2008;336:226-7.
2. Cleland JG, Witte K, Steel S. Calcium supplements in people with osteoporosis. *BMJ* 2010;341:c3856.
3. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* 2012;98:920-5.
4. Michaelsson K, Melhus H, Warensjo Lemming E, Wolk A, Byberg L. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. *BMJ* 2013;346:f228.
5. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality. The National Institutes of Health–AARP diet and health study. *JAMA Intern Med* 2013 Feb 4:1-8.

6. Larsson SC. Are calcium supplements harmful to cardiovascular disease?: Comment on "Dietary and Supplemental Calcium Intake and Cardiovascular Diseases Mortality: The National Institutes of Health-AARP Diet and Health Study". *JAMA Intern Med* 2013;173:647-8.
7. Moyer VA. Vitamin D and Calcium Supplementation to Prevent Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2013 Feb 26.
8. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691.
9. 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.
10. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007;370:657-66.
11. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* 2007;86:1780-90.
12. Anderson JJ, Roggenkamp KJ, Suchindran CM. Calcium intakes and femoral and lumbar bone density of elderly U.S. men and women: National Health and Nutrition Examination Survey 2005-2006 analysis. *J Clin Endocrinol Metab* 2012;97:4531-9.

Editor, – I read the article on calcium supplements (*Aust Prescr* 2013;36:5-8). Nowhere did it mention the form of calcium that was studied. My understanding is that calcium carbonate is the dangerous form with respect to heart attacks and strokes, but that other forms such as calcium citrate are not.

Sylvia Hicks
Clinical manager
Older Persons Mental Health Community Team
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Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

 There is no evidence that cardiovascular risks differ substantially between calcium supplement types. In our patient-level meta-analysis of calcium monotherapy, there was no relationship between the risk of myocardial infarction with calcium and supplement type (calcium carbonate: hazard ratio 1.24, calcium citrate:hazard ratio 1.60, $p=0.4$ for difference in risk between supplement types).^{1,2} There was also no relationship between the risk of stroke with calcium and supplement type ($p=0.5$).¹

REFERENCES

1. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691.
2. Reid IR, Bolland MJ, Avenell A, Grey A. Cardiovascular effects of calcium supplementation. *Osteoporos Int* 2011;22:1649-58.

Editor, – I have read the article on calcium and cardiovascular risk (*Aust Prescr* 2013;36:5-8) and I was puzzled by the paragraph about the re-analysis of data on users and non-users of personal calcium (page 6).

If I am interpreting the statement correctly, there was a cardiovascular protective effect when calcium was being taken before being allocated to add calcium and vitamin D, compared to when they were not taking calcium beforehand.

This seems to contradict the article's conclusion that calcium supplements increase cardiovascular risk, as the opposite might be expected if they were already on calcium.

Robert Gates
Consultant physician
Sydney

Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

 We disagree with this interpretation. In women not using their own calcium supplements, co-administered calcium and vitamin D increased cardiovascular risk. In women already using their own calcium, taking additional calcium supplements did not further increase cardiovascular risk. In this latter subgroup, participants in both treatment groups were taking calcium, thus inferences about whether calcium supplements might alter cardiovascular risk (compared to not taking calcium) cannot be drawn. The findings do suggest that there is no dose-response relationship with calcium supplements and cardiovascular risk at doses used in current practice. Women taking lower doses of calcium supplements thus have a similar cardiovascular risk to those taking higher doses, and this risk is elevated compared to women not taking calcium supplements.

Editor, – What happens to institutionalised elderly women once vitamin D levels are replete? Are they now at increased cardiovascular risk if vitamin D and calcium are continued?

Can this statement be applied to elderly frail men?

Mark Raines
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Mark Bolland, Andrew Grey and Ian Reid, the authors of the article, comment:

 Current trial data do not suggest there are important differences in cardiovascular risk between the use of co-administered calcium and

vitamin D and the use of calcium monotherapy.¹ Although two trials of frail, institutionalised elderly women prescribed calcium and vitamin D reported reductions in fracture risk,^{2,3} cardiovascular event data were not reported. The balance of risk and benefit from calcium and vitamin D in these studies cannot be established. However, a more recent Australian trial in elderly nursing home residents reported that adding calcium to sunlight exposure increased cardiovascular risk,^{4,5} suggesting that the balance between risk and benefit may be unfavourable.

We think that elderly frail men and women at high risk of marked vitamin D deficiency should be treated with vitamin D supplements or sunlight exposure to prevent osteomalacia. They should also be assessed for fracture risk. If it is high, appropriate treatment to prevent fractures should be considered.

REFERENCES

1. 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.
2. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;327:1637-42.
3. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalys II study. *Osteoporos Int* 2002;13:257-64.
4. Reid IR, Bolland MJ, Sambrook PN, Grey A. Calcium supplementation: balancing the cardiovascular risks. *Maturitas* 2011;69:289-95.
5. Sambrook PN, Cameron ID, Chen JS, Cumming RG, Durvasula S, Herrmann M, et al. Does increased sunlight exposure work as a strategy to improve vitamin D status in the elderly: a cluster randomised controlled trial. *Osteoporos Int* 2012;23:615-24.

Drug treatment of acne

Editor, – In the article on drug treatment of acne (*Aust Prescr* 2012;35:180-2), Dr Jo-Ann See has omitted the important role of azithromycin in treatment of acne. In cases of severe inflammatory and papulopustular acne, azithromycin pulses (for example three days every week for up to 8-12 weeks) with or without systemic isotretinoin have been found to be safe, well tolerated, effective and promote patient compliance.^{1,2} In fact, in a randomised study, pulsed azithromycin treatment for acne vulgaris was as effective and safe as daily doxycycline for two weeks.³ Tetracyclines (including doxycycline and minocyclin) cannot be combined with isotretinoin because of the risk of the shared adverse effect of raised intracranial tension. This is

not the case with macrolides, and early in therapy, when isotretinoin may cause an initial flare in some patients, concomitant azithromycin can be safely used.

Secondly, it should be emphasised that a patient who is taking oral isotretinoin should not donate blood during and for up to one month after completion of therapy, as the blood may be transfused to a female of child-bearing age.

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REFERENCES

1. Antonio JR, Pegas JR, Cestari TF, Do Nascimento LV. Azithromycin pulses in the treatment of inflammatory and pustular acne: efficacy, tolerability and safety. *J Dermatolog Treat* 2008;19:210-5.
2. De D, Kanwar AJ. Combination of low-dose isotretinoin and pulsed oral azithromycin in the management of moderate to severe acne: a preliminary open-label, prospective, non-comparative, single-centre study. *Clin Drug Investig* 2011;31:599-604.
3. Maleszka R, Turek-Urasinska K, Oremus M, Vukovic J, Barsic B. Pulsed azithromycin treatment is as effective and safe as 2-week-longer daily doxycycline treatment of acne vulgaris: a randomized, double-blind, noninferiority study. *Skinmed* 2011;9:86-94.

Jo-Ann See, author of the article, comments:

 Many thanks for your interest in the article on drug treatment of acne. The aim was to outline a 'first-line' approach for acne treatment in Australian general practice. Azithromycin is not commonly used for acne in Australia and the intermittent dosing, while effective, may be questioned from an adherence point of view. There have also been recent safety concerns about azithromycin and arrhythmia. The combination of azithromycin with oral isotretinoin was outside the scope of the article. GPs do not prescribe oral isotretinoin, so the discussion of it was aimed at supporting GPs who may have patients they are considering for specialist referral or patients taking isotretinoin who they co-manage with a dermatologist.

As every medicine has potential adverse effects, I have not written about the plethora of potential interactions or concerns that oral isotretinoin may have, including blood donation. It is routine practice for the Australian Red Cross to interview potential blood donors. Donors are also given a questionnaire about medicines taken in the previous 12 months. This would identify any potential risks regarding blood transfusion.