Following the publication of an article by Mark Bolland and co-workers\(^1\) in the British Medical Journal of 29 July 2010, on the association between calcium supplementation for osteoporosis and an increased risk of myocardial infarction, much concern and confusion exist among patients and doctors alike as to the safety and efficacy of these agents.

**Is there an association between osteoporosis and cardiovascular disease (CVD)?**

An association between osteoporosis and CVD is well established and numerous studies have demonstrated that CVD and cardiovascular mortality are associated with reduced bone mineral density (BMD) and/or skeletal fractures.\(^2-4\) These two conditions may be sustained by similar pathophysiological mechanisms (e.g. age-related hypogonadism; proinflammatory cytokines like IL-1, TNF-\(\alpha\); alterations in the RANKL/osteo protegerin system which is present in both vascular and skeletal tissue) and risk factors (e.g. ageing, smoking, sedentary lifestyle), and may even be amenable to common therapeutic approaches (e.g. bisphosphonates, statins, vitamin D).

Postmenopausal women with osteoporosis have a 3.9-fold higher risk of CVD than women with osteopenia or a normal BMD.\(^4\) Each one standard deviation (SD) decrease in BMD is associated with a 70% increase in stroke risk.\(^5\) The severity of aortic calcification is a good predictor of both hip fracture and myocardial infarction.\(^6\) These associations are well documented in postmenopausal women, but have also recently been demonstrated in men, where a strong correlation between increased bone resorption and CVD was also found.\(^7\) Subjects with osteoporosis may thus benefit from screening for cardiovascular disease. Moreover, treatment of osteoporosis with potent bisphosphonates like zoledronic acid has been shown to reduce overall mortality by 25–30%. A decrease in fracture incidence accounted for less than 10% of the reduction in overall mortality, which largely resulted from a reduction in CVD.\(^8\)

**What was known about the efficacy and safety of calcium supplementation in osteoporosis prior to the Bolland article?**

The effects of calcium with or without vitamin D supplementation on peak bone mass attainment, age-related bone loss and fracture risk remain uncertain. The influence of calcium supplementation on the largely genetically determined peak bone mass is modest at best, and appears to vary depending on the dose, baseline calcium intake, skeletal sites examined, pubertal maturation and genetic factors.\(^9-12\) Calcium deficiency has a more pronounced effect on age-related bone loss, and intervention later in life appears to be more beneficial, but again the data are not robust.\(^13-17\) What about the role of calcium in reducing the risk of fracture? Earlier studies showed that calcium and vitamin D supplementation significantly reduced the risk of fracture, and meta-analyses in 1997\(^18\) and in 2005\(^19\) suggested that supplementation with 1 g of calcium plus vitamin D 800 IU per day, was associated with a 20–25% reduction in hip fracture. A number of recent publications have, however, challenged the anti-fracture efficacy of calcium and vitamin D.\(^20-22\)

Although many of these studies did not target individuals at high fracture risk, often employed an inadequate dose of vitamin D (≤ 400 IU per day) and/or did not take cognisance of the poor compliance with calcium supplementation, the role of calcium in fracture prevention would appear to be modest. Calcium has, however, been a mandatory component of every drug trial using potent antifracture medicines (e.g. the bisphosphonates or strontium ranelate) and is thought to have an additive effect when used in combination with these drugs.\(^23,24\) These studies employing...
antifracture drugs plus calcium have generally been associated with a significant reduction in all-cause mortality, not infrequently with a significant reduction in cardiovascular mortality.\(^1\)

Although the antifracture efficacy of calcium may be uncertain, calcium supplementation has generally been regarded as safe. An adequate dietary calcium intake is associated with a significantly lower incidence of CVD and stroke.\(^2,5\)–\(^7\) Calcium supplements have been shown to reduce risk factors for CVD like hypertension and dyslipidaemia.\(^8\)\(^\text{–}\)\(^11\) To date, calcium supplementation has been regarded as safe, although it is known to increase arterial calcification and mortality in subjects with renal failure.\(^12\)\(^,\)\(^13\) The large Women’s Health Initiative (WHI) (27 000 subjects) showed that individuals taking calcium and a low dose Vitamin D supplement tended to have a lower mortality.\(^13\)\(^,\)\(^15\) and no adverse effects on cardiovascular health.\(^24\)

The Bolland articles

In 2008, Bolland and co-workers published the results of their randomised controlled trial (RCT) on vascular events in healthy elderly women receiving calcium supplements, which showed a non-significant trend towards a higher incidence of CVD in those subjects receiving calcium.\(^26\) This was followed up in 2010 by a meta-analysis of 15 RCTs involving some 12 000 subjects taking calcium supplements for osteoporosis.\(^1\) Of note is the fact that trials involving additional vitamin D supplementation were excluded from the study. Compared with placebo, patients taking calcium supplements had a modest (27%), but significant increase in myocardial infarction. None of the individual RCTs from which this meta-analysis was compiled, reported any significant cardiovascular effects. No significant increase in mortality or incidence of stroke was reported in this study.

The current study selected RCTs with an exceptionally high dose of supplemental calcium, the average dose being 1 200 mg/day, with some studies employing 1 500–2 000 mg/day. Furthermore, the dietary calcium intake in these subjects was above average (900 mg/day) and a positive correlation was found between the proposed increase in cardiovascular disease (CVD) and the dietary intake of calcium. In fact, the increase in CVD was entirely limited to those with a dietary calcium intake of more than 800 mg/day – no increased risk being found in subjects with a dietary calcium intake below 800 mg/day.

National Osteoporosis Foundation of South Africa (NOFSA) recommendations

The Bolland meta-analysis clearly differs from previous epidemiologic studies which documented a 30–40% lower risk of CVD and ischaemic stroke in subjects in the top quartile of calcium intake.\(^25\)\(^\text{–}\)\(^27\) Whether this reflects a fundamental difference in the source (dietary vs. supplements) or total dose of calcium remains unclear. The Bolland paper also differs from previous intervention studies, including the WHI, which showed that individuals taking calcium and a low dose Vitamin D supplement tended to have a lower mortality,\(^29\)\(^,\)\(^30\) and no adverse effects on cardiovascular health.\(^24\) Again it is unclear whether this is a function of the supplemental vitamin D which was included in studies like the WHI and specifically excluded in the Bolland meta-analysis.

Clearly more information is necessary before robust evidence-based recommendations can be made. In the interim, NOFSA would recommend the following:

- An adequate calcium intake is important for normal bone health. This should preferably be accomplished by consuming sufficient dairy (low fat) products in the diet.
- Calcium supplementation is, however, often required and in a dose of 500 mg/day is acceptable and safe.
- Such calcium supplementation, especially when it accompanies vitamin D and/or one of the potent bone-active drugs for the management of osteoporosis, should be continued since there is no evidence that it increases the risk of CVD.
- High-dose calcium supplementation in patients already consuming ample dairy, and especially in those with known kidney failure or CVD, is unnecessary and should be avoided.

References

1. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: a meta-analysis. Br Med J 2010;341:c3691.
2. Samelson EJ, Kiel DP, Broe KE, et al. Metacarpal cortical area and risk of coronary heart disease. The Framingham Study. Am J Epidemiol 2004;159:589–595.
3. Magnus JH, Broussard DL. Relationship between bone mineral density and myocardial infarction in US adults. Osteoporos Int 2005;16:2053–2062.
4. Tankó LB, Christiansen C, Cox DA, et al. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J Bone Miner Res 2005;20:1912–1920.
5. Mussolini ME, Madans JH, Gilum RF. Bone mineral density and stroke. Stroke 2003;34:e20–e22.
6. Schulz E, Arhai K, Liu X, et al. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab 2004;89:4246–4253.
7. Szulc P, Samelson EJ, Kiel DP, Delmas PD. Increased bone resorption in association with increased risk of cardiovascular events in men: The MINOS Study. J Bone Miner Res 2009;12:2023–2031.
8. Lytes KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical features and mortality after hip fracture. N Engl J Med 2007;357:1–11.
9. Johnston CC, Miller JZ, Stelmenda CW, et al. Calcium supplementation and increases in bone mineral density in children. N Engl J Med 1992;327:82–87.
10. Lloyd T, Andon MB, Rolings N, et al. Calcium supplementation and bone mineral density in adolescent girls. JAMA 1993;270:841–844.
11. Chevalley T, Bonjour JP, Ferrari S, et al. Skeletal site selectivity in the effects of...
calcium supplementation on areal bone mineral density gain: a randomized, double-blind, placebo-controlled trial in prepubertal boys. J Clin Endocrinol Metab 2005;90:3342–3349.

12. Winzenberg T, Shaw K, Fryer J, et al. Effects of calcium supplementation on bone density in healthy children: a meta-analysis of randomized controlled trials. Br Med J 2006;333:1415–1423.

13. Heaney RG. Thinking straight about calcium. N Engl J Med 1993;328:503–504.

14. Reid IR, Ames RW, Evans MC, et al. Effect of calcium supplementation on bone loss in postmenopausal women. N Eng J Med 1993;328:460–464.

15. Dawson-Hughes B, Dallal GE, Krall EA, et al. A controlled trial on the effect of calcium supplementation on bone density in postmenopausal women. N Eng J Med 1990;323:878–883.

16. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Eng J Med 1997;337:670–676.

17. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Eng J Med 1992;327:1637–1642.

18. Cumming RG, Nevitt MC. Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res 1997;12:1321–1329.

19. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation. JAMA 2005;293(2):2257–2264.

20. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol(vitamin D3) for prevention in primary care. Br Med J 2005;330:1003.

21. Reid IR, Mason B, Horne A, et al. Randomised controlled trial of calcium in healthy older women. Am J Med 2006;119:775–785.

22. Grant AM, Avenell A, Campbell MK, et al. Randomised evaluation of calcium or vitamin D (RECORD): a randomised placebo-controlled trial. Lancet 2005;365:1621–1628.

23. Prince R, Smith M, Dick I, et al. Preventing postmenopausal osteoporosis: a comparative study of exercise, calcium supplementation and hormone replacement therapy. N Eng J Med 1991;325:1189–1195.

24. Nieves JM, Komar L, Cosman F, Lindsay R. Calcium potentiates the effect of estrogen and calcitonin on bone mass: review and analysis. Am J Clin Nutr 1998;67:18–24.

25. Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. Lancet 1973;1:1465–1467.

26. Iso H, Stampfer MJ, Manson JE, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke 1999;30:1772–1779.

27. Bostick RM, Kushin LH, Wu Y, et al. Relation of calcium, vitamin D, and daily food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 1999;149:151–161.

28. Pitz S, Tomaschitz A, Ritz E, Pieber TR. Vitamin D status and arterial hypertension: a systematic review. Nat.Rev.Cardiol. 2009 Oct;6(10):621–630.

29. Hofmeyr GJ, Lawrie TA, Atalah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst.Rev. 2010;8:CD001059.

30. Reid IR, Ames R, Mason B, et al. Effects of calcium supplementation on lipids, blood pressure, and body composition in healthy older men: a randomized controlled trial. Am J Clin Nutr. 2010;91:131–139.

31. West SL, Swan VJ, Jamal SA. Effects of calcium on cardiovascular events in patients with kidney disease and in a healthy population. Clin J Am Soc Nephrol. 2010;5 Suppl 1:S41–7.

32. Block GA, Raggi P, Bellasi A, et al. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007;71:438–441.

33. LaCroix AZ, Kocez J, Anderson G, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women’s Health Initiative calcium-vitamin D randomized controlled trial. J Gerontol.Biol.Sci.Med.Sci. 2009;64:559–567.

34. Manson JE, Allison MA, Carr JJ, et al. Women’s Health Initiative and Women’s Health Initiative-Coronary Artery Calcium Study Investigators. Calcium/vitamin D supplementation and coronary artery calcification in the Women’s Health Initiative. Menopause 2010;17:683–691.

35. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. Br Med J 2008;336:262–266.