EDITORIAL

Do calcium supplements raise cardiovascular risk?

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CALCIUM SUPPLEMENTS ARE ROUTINELY USED BY PATIENTS EITHER AT RISK OF, OR WITH ESTABLISHED, osteoporosis and many of these are elderly women who may also be at high risk of cardiovascular disease.

Bolland and colleagues published a meta-analysis in the *BMJ* last year which showed that calcium supplements, without co-administered vitamin D, were associated with a raised risk of MI.[1] Although this risk was small, given the widespread use of calcium supplements it was considered important. The proposed mechanism was the long-term accumulation of calcium in vessel walls and a more immediate effect of calcium on platelet function, blood coagulability and endothelial cell activity.

These researchers have now extended their original meta-analysis to look at the effects of the personal use of calcium supplements on cardiovascular (CV) risk and include calcium supplements given with vitamin D.[2] They included a re-analysis of the Women's Health Initiative Calcium/Vitamin D Supplementation (WHI CaD) Study which was a seven-year randomised, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36,282 post-menopausal women.

'Be cautious in using calcium and vitamin D in high risk CV patients until more evidence is available'

The WHI CaD trial originally reported no increase in CV risk with calcium and vitamin D supplementation. However, no allowance was made for the fact that some of the participants were taking calcium supplements outside the trial protocol. These patients have been excluded in the re-analysis. This new WHI CaD dataset was analysed along with an additional two randomised trials and the authors' original meta-analysis. The primary outcome measures were the incidence of MI, coronary revascularisation, death from CHD, stroke and combinations of these events.

In the WHI CaD trial an interaction was found between personal use of calcium supplements and allocated calcium and vitamin D for CV events. In 16,718 women not taking personal calcium supplements at randomisation the hazard ratios for CV events with calcium and vitamin D ranged from 1.13 (95% CI: 0.99-1.29, p=0.07) for total MI, CHD death or revascularisation to 1.22 (95% CI: 1.00-1.50, p=0.05) for clinical MI. In women taking personal calcium supplements CV risk did not change with allocation to calcium and vitamin D as seen in the original WHI CaD analysis.

In meta-analyses of placebo controlled trials of calcium or calcium and vitamin D, there were complete trial-level data for 28,072 patients from eight trials of calcium supplements and the WHI CaD participants who were not taking personal calcium supplements. A total of 1,384 individuals had an MI or stroke. Calcium or calcium and vitamin D raised the risk of MI, relative risk (RR) 1.24 (95% CI: 1.07-1.45, p=0.004) and the composite of MI or stroke, RR 1.15 (95% CI: 1.03-1.27, p=0.009).

The authors conclude that calcium supplements with or without vitamin D modestly increase the risk of CV events, particularly MI, and call for a reassessment of the role of calcium supplements in osteoporosis.

However, there are limitations to this study. The original WHI CaD trial was randomised and each arm of the study adjusted for confounding factors. By removing patients who personally supplemented with calcium and vitamin D the re-analysis would have lost this adjustment and cannot be considered to be truly randomised. This may account for the findings. Also, the WHI and other studies included were not designed for CV outcomes and other trials have supported the role of calcium and vitamin D as an adjunct to bisphosphonates in osteoporosis in terms of CV safety and all cause mortality.[3-7]

The jury is still out on calcium and vitamin D supplements and CV risk. On the current evidence we cannot be sure if there is a risk or not. However, in practical terms I think we should probably be cautious in using calcium and vitamin D in high-risk CV patients until more evidence is available.

REFERENCES
1 Bolland MJ, Avenell A, Baron JA et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691
2 Bolland MJ, Grey A, Avenell A et al. 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
3 Camm JA. Review of the cardiovascular safety of zoledronic acid and other bisphosphonates for the treatment of osteoporosis. *Clin Ther* 2010;32:426-36
4 Christensen S, Mehnert F, Chapurlat RD et al. Oral bisphosphonates and risk of ischaemic stroke: a case-control study. *Osteoporos Int* 2010; online 13 October
5 Center JR, Bliuc D, Nguyen ND et al. Osteoporosis medication and reduced mortality risk in elderly women and men. *J Clin Endocrinol* Metab 2011; online 2 February
6 Nurmi-Lüthje I, Sund R, Juntunen M et al. Post-hip fracture use of prescribed calcium plus vitamin D or vitamin D supplements and anti-osteoporotic drugs are associated with lower mortality. A nationwide study in Finland. *J Bone Miner Res* 2011; online 23 February
7 Bolland MJ, Grey AB, Gamble GD et al. Effect of osteoporosis treatment on mortality: a meta-analysis. *J Clin Endocrinol Metab* 2010;95:1174-81