"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"

Clinical Case: 65-year-old female with a history of hypertension, BMI 25, and hypothyroidism presents for health maintenance examination. Her only prescription medications are HCTZ 25 mg daily and levothyroxine 75 mcg daily. She feels well and BP is well-controlled. You are updating her health maintenance and are discussing her recent DEXA scan. Her T scores show -1.9 on lumbar spine and -2.5 in left femur and you plan to start a bisphosphonate for osteoporosis. She has already been taking 1,000 mg daily of calcium plus 600 IU of Vit D daily. However, she heard a story on the news about increased cardiovascular events associated with calcium, and wonders if it is safe to continue.

Search strategy:
PubMed "calcium supplementation" with limits to articles in English pertaining to women. Found under “free full text articles in Pub Med Central.”
Article cited in an UptoDate article on calcium supplementation.

Description of Study
Type of question asked: therapeutic
Study method: meta-analysis
This was a re-analysis of WHI CaD, followed by incorporation of subset of the study population with a previous meta-analysis by BMJ

Research Question (PICO)
Does calcium with or without vitamin D increase the risk of cardiovascular disease in post-menopausal women?

Importance/Relevance of Question:
Calcium supplements are recommended and used by many for the prevention and treatment of osteoporosis, as there is a high mortality of hip fractures in elderly women. Previous studies of calcium supplementation without Vit D have shown increased risk of MI. However, the WHI study reported NO adverse effect of Ca with vitamin D. Aside from study subjects being randomized to control vs placebo groups, 54% of women were taking their own additional supplements. Thus, a dose-dependent effect was not analyzed. Giving patients free access to the intervention studied could have potentially obscured both adverse and beneficial effects. Therefore, the study focused on the subgroup of patients who were not taking their own calcium supplements, and then were assigned to calcium and D vs placebo to obtain a more pure analysis of effects of the treatment. These results were then combined with a previous meta-analysis.

Methods:
Population:
WHI: 36,282 community dwelling postmenopausal women (see Table 1)
Previous meta-analysis: 11 studies, all with at least 100 patients over age 40 (average age 69) 88% were female
Intervention/Control
WHI: any personal use of calcium allocated to CaD or placebo VS. no use of calcium allocated to CaD or placebo
Previous meta-analysis: ca citrate or ca carbonate at least >500 mg/day vs placebo
Outcome Studied
WHI:
total deaths from clinical MI or CHD
clinical MI or coronary revascularization (PCI, CABG)
clinical MI or stroke
total MI (includes silent MIs), coronary revascularization and death from CAD (representing all CHD events)
Previous meta-analysis: MI, stroke or sudden death

Validity
Did experimental and control groups start out with a similar prognosis? It seemed like some of the women in the group NOT using supplements at baseline had more risk factors for MI and cardiovascular disease
Since this is a meta-analysis, no details of randomization or blindness to study groups.
Primary Results
1. WHI CaD
   Table 2: Effect of Ca and D on CV events grouped by personal use at randomization
   Hazard ratios for women not taking personal calcium at baseline
   1.16 for clinical MI or coronary revascularizations
   1.16 for clinical MI or stroke
   1.22 for clinical MI
   1.13-1.20 for other CV endpoints
   Hazard ratios for women taking personal calcium supplements at baseline
   0.83 - 1.08
   Figure 1: No dose-dependent effects significantly changed the hazard ratios
2. Calcium and vitamin D vs placebo
   Figure 2: Effect of Ca and vitamin D on cardiovascular events
   Relative risks
   1.21 for MI
   1.20 for stroke
   1.16 MI or stroke composite
3. Calcium with or without vitamin D vs placebo
   Figure 3 (patient level data from meta-analysis): Effect of calcium supplements with or without vitamin D
   on CV events
   Hazard ratios
   1.26 for risk of MI
   1.19 for risk of stroke
   1.17 for composite endpoint of MI or stroke
   NNT with Ca and vitamin D for 5 years to cause 1 incident event
   240 for MI
   238 for stroke
   178 for composite of MI or stroke
   NNT to prevent 1 fracture
   302
   Figure 4 (trial level data): Effect of calcium supplements with or without vitamin D on cardiovascular
   events
   Relative risk
   1.24 for MI
   1.15 for MI or stroke

When data from WHI are pooled with previous trials of Ca and D there are consistent increases in stroke and MI, similar to that seen with calcium supplementation alone; there also did not seem to be a dose-dependent relationship. Size of risk: 25-30% for MI, 15-20% for stroke. Restricting the analysis to women who had not been taking Ca and D at baseline allowed for purer analysis of effects of these medications on CV outcomes. Notion that abrupt change in plasma calcium may cause adverse effects rather than total load ingested.

Used a limited dataset of WHI. Patients in WHI trial had free access to the intervention studied. Women using personal calcium seemed to differ from women not using calcium in ways that might change CV outcomes. Study only used WHI patients not using Ca and D at baseline so was biased toward this outcome. The WHI has a 75-80% weight in meta-analysis of Ca and D; 45-55% weight in comparison of Ca with or without D.

Can these results be applied to my patients? Important to assess this on an individual basis. In women already taking these, probably safe to continue. If patient's cardiovascular risk is high it may be safer to stress dietary calcium over supplementation.

Resolve the case or question
I would reassure the patient that given her few risk factors for cardiovascular disease and osteoporosis on DEXA she would benefit from calcium and vitamin D.