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Evidence Updated: Systematic review added
Bottom Line: Unchanged
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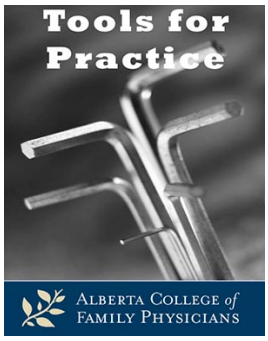

Does calcium supplementation increase the risk of MI?

Clinical Question: Do calcium supplements increase risk of myocardial infarction (MI) and other cardiovascular disease (CVD)?

Bottom-Line: Evidence suggests that calcium supplementation might slightly increase the risk of MI and perhaps other CVD. Although there are limitations to the evidence and the increased CVD risk is likely <1%, the benefit-to-harm ratio might not favour calcium supplementation.

Evidence:

- Five recent systematic reviews had differing conclusions:
  - The first reviewed 15 Randomized Controlled Trials (RCTs) comparing calcium supplementation (≥500 mg/day) vs. placebo.[1]
    - Only one CVD outcome reached statistical significance:
      - Calcium increased MI risk, Relative Risk 1.27 (1.01-1.59).
      - Absolute risk was <1% and Number Needed to Harm (NNH) for one MI was 135 to 211 over four years.
  - Another examined 17 studies comparing vitamin D, calcium, or both vs. placebo:[2]
    - No comparisons reached statistical significance.
    - More than 99% of data for calcium and vitamin D vs. placebo were from the Women's Health Initiative (WHI),[3] and 54% of participants were taking extra calcium.[4]
  - A subgroup (similar to per-protocol) analysis of WHI data[5] excluding those taking extra calcium found borderline significant increases in hazard ratios for MI [1.22 (1.00-1.50)] and MI or Stroke [1.16 (1.00-1.35)].
    - Updating the previous meta-analysis[1] with this data, calcium (with or without vitamin D) significantly increased:[5]
      - MI NNH=240 over five years, p=0.004 and,
      - MI or stroke NNH=178 over five years, p=0.009.

- A systematic review on a variety of calcium-related topics concluded there is no interaction between calcium and CVD risk.[6]
- The newest systematic review of 11 RCTs (50,252 participants):[7]
  - Trends toward harm in odds ratios:
    - CVD [1.16 (0.97-1.68)],
    - MI [1.28 (0.97-1.68)],
    - Stroke [1.14 (0.90-1.46)].
- Limitations: Over-interpretation of data (including calculating NNH for non-statistically significant outcomes),[1] excluded relevant studies,[2,7] small sample size,[2] no analysis of different outcomes,[2] large number of comparisons,[5] sub-group analyses, [5] possible conflict of interest,[5] absolute numbers not reported.[7]

Context:

- No RCT of calcium supplementation was designed to assess CVD outcomes.[1,2]
  - These meta-analyses[1-3,7] represent post-hoc analyses of secondary or unplanned outcomes, possibly inadequately reported.[8]
- Trials of vitamin D alone do not suggest CVD harm.[9]
- Calcium (88% with vitamin D) reduces fracture (any type), Number Needed to Treat of 63 over 3.5 years.[10]
  - Calcium alone just failed to reach statistical significance.
  - Other studies suggest calcium alone does not reduce non-vertebral fracture and might increase hip fracture.[11,12]

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