ADA Evidence Analysis Worksheet

Date of review	11/7/11
Reviewer	Dana Kent

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Complete Reference: Bollard M., Grey A., Gamble., Reid I. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011. 342 pgs 1-9. http://www.ncbi.nlm.nih.gov/pmc/articles /PMC3079822/pdf/bmj.d2040.pdf

Design Type: Meta Analysis

Class: M

Purpose/Population Studied/Practice Studied

Purpose: To evaluate 8 randomized placebo controlled trials to see if calcium supplementation with and without supplementation of vitamin D would increase the risk for cardiovascular disease.

Inclusion Criteria: Postmenopausal women involved in one of the eight placebo controlled trials.

Exclusion Criteria: Myocardial infarction, coronary revascularization, death from coronary heart disease and stroke.

Study Protocol

Recruitment: Analysis of Women's Health Initiative (WHI) CaD Study of 36, 282 community dwelling postmenopausal women and two additional studies.

Design: Meta-analysis

Blinding used: not mentioned

Intervention: Analyzed data from women not taking personal use of calcium supplements in the WHI study, compared group taking calcium with vitamin D and without Vitamin D, along with two unpublished studies that compared co administered calcium and vitamin D with placebo. The study looked at interactions between pre-specified subgroups based on use, no use, or any use and dose of 0, 1-499, 500-999, >1000 mg/day. Of personal calcium supplements at randomizations for cardiovascular events.

Statistical Analysis: Cox proportional hazards models by age, cardiovascular disease risk at baseline, and randomization status in the WHI Postmenopausal Hormone Therapy Trials and Dietary Modification Trial was used to analyze effect of calcium and vitamin D and the time the study started to the first event of end point. All analyses were performed using SAS version 9.1 or Comprehensive Meta-analysis version 2. All tests were two tailed and $P<.05$ was considered significant.

Data Collection:

Anthropometric data: used the latest value recorded between screening and one month after randomization for body mass index and for dietary and supplemental calcium intake.

Timing of collection: average trial duration weighted by study size of 6.2 years. The Women's Health Initiative study was a seven year trial, and another study that was used was a small one

year trial with 191 participants.

Dependent variables**:**

- The end points were the total number of myocardial infarction, coronary revascularization, and death from coronary heart disease and stroke

Independent variables**:**

- Calcium and/or vitamin D supplementation
- No supplementation
- Personal use or no personal use of calcium

Confounding variables:

- Randomization status in the Women's Health Initiative Postmenopausal Hormone Therapy Trials and Dietary Modification Trial, following the approach of the Women's Health Initiative investigators.

Primary Outcome(s) /Results & Significance

Actual Sample:

Meta analysis of calcium and vitamin D vs Placebo: 20,090 participants from three trials

Meta-analysis of calcium with or without vitamin D versus placebo: Patient Level: 24, 869 participants in six trials

Trial Level Data: 28, 072 in nine trials

Results: Supplementation of calcium or calcium and vitamin D increase the risk of myocardial infarction by 31% in 8151 participants from 5 studies.

Table 1 Summary:

Table 1 compares the no personal use of calcium with any personal use of Calcium and it shows that the group with any personal calcium use had a higher mean age in years, a lower mean body mass index, lower systolic and diastolic blood pressure, an increase in hormone replacement therapy, a decrease in medical history of hypertension, stroke, and myocardial infarction, and fewer people that were current smokers at the time of the study.

WID CaD Study: Table 2

Participants with no personal use of calcium receiving CaD supplements and their risk of developing cardiovascular endpoints.

- Clinical MI: HR=1.22 increased risk; CI=1.00 to 1.50 not significant; P value=0.05 not significant.
- Clinical MI or revascularization: HR=1.16 increased risk, CI=1.01 to 1.34 significant; P value=0.04 significant.
- Clinical MI or stroke: HR=1.16 increased risk; CI=1.00 to 1.35 not significant; P value= 0.05 not significant.

Participants with any personal use of calcium receiving CaD compared with placebo group receiving CaD supplementation and their risk of developing cardiovascular endpoints.

- Stoke: HR=0.83, 17% decrease risk, CI=0.67 to 1.02 not significant; P value=0.08 not significant.
- Clinical MI or Stroke: HR=0.88, 12% decrease risk; CI=0.76 to 1.02 not significant; P value=0.09 not significant.

Value Interaction: looking at the P values and comparing interaction between CaD allocation and use of non-use of personal calcium supplements for each end point it indicates that there is a raised risk of participants taking CaD supplements that had no prior personal use of calcium. The risk for participants taking CaD with no prior personal calcium use has significant P values for clinical MI: P value=0.04, Stroke: P value=0.02, and clinical MI or stroke: P value=0.006.

Figure 1 Comparing Dose:

There is a significant P value=0.02 for Clinical MI/Stroke when a participant was given supplementation of CaD but had no prior use of calcium.

Meta analysis of calcium and vitamin D vs Placebo:

Calcium and vitamin D significantly increased the risk of :

- Myocardial infarction by 21%; HR= 1.21; CI=1.01 to 1.44 significant; P value=0.04 significant.
- Stroke by 20%; HR=1.20; CI=1.00 to 1.43 not significant; P value=0.05 not significant.
- Myocardial infarction and stroke risk was increased by 16%; HR=1.16; CI=1.02 to 1.32 significant; P value=0.02 significant.

Meta-analysis of calcium with or without vitamin D versus placebo: Calcium or calcium and vitamin D supplementation increased risk for:

- Myocardial infarction by 26%; HR=1.26; CI=1.07 to 1.47 significant; P value= 0.05 not significant .
- Stroke by 19%; HR=1.19, CI=1.02 to 1.39 significant; P value=0.03 significant.
- Myocardial infarction or stroke by 17%; HR=1.17, CI=1.05 to 1.31 significant; P value= 0.05 not significant.

Author's Conclusions:

Consistent results suggest that participants not taking personal calcium supplementation and being administered to take calcium with or without vitamin D will increase the risk of myocardial infarction and stroke. Doing a risk and benefit analysis, calcium and vitamin D supplements are more like to cause myocardial infarctions or stroke than prevent fracture from osteoporosis by a 6/3 ratio.

Reviewer's Comments: The confounding variable of letting the participants take unmonitored calcium and vitamin D supplements would create inaccurate results. The results were that calcium and vitamin D supplementation lead to cardiovascular events, the results do not make sense that patients not taking personal calcium supplementation would be more likely to have cardiovascular events than participants that were consuming personal use of calcium; because this states that more calcium makes a participant less likely to have cardiovascular events.