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Effects of Vitamin K2 Supplementation on the Progression of Coronary Artery Calcium: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review stage at the time of initial registration - Preliminary searches.

Conflicts of interest - The authors declare no financial or non-financial conflicts of interest relevant to this review.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 November 2026 and was last updated on 28 November 2026.

INTRODUCTION

Review question / Objective Does supplementation containing vitamin K2 influence the progression of coronary artery calcium compared with interventions without vitamin K2? This review also examines whether supplementation affects circulating dephosphorylated-uncarboxylated matrix Gla protein concentrations and the occurrence of adverse events.

Rationale Coronary calcium accumulation is associated with an increased risk of cardiovascular disease, yet few interventions specifically target this process. Vitamin K2 is involved in the activation of proteins that regulate tissue mineralization, providing a potential mechanism for limiting vascular calcium deposition.
Clinical trials have produced differing results, and previously published evidence syntheses have combined multiple forms of vitamin K and several vascular calcification outcomes. The availability of newer randomized trials provides an opportunity to reassess the evidence with a specific focus on vitamin K2 and coronary calcium progression.

Condition being studied Coronary artery calcification is a manifestation of coronary atherosclerotic disease and an established marker of cardiovascular risk. It can be quantified using computed tomography and expressed as an Agatston score. This review evaluates whether vitamin K2-containing supplementation influences the progression of coronary artery calcification over time.

METHODS

Search strategy The literature search was conducted in PubMed, Embase, Cochrane CENTRAL, Scopus, and ClinicalTrials.gov from

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database inception to the final search date, without language or publication date restrictions.
The core search strategy was:
("vitamin K2" OR "vitamin K" OR "menaquinone" OR "menatetrenone" OR "MK-4" OR "MK-7") AND ("coronary artery calcification" OR "coronary artery calcium" OR "coronary calcification" OR "coronary calcium" OR "coronary calcium score" OR Agatston)

Participant or population Participants of any age or clinical background enrolled in randomized trials reporting coronary artery calcium measurements. No eligibility restrictions are applied according to sex, renal function, cardiovascular disease status, or initial coronary calcium burden.

Intervention Oral vitamin K2 supplementation, including regimens in which vitamin K2 is administered together with vitamin D or other nutritional supplements. Different vitamin K2 doses, formulations, dosing schedules, and treatment durations are eligible.

Comparator Placebo, usual care, or an active comparator that does not contain additional vitamin K2. Other supplements may be provided as background treatment when administered equally to the intervention and comparator groups.

Study designs to be included Randomized controlled trials, including blinded and open-label trials.

Eligibility criteria Studies were eligible if they: (1) were randomized controlled trials involving human participants; (2) evaluated vitamin K2-containing supplementation; (3) included a placebo or appropriate control group; and (4) assessed coronary artery calcification quantitatively using computed tomography.
Trials providing relevant coronary artery calcification findings but insufficient comparable data for quantitative pooling were retained for qualitative synthesis when applicable.

Information sources PubMed, Embase, Cochrane CENTRAL, Scopus, ClinicalTrials.gov, and reference lists of relevant systematic reviews and eligible studies. Searches covered database inception through the final search date.

Main outcome(s) Primary outcome: Change in coronary artery calcification score from baseline to the final follow-up assessment, measured by computed tomography and expressed in Agatston units.

Treatment effects were summarized primarily using standardized mean differences and mean differences calculated with Hedges' g and corresponding 95% confidence intervals

Additional outcome(s) Circulating dephosphorylated-uncarboxylated matrix Gla protein: Differences in changes in circulating concentrations between intervention and control groups.
Adverse events: Reported treatment-related and overall adverse events, including serious events when available.

Data management Records retrieved from electronic databases were imported into EndNote for reference management and duplicate removal. Two reviewers independently screened titles, abstracts, and full-text articles. Two reviewers independently extracted study characteristics and outcome data. Disagreements were resolved through discussion and consensus, with consultation of a third reviewer when necessary.
Extracted information included study design, participant characteristics, intervention and control regimens, sample sizes, follow-up duration, coronary artery calcification outcomes, dephosphorylated-uncarboxylated matrix Gla protein levels, and adverse events.

Quality assessment / Risk of bias analysis The methodological limitations of the randomized trials were evaluated independently by two investigators using the Cochrane Risk of Bias 2 tool. Judgments were made for the randomization process, deviations from assigned interventions, incomplete outcome information, outcome ascertainment, and selective reporting of results. Domain-level and overall judgments were categorized as low risk, some concerns, or high risk.

Strategy of data synthesis A random-effects framework was used for the quantitative synthesis, implemented in Comprehensive Meta-Analysis version 4. For coronary calcium progression and circulating dephosphorylated-uncarboxylated matrix Gla protein, treatment effects were expressed as Hedges' g and mean differences with 95% confidence intervals. When reports did not directly provide the required summary statistics, appropriate conversion procedures were applied following established meta-analytic methods. The I^2 statistic was used to describe inconsistency between studies. Statistical tests were evaluated using a two-sided significance threshold of 0.05. Adverse events were described narratively when differences in reporting prevented meaningful pooling.

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Subgroup analysis Exploratory subgroup analyses were conducted according to supplementation regimen and study population when applicable. An exploratory random-effects meta-regression examined whether the vitamin K2 dose administered in individual trials was associated with the estimated treatment effect on coronary calcium progression.

Sensitivity analysis The influence of individual trials was examined by recalculating the pooled effect after removing one study at a time. Results obtained using standardized mean differences were also compared with analyses using mean differences to evaluate whether the overall interpretation was consistent across effect measures.

Language restriction No language restrictions will be applied during the literature search.

Country(ies) involved Taiwan.

Other relevant information Current review status: Ongoing.

Keywords Vitamin K2; Coronary artery calcification; Vascular calcification; Matrix Gla protein; Randomized controlled trials; Meta-analysis.

Dissemination plans The findings will be submitted for publication in a peer-reviewed medical journal.

Contributions of each author

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