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ORIGINAL ARTICLE

Vitamin K supplementation impact in dialysis patients: a systematic review and meta-analysis of randomized trials

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ABSTRACT

Vitamin K supplementation has been considered recently as a potential treatment for addressing vascular calcification in chronic kidney disease patients.

We conducted a systematic review and meta-analysis to summarize the impact of vitamin K supplementation in dialysis patients. Electronic databases were searched for clinical randomized trials among patients treated with vitamin K. Random effects models were performed and risk of bias was evaluated with Cochrane tools and the search was conducted until 15 of September 2023.

Eleven trials comprising 830 patients (both adult and pediatric, mainly hemodialysis) compared vitamin K with different controls: lower doses of vitamin K, standard care or placebo. Vitamin K supplementation had no effect on mortality. Vitamin K administration improved vitamin K levels and led to lower levels of dp-uc-MGP and moderately increased calcium levels [0.18 (0.04–0.32)]. Vitamin K1 proved more potency in reducing dp-uc-MGP [SMD −1.64 (−2.05, −1.23) vs. −0.56 (−0.82, −0.31)] and also raised serum vitamin K levels in comparison with vitamin K2 [5.69 (3.43, 7.94) vs. 2.25 (−2.36, 6.87)]. While it did not have a proved benefit in changing calcification scores [−0.14 (−0.37 ± 0.09)], vitamin K proved to be a safe product. There was some concern with bias.

Vitamin K supplementation has no impact on mortality and did not show significant benefit in reversing calcification scores. Vitamin K1 improved vitamin K deposits and lowered dp-uc-MGP, which is a calcification biomarker more than vitamin K2. As it proved to be a safe product, additional randomized well-powered studies with improved treatment regimens are needed to establish the true impact of vitamin K in dialysis patients.

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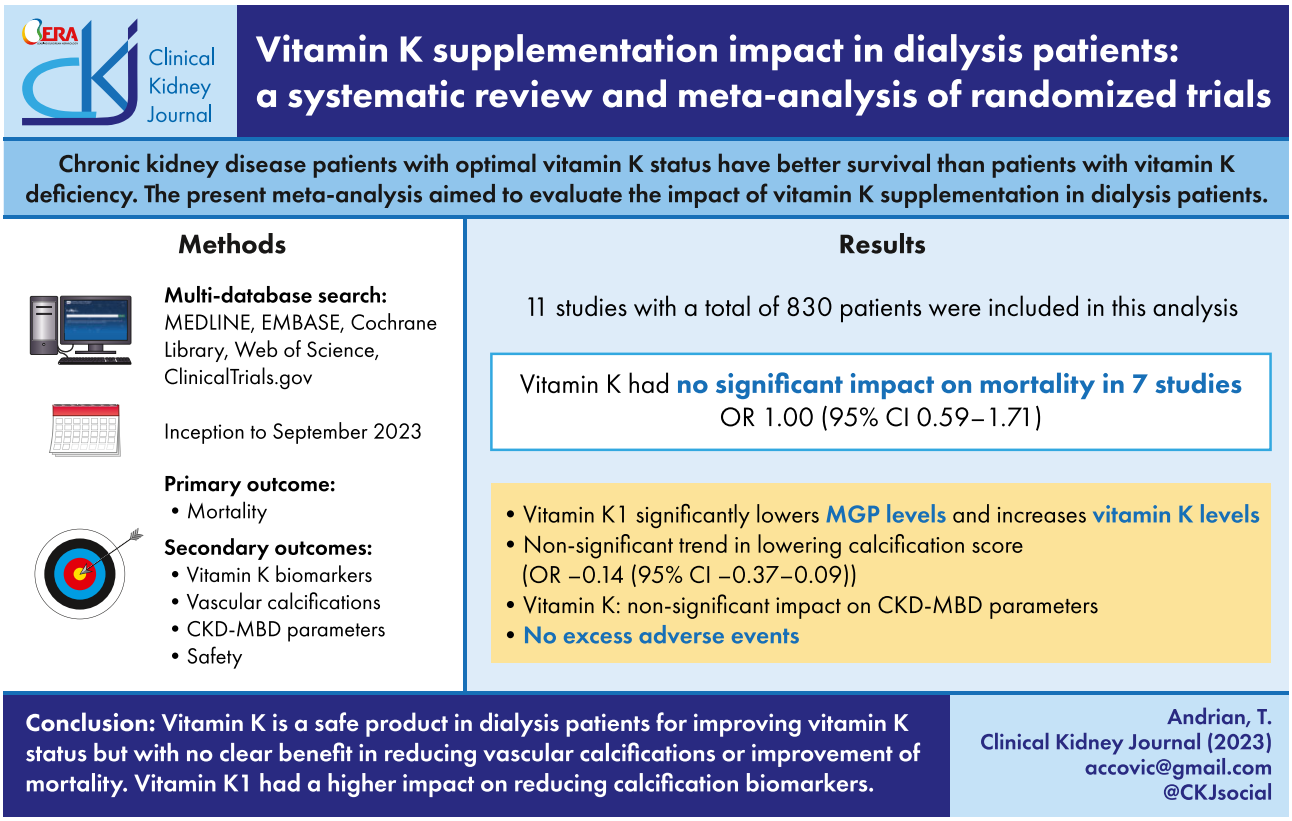
GRAPHICAL ABSTRACT



Keywords: CKD-MBD, dialysis, mortality, vascular calcifications, vitamin K

KEY LEARNING POINTS

What was known:

- Chronic kidney disease and dialysis patients with optimal vitamin K status have better survival than patients with vitamin K deficiency.

This study adds:

- Vitamin K supplementation is considered as a potential treatment for slowing progression of vascular calcification.

Potential impact:

- This meta-analysis proves that vitamin K has no significant impact on mortality and proved no benefit in reducing vascular calcification although supplementation with vitamin K1 improved calcification biomarkers and vitamin K status.

INTRODUCTION

Vitamin K metabolism in chronic kidney disease

Vitamin K encompasses several similar compounds that share a common core: 2-methyl-1,4-naphthoquinone or menadione. Vitamin K_1 (phylloquinone) and vitamin K_2 (menaquinone) are obtained via dietary plant and animal sources, respectively. Vitamin K_3 cannot be obtained exogenously and represents an intermediate metabolite. Vitamin K is an essential factor for the process of γ-glutamyl carboxylation of several human proteins. Most of these proteins are physiological and exert a role in the coagulation cascade (coagulation factors II, VII, IX, X, proteins C, S and Z). Other are involved in mineralization processes of connective tissues (matrix Gla protein—MGP, osteocalcin, Gla-rich protein, nephrocalcin) [1]. The quantities that are considered adequate from intake show small gender differences and differ between vitamin K_1 and vitamin K_2: 120 μg/day and 54 μg/day for men and 90 μg/day and 36 μg/day, respectively, for women [2].

Biomarkers and vitamin K status

Matrix Gla protein (MGP) originates from the vascular smooth muscle cells and chondrocytes [3]. Complete carboxylation of this protein depends on availability of vitamin K that acts as a cofactor. Carboxylated MGP has the capacity of binding calcium ions and hydroxyapatite molecules, thus inhibiting vascular calcification. On the other hand, the inactive form, dephosphouncarboxylated MGP (dp-ucMGP) is associated with progression of vascular calcification [4]. Vitamin K deficiency is suggested by high levels of dp-ucMGP [5]. Chronic kidney disease (CKD) and low renal function lead to elevated concentrations of this biomarker [2].

Osteocalcin is also known as bone γ-carboxyglutamic acid (Gla) protein. Carboxylation leads to increased binding capacity of osteocalcin to the mineral component of the extracellular matrix. Under or un-carboxylated osteocalcin loses its affinity and acts a hormone in the systemic circulation where it has a role in glucose and lipid homoeostasis [6]. UcOC is increased in vitamin K depletion [7].

Vitamin K status can be assessed by measurement of phylloquinone (vitamin K_1) or of menaquinone (MK-4). They are indicators of tissular stores. MK-4 levels are low in dialysis patients [8].

PIVKA-II (proteins induced in vitamin K absence or antagonism—factor II) is a potential indicator for suboptimal vitamin K status. Increased levels suggest tissular depletion and importantly, there is no interference with kidney function [9].

Causes of vitamin K deficiency

Vitamin K circulating levels and tissular stores appear to be low in dialysis patients [10, 11]. Low intake could be explained by adherence to typical dialysis diets with important limitations of sodium, potassium, green vegetables, and dairy [12]. Moreover, uremia may alter vitamin K metabolism by interfering with lipoprotein mediated transport and by influencing γ-glutamyl carboxylase activity [13, 14]. Certain medications commonly prescribed to dialysis patients can influence vitamin K concentrations. Anticoagulants such as warfarin act as vitamin K antagonists with proved predisposition to increased risk of vascular calcifications [15]. Sevelamer (a phosphate binder) is associated with altered vitamin K status suggested by MK-4 deficiency and increased levels of dp-ucMGP [16]. Clinical and experimental data also suggest subclinical vitamin K deficiency under treatment with proton pump inhibitors and statins [13]. Gut dysbiosis is another mechanistic speculative reason for altered vitamin K status in dialysis patients [17].

Consequences of vitamin K deficiency

Low vitamin K intake leads to increased risk of severe aortic calcification and increased mortality in elderly patients [18].

Chronic kidney disease patients with optimal vitamin K status (low plasma dp-ucMGP and high plasma phylloquinone) have better survival than patients with vitamin K deficiency. Furthermore, lower levels of dp-ucMGP are associated with lower risk of congestive heart failure and atrial fibrillation [19].

Altering vitamin K status with anti-vitamin K agents can lead to increased risk of fractures [20]. Vitamin K deficiency is predictive for vertebral fractures and vascular calcifications [11]. Also, altered integrity of matrix Gla protein by vitamin K deficiency may increase the risk of calciphylaxis [21].

Role of vitamin K supplementation in cardiovascular and bone health

Given the putative beneficial mechanism, vitamin K has been considered as a potential therapeutic tool in reversing vascular calcification and improving bone health. Several studies have found a beneficial association of vitamin K supplementation and delaying progression of vascular and valvular calcification [22, 23]. Recent meta-analyses have underlined the beneficial effect of vitamin K on osteoporosis outcomes: vitamin K is associated with decreased fracture risk and may prove beneficial in maintaining and improving bone mineral disease, without associated risks [24–26]. A recent metanalysis evaluating the effects of vitamin K supplementation on vascular calcifications in CKD patients (including dialysis patients) found no significant benefit in reducing calcification scores.

In this study we aimed to evaluate the impact of vitamin K supplementation in dialysis patients by realizing a systematic review and metanalysis of randomized trials.

MATERIALS AND METHODS

Protocol and registration

We performed this systematic review and meta-analysis respecting recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. The protocol and employed methods were registered previously in an international prospective register for systematic reviews (OSF: 10.17605/OSF.IO/Z63UG).

Search strategy

We conducted a multi-database search including MEDLINE/Pubmed, EMBASE, Cochrane Library, Web of Science, ClinicalTrials.gov. Key-words for the search were: ‘vitamin K’, ‘phylloquinone’, ‘menadione’, ‘calcifications’, ‘CKD-MBD’, ‘dialysis’. Where data was missing or not available in the supplementary materials, we contacted the authors. We aimed to include studies published before 15 September 2023. No language restriction was applied.

Study inclusion criteria and data extraction

We considered randomized studies for inclusion in the presence of the following criteria: dialysis patients (hemodialysis or peritoneal dialysis), treatment with one vitamin K preparation (phylloquinone, MK-4, MK-7, menatetrone, menaquinone), randomized trials with control represented by placebo, standard care or lower doses of vitamin K. Studies were excluded in the absence of the randomization.

Two authors (T.A. and A.S.) independently conducted the search, screened the records, proposed eligible studies, extracted the characteristics and data of studies. Differences or discrepancies were evaluated by a third author (I.N.).

Risk of bias assessment

We assessed the quality and characteristics related to bias in accordance with the revised Cochrane tool for randomized trials [29].

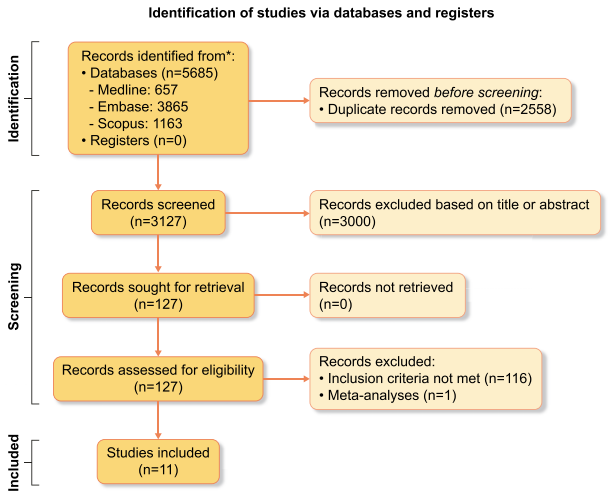


Figure 1: Flow-chart of included studies.

Data synthesis and statistical analysis

Extracted data was synthesized by means of random-effects modelling. The primary outcome we addressed was mortality. Secondary outcomes included changes in vitamin K status biomarkers (dp-ucMGP, osteocalcin, PIVKA-II), descriptors of vascular calcifications (Agatston scores, calcifications volumes, pulse wave velocity measurements, valvular calcifications scores), changes in chronic kidney disease—mineral bone disease (CKD-MBD) parameters (intact parathyroid hormone—iPTH, calcium, phosphate, fibroblast growth factor 23 FGF-23), safety assessment and adverse reactions (deaths, anaphylaxis, digestive and thrombotic manifestations). Mean difference (MD) and standard deviation (SD) of continuous variables were computed to weighted MD. Relative risk (RR) and 95% confidence interval were calculated for dichotomous data. Values were displayed with pooled estimation and according 95% confidence intervals. I^2 statistic was used as a measure of heterogeneity: values of 25%, 50%, and 75% corresponded to cut-offs for low, moderate, and high heterogeneity, respectively [30]. Statistical analysis was performed using Review Manager, Version 5.4 (RevMan 5) [31].

RESULTS

Description of the included studies

In total, 127 publications were selected after search protocol and assessed for eligibility in the final analysis. The schematic flow chart of search and choice strategy are shown in Fig. 1. Table 1 depicts general characteristics of the eligible and included studies [32–42]. We included 11 papers that included 830 patients in total. Studies mainly included adult hemodialysis (HD) patients. One study included pediatric patients on maintenance HD [34] and one study also included PD patients [37]. Treatment interval ranged from six weeks to two years. Vitamin K administration regimens were different between studies regarding dosages and intake (daily vs. post-dialysis session). Five studies had a three-weekly regimen with direct observation treatment administered post-dialysis [32, 33, 35, 36, 41]. In the study by Caluwé *et al.* [32] the comparator was a lower dose of vitamin K, while in the study conducted by De Vriese *et al.* [33], we assessed comparisons with Rivaroxaban and not with vitamin K antagonists, which was another treatment arm.

Effect of vitamin K on mortality

Vitamin K had no significant impact in the seven included studies that reported data on mortality. After assessing the separate impact of vitamin K1 and vitamin K2, there was no change and intervention did not impact mortality (Fig. 2).

Effect of vitamin K on calcification biomarkers

Vitamin K1 supplementation led to a statistically significant and important increase in vitamin K levels [MD = 5.69 (3.43, 7.94)]. Vitamin K2 proved no significant impact on plasmatic vitamin K levels [MD = 2.25 (−2.36, 6.87)] (Fig. 3).

Both vitamin K1 and vitamin K2 significantly lowered serum levels of MGP although effect magnitude was higher in vitamin K1 [SMD −1.64 (−2.05, −1.23) vs. −0.56 (−0.82, −0.31)] (Fig. 4).

In two studies that reported the effect of vitamin K supplementation on plasmatic PIVKA-II levels, there was no observed statistically significant benefit (Fig. 5).

Effect of vitamin K on calcification score

There was no significant between-groups difference fort the post-interventional Agatston score (Fig. 6).

Effect of vitamin K on pulse wave velocity

Four studies have assessed the impact of vitamin K supplementation on arterial stiffness. There was no significant impact of vitamin K on pulse wave velocity [MD = 0.45 (−0.16, 1.07)] (Fig. 7).

Effect of vitamin K on CKD-MBD parameters

Vitamin K exhibited a significant effect on calcium levels [MD 0.18 (0.04, 0.32)]. The recorded increase was mainly attributed to one study which weighted significantly [35]. There was no change in serum levels of PTH, FGF-23, or phosphate levels (Fig. 8).

Safety of vitamin K

There were no excess adverse events recorded with vitamin K administration (Fig. 9).

Sensitivity analysis

For each analysis, we also performed a duplicate estimation using a fixed-effect model with no significant differences reported in effect sizes.

Heterogeneity

Heterogeneity was judged high across the performed analysis. The origin of these differences mainly arisse from different clinical features between included patients, dialysis modality, CKD-MBD profile at baseline, and vitamin K dosage and duration of treatment.

Table 1: Characteristics: of included clinical studies.

Study ID	Country	Groups	Population	No. of participants	Age (years)	Gender	Time on dialysis	Duration	Primary Outcomes
Caluwé, 2013 [32]	Belgium	Intervention = 1080 μg MK-7 × 3/week	HD patients	N = 53	71.2 +/−48	54.7% women	41.9 +/− 192 M	8 weeks	Required dose of MK-7 to optimize MGP carboxylation
		Control = 360 μg MK-7 × 3/week		N = 59	72.2 +/− 41	52.5% women	30.9 +/− 86 M		
De Vriese, 2020 [33]	Belgium	Intervention = 2000 μg MK-7 × 3/week + Rivaroxaban	HD patients	N = 42	79.6 +/− 7.5	33.3% women	2.7 +/− 3.4 Y	18 months	Change of CAC, TAC and PWV over 18M
		Control = Rivaroxaban		N = 46	79.9+/− 7.26	23.9% women	2.7 +/− 3.8 Y		
El Borolossy, 2021 [34]	Egypt	Intervention = 100 μg MK-7 daily	HD pediatric patients	N = 15	12.3 +/− 2.1	40% women	NR	4 months	Efficacy of MK-7 on vascular calcification
		Control = standard therapy		N = 15	11.9 +/− 2.9	40% women			
Haroon, 2023 [35]	Singapore	Intervention = 360 µg MK-7 × 3/week	HD patients	N = 89	62 +/− 12.7	35% women	3 +/− 4.4 Y	18 months	Difference of CAC score
		Control = standard therapy		N = 89	61 +/− 13.5	42% women	4 +/− 3.7 Y		
Holden, 2022 [36]	Canada United Kingdom	Intervention = 5 mg × 2 phylloquinone × 3/week	HD patients	N = 41	63 +/− 12.2	34% women	278 +/− 470 D	12 months	Feasibility
		Control = Placebo		N = 45	61 +/− 16.8	52% women	413 +/− 903 D		
Levy-Schousboe, 2021 [37]	Denmark	Intervention = 360 μg MK-7 daily	HD patients (n = 27)	N = 24	62 +/− 11	21% women	28 +/− 32 M	24 months	Change in PWV
		Control = Placebo	PD patients (n = 18) Hybrid (n = 3)	N = 24	66 +/− 11	25% women	22 +/− 26 M		
Naiyarakseree, 2023 [38]	Thailand	Intervention = 375 µg MK-7 daily	HD patients	N = 50	59.7 +/− 11	48% women	6.5 +/− 10.9	24 weeks	Change in PWV
		Control = Standard therapy		N = 46	60 +/− 11.8	43% women	10.2 +/− 11		
Ochiai, 2011 [39]	Japan	Intervention = 45 mg menatetrone daily	HD patients	N = 20	64.7 +/− 10.2	55% women	9.5 +/− 8.1 Y	12 months	Effect of vit K2 in adynamic bone disease
		Control = Standard therapy		N = 13	65.3 +/− 12.6	30,2% women	8.9 +/− 6.4 Y		
Oikonomaki, 2019 [40]	Greece	Intervention = 200 μg MK-7 daily	HD patients	N = 22	70.1 +/− 12	NR	8.3 +/− 5.9 Y	12 months	Levels of MGP at randomization, 3 and 12 M
		Control = standard therapy		N = 30	66.6 +/− 16	NR	7.7 +/− 6.3 Y		
Saritas, 2022 [41]	Germany Belgium Sweden	Intervention = 5 mg vitamin K1 × 3/week	HD patients	N = 17	62.5 +/− 12	38% women	65.2 +/− 12 M	18 months	Progression of TAC, CAC
		Control = Standard therapy		N = 23	64.4 +/− 13.3	26% women	82.1 +/− 65 M		
Westenfeld, 2011 [42]	Germany Netherlands	Intervention = 360μg MK-7 daily	HD patients	N = 14	68.2	35.7% women	NR	6 weeks	Plasma levels of MGP, uncarboxylated osteocalcin, PIVKA-II
		Control = Standard therapy		N = 53	60.5	66% women	NR		

CAC: coronary artery calcification; D: days; HD: hemodialysis; M: months; MGP: matrix Gla-protein; MK-7: menaquinone 7; NR: not reported; PD: peritoneal dialysis; PIVKA-II: protein induced by vitamin K absence-II; PWV: pulse wave velocity; TAC: thoracic aorta calicification; Y: years.

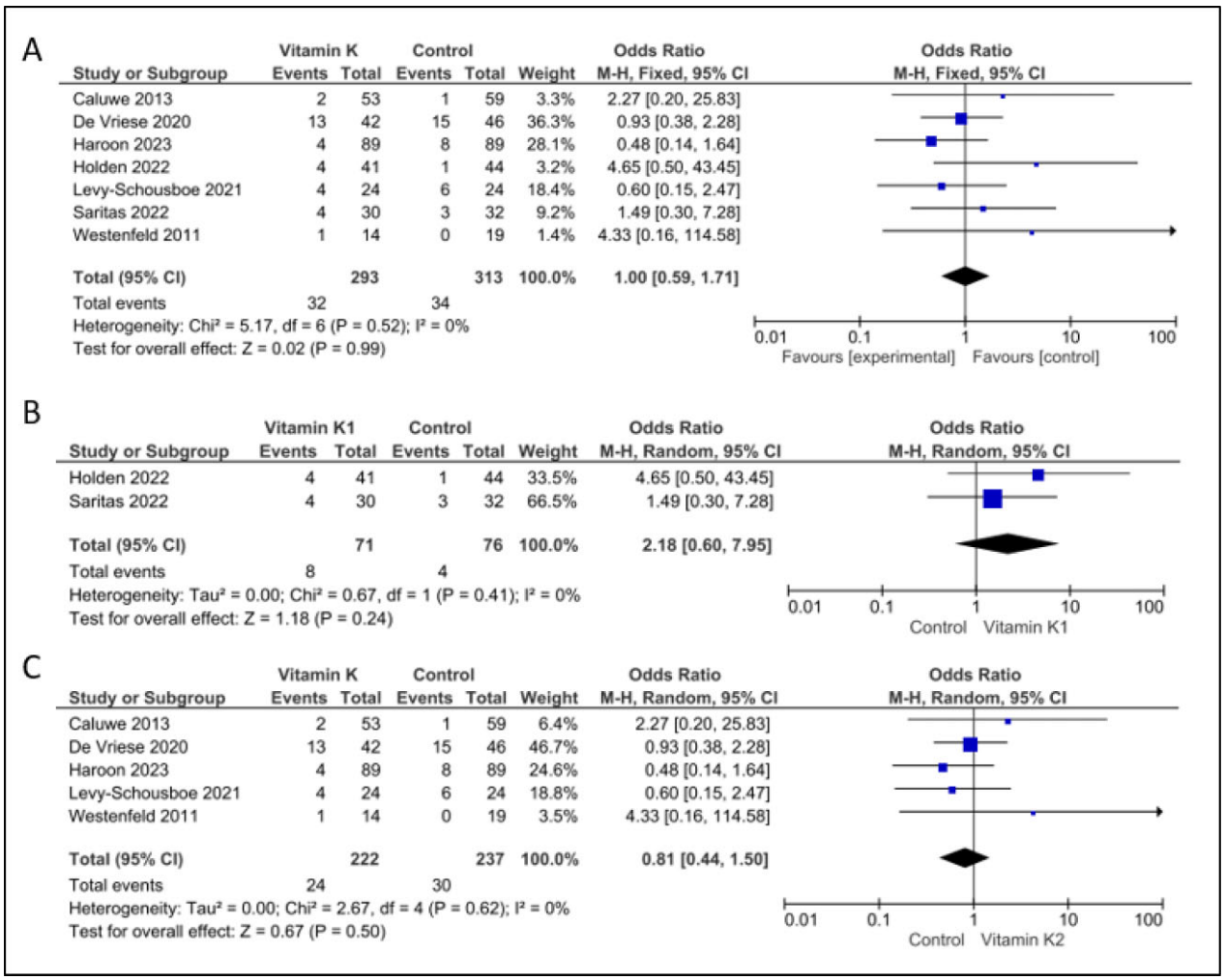


Figure 2: Effect of vitamin K supplementation on mortality. (**A**) Pooled results of studies reporting mortality; (**B**) impact of vitamin K1 supplementation on mortality; (**C**) impact of vitamin K2 supplementation on mortality.

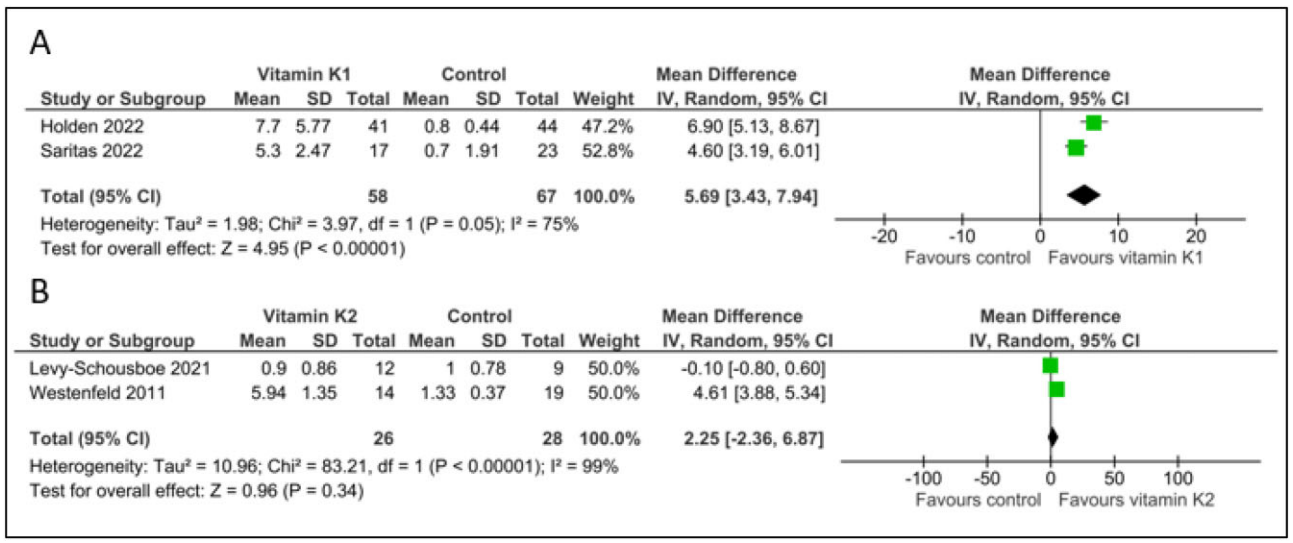


Figure 3: Separate effect of vitamin K preparation on serum vitamin K. (**A**) Effect of vitamin K1 on vitamin K plasmatic levels; (**B**) effect of vitamin K2 on vitamin K plasmatic levels.

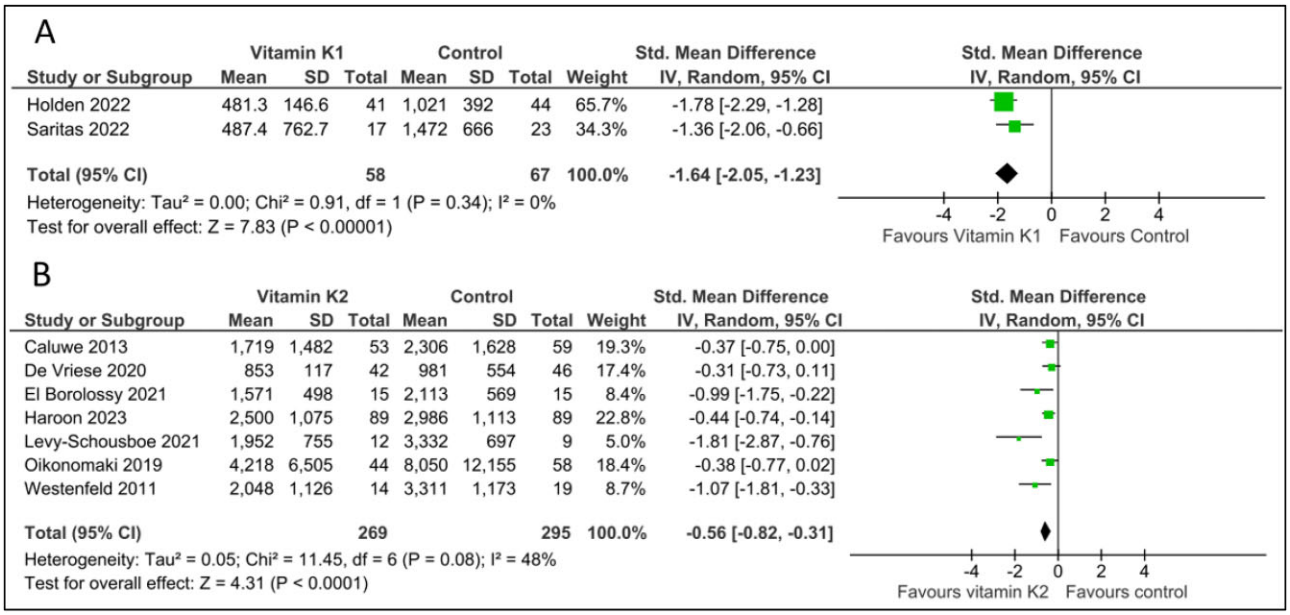


Figure 4: Separate effect of vitamin K products on serum MGP status. (**A**) Effect of vitamin K1 on serum MGP; (**B**) effect of vitamin K2 on serum MGP.

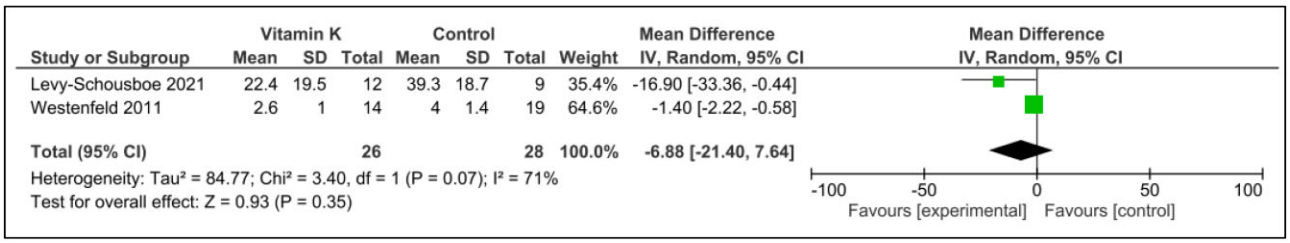


Figure 5: Effects of vitamin K on plasmatic PIVKA-II levels.

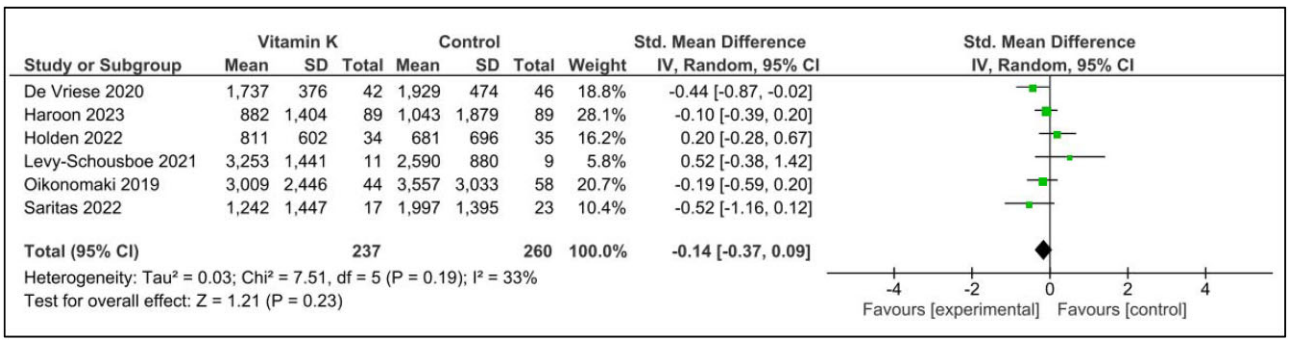


Figure 6: Effect of vitamin K on coronary artery calcification Agatston score.

Risk-of-bias assessment

We assessed the risk of bias using the RoB2 tool and we found concerns of bias mainly due to founding and providing of medications and also due to randomization and concealment issues (Fig. 10).

DISCUSSION

Extra skeletal calcifications represent important contributors to the excessive cardiovascular burden present in dialysis patients. End-stage kidney disease (ESKD) constitutes an aggregate of different pathological pathways that lead to the final result of

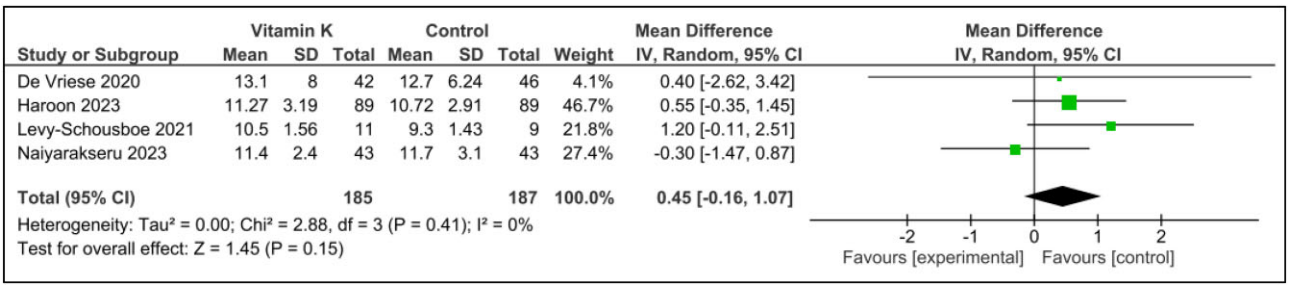


Figure 7: Effect of vitamin K supplementation on PWV.

hydroxyapatite deposition in the extracellular matrix of the intima or media of vascular walls. Among those, dysregulated mineral metabolism with low levels of calcification inhibitors (such as MGP) and high levels of uremic toxins have been associated with increased risk of cardiovascular morbidity. There is a significant heterogenous pattern of calcific vascular deposits. This wide array of anatomical, tissular, and biochemical manifestations makes diagnosis ambiguous and difficult. In order to accurately assess calcification magnitude, it is important to use multiple complementary tests (serum biomarkers such as fetuin-A, MGP, osteoprotegerin; imaging studies such as plain radiographs, dual-energy X-ray absorptiometry, computed tomography, or ^{18}F-fluoride positron emission tomography) [43]. Due to these considerations, vascular calcification (VC) assessment is contemplated more as a surrogate end point for cardiovascular disease. Multiple therapeutic strategies have addressed specific pathogenic mechanisms in order to reduce progression of vascular calcifications. However, debate also exists upon the effectiveness of VC improvement on true hard clinical outcomes such as survival and cardiovascular events.

In this metanalysis, vitamin K administration showed signs of metabolic benefit by improving serum levels of vitamin K and by reducing MGP levels. However, these biological benefits did not translate into clinical improvement of vascular calcification score assessed post-intervention and did not reduce mortality.

In this meta-analysis, vitamin K1 showed increased potency in reducing MGP levels in comparison with vitamin K2 and also had an impact on improving vitamin K plasmatic levels. These differences may be explained by different drug metabolic pathways that have been already described. In advanced renal disease, dialysis patients are incapable of incorporating menaquinone 7 in lipoprotein particles and there was very low activity of vitamin K even after supplementation. These uremic derangements may explain the lack of benefit seen with vitamin K2 in advanced kidney disease [13].

A recent systematic review of interventions to attenuate vascular calcifications confirmed several effective evidence-based strategies to reduce progression of VC in CKD: magnesium supplementation, sodium thiosulfate, etidronate, and reducing exogenous calcium loading. Other therapies such as calcimimetics, oral activated charcoal, sotatercept, and a novel molecule that inhibits hydroxyapatite formation directly (SNF472) may possibly reduce VC progression but there are significant conflicting results or paucity of data to support their use. Furthermore, authors cited vitamin K2 supplementation as a therapy unlikely to reduce VC progression [44].

Several randomized studies have assessed the effect of vitamin K supplementation on non-dialysis renal population. A small study conducted in Poland on 42 patients with CKD stages 3–5 showed that 90 μg MK7 combined with 10 μg cholecalciferol led to lower progression of carotid intima-media thickness after 9 months compared to cholecalciferol alone. There was no benefit on coronary artery calcification progression [45]. A British study on stage 3b-4 CKD patients compared a higher vitamin K2 (400 μg) daily dose to placebo. After 1 year of follow-up there was no improvement of vascular stiffness, blood pressure, B-type natriuretic peptide or physical function [46]. Vitamin K supplementation (menadiol diphosphate 5 mg thrice weekly for 1 year) in prevalent kidney transplant recipients failed to show impact on slowing vascular stiffness or calcifications [47]. Another recent study included 40 vitamin K-deficient transplanted patients. Patients were supplemented with 360 μg/day menaquinone (vitamin K2) or placebo for 3 months. There was a slight benefit in preventing progression of pulse-wave velocity and in improving vitamin K status. There was no effect on calcification propensity [48].

A Chinese study on HD patients assessed the effect of a vitamin K enriched dialysate on vascular calcifications. Intervention resulted in decreased calcification scores. Vitamin K enriched dialysate led to elevated levels of Ca, P, bone specific alkaline phosphatase, and fetuin A and to lower levels of CRP [49].

Vitamin K proved to be a safe product in our metanalysis. There was no recorded excess of gastrointestinal symptoms, thrombotic events or deaths.

Regarding the effect of vitamin K supplementation on CKD-MBD parameters, the only statistically significant effect was noted in calcium levels. Vitamin K did not result in significant changes of PTH, FGF-23, or phosphate levels (Fig. 5). Lack of significant effect is probably multifactorial. Results were discordant between studies and inclusion criteria were different: one study included patients with adynamic bone disease [39]. Furthermore, baseline phosphate lowering medication may interfere with vitamin K metabolism and was not reported uniformly.

The present metanalysis is limited by several findings. The different treatment administration protocols and the several phenotypes of included populations (pediatric HD patients, HD adult patients, PD patients, etc.) are both sources of the observed heterogeneity. We also noted that sample sizes were limited in all studies. We considered mortality the primary outcome that was not influenced by vitamin K administration. However, included studies were not powered to detect differences in mortality.

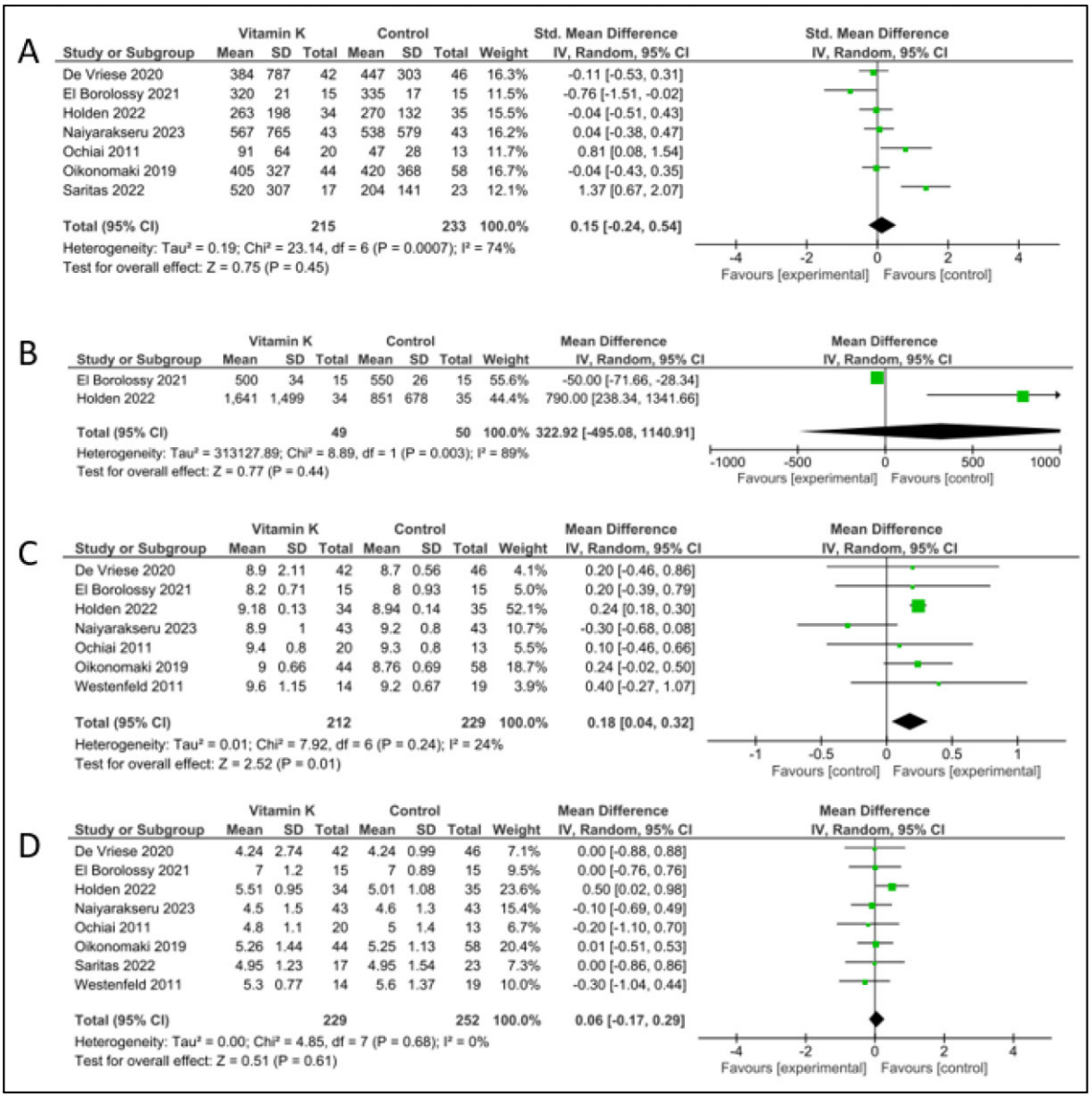


Figure 8: Effect of vitamin K supplementation on CKD-MBD parameters. (**A**) Effect on PTH levels; (**B**) effect on FGF-23; (**C**) effect on calcium levels; (**D**) effect on phosphate levels.

A quite obvious source of heterogeneity is represented by the metabolic and pharmacologic profile of vitamin K products. In this context we performed a separate analysis regarding mortality, assessing dichotomously the impact of vitamin K1 and K2, which were not associated with any benefit or harm. Furthermore, treatment protocols were different and dosages ranged between the studies.

The present study is important as it reflects the current understanding of vitamin K supplementation impact in dialysis population. Given the important differences between employed protocols, outcomes and supplementation strategies until this moment, there will be a need to try and harmonize these concepts in upcoming major and adequately powered trials.

This study is the first to systematically review the impact of vitamin K supplementation specifically in dialysis patients on vascular calcification, mortality, and CKD-MBD parameters.

Future research may need to focus on finding the correct treatment protocol and dosages in dialysis patients in order to obtain significant benefits.

In conclusion, vitamin K is a safe product in dialysis patients for improving vitamin K status but with no clear benefit in reducing vascular calcifications or improvement of mortality. Vitamin K1 showed better efficacy and may represent an agent with better promise in the uremic milieu. High-dosage administration assessed in well-empowered randomized controlled trials will establish the effect of vitamin K supplementation on vascular and bone health of dialysis patients.

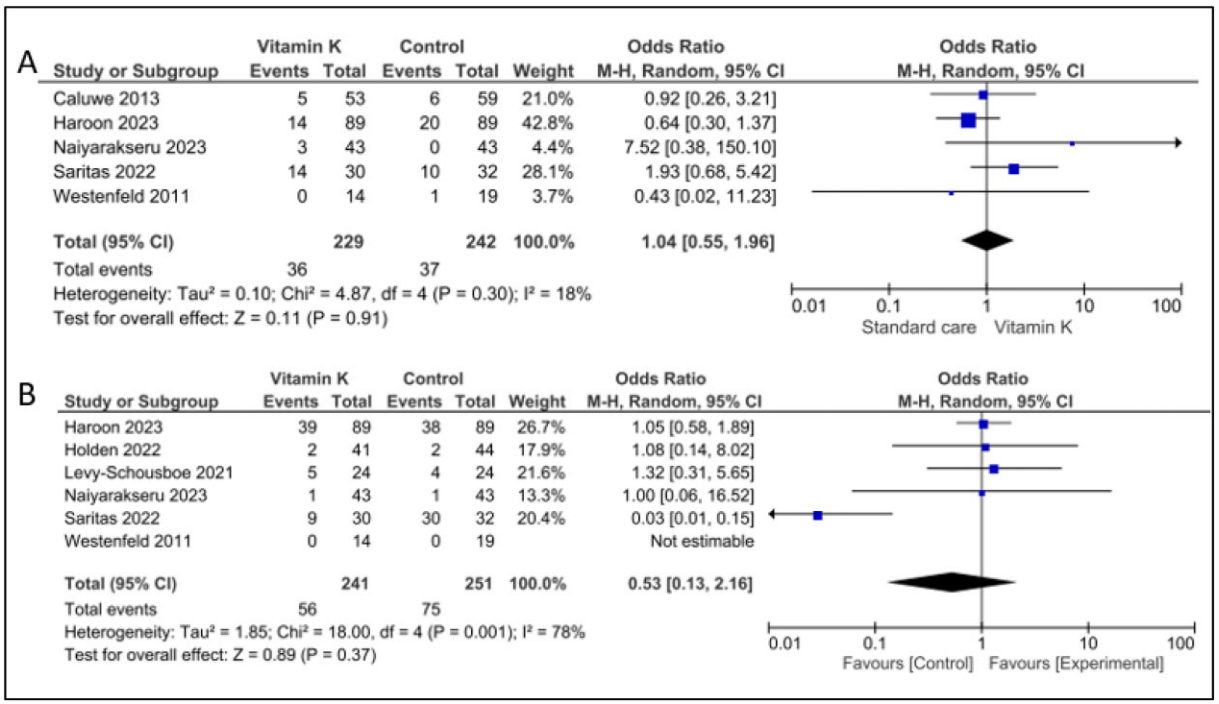


Figure 9: Adverse events linked to vitamin K supplementation. (**A**) Gastrointestinal adverse events; (**B**) thrombotic events.

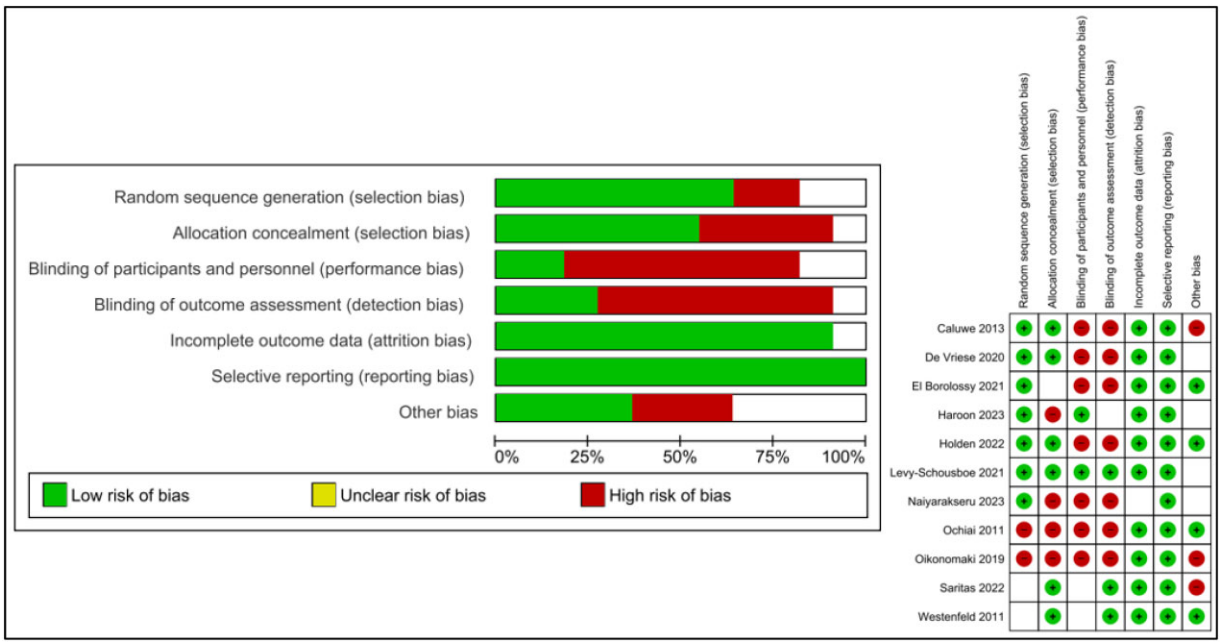


Figure 10: Risk-of-bias judgement of RCT using RoB2 tool.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

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