

Review Article

Impact of Vitamin K supplementation on cardiovascular health outcomes associated with kidney disease – A systematic review and meta-analysis

Prithpal Singh Matreja¹, Seema Awasthi², Sudhir Singh³, Sanjeev Kumar Jain⁴

Departments of ¹Pharmacology, ²Pathology, ³Microbiology, ⁴Anatomy, Teerthanker Mahaveer Medical College and Research Centre, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India.

***Corresponding author:**

Prithpal Singh Matreja,
Department of Pharmacology,
Teerthanker Mahaveer
Medical College and Research
Centre, Teerthanker Mahaveer
University, Moradabad, Uttar
Pradesh, India.

singhmatreajprithpal@gmail.com

Received: 27 March 2025
Accepted: 08 August 2025
Epub Ahead of Print: 13 November 2025
Published:

DOI
10.25259/IJPP_169_2025

Quick Response Code:



ABSTRACT

Cardiovascular disease is the leading cause of morbidity and mortality among patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Vitamin K2, through its role in Vitamin K-dependent proteins, has been proposed to attenuate vascular calcification (VC) and arterial stiffness, yet deficiency is common in CKD. This systematic review and meta-analysis evaluated randomised controlled trials and cohort studies comparing Vitamin K2 supplementation with placebo or no treatment in CKD and ESKD patients. Outcomes included pulse wave velocity, coronary artery calcification, abdominal aortic calcification, and mortality. Eight eligible studies were included. Pooled analyses revealed no significant effect of Vitamin K2 on arterial stiffness, VC, or cardiovascular mortality, although a modest reduction in all-cause mortality was noted, largely driven by cohort data. While biochemical improvements such as reduced dp-ucMGP were observed, these did not consistently translate into clinical benefit. Overall, Vitamin K2 supplementation shows potential for improving vascular biomarkers but lacks strong evidence for reducing cardiovascular events or mortality. Larger, well-designed trials are needed to establish its clinical role in CKD populations.

Keywords: Arterial stiffness, Cardiovascular mortality, Chronic kidney disease, Coronary artery calcification, End-stage renal disease, Meta-analysis, Pulse wave velocity, Systematic review, Vascular calcification, Vitamin K2

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in chronic kidney disease (CKD) and end-stage kidney disease (ESKD) patients, with a strongly increased risk of vascular calcification (VC), arterial stiffness and cardiovascular events compared with the general population.^[1] The rapid progression of arterial calcification in CKD is due to various pathophysiological mechanisms, including chronic inflammation, oxidative stress, mineral metabolism disturbances and deficiency of calcification inhibitors.^[2] Vitamin K-dependent proteins (VKDPs), like matrix Gla protein (MGP), play a fundamental role in the regulation of vascular homeostasis through the prevention of ectopic calcification.^[3] Vitamin K deficiency, very common in CKD patients, is the cause of increased concentrations of dephosphorylated-uncarboxylated MGP (dp-ucMGP), a risk marker for VC.^[4]

Vitamin K is present in two primary forms: Phylloquinone (Vitamin K1), the majority of which are found in leafy green vegetables and is essential to liver coagulation, and menaquinones

(Vitamin K2, ranging from MK-4 to MK-13), which are found in fermented foods and are involved in extrahepatic activity, such as regulating VC and bone turnover.^[5] In contrast to Vitamin K1, Vitamin K2's long half-life, increased bioavailability and effectiveness as an activator for VKDPs such as MGP and osteocalcin (OC) persist.^[6] In CKD, low Vitamin K2 has been associated with arterial stiffening, coronary artery calcification (CAC) and a cardiovascular mortality risk dominated by defective VKDP carboxylation, followed by uncontrolled vascular mineralisation.^[7]

Preclinical assessments and observational analysis have indicated the promise of supplementing Vitamin K2 to restrain VC and enhance the cardiovascular outcome among CKD and dialysis patients.^[8] Randomised trials to ascertain Vitamin K2 effects on vascular stiffening, coronary and abdominal aortic calcification and the risk of mortality have yielded conflicting results, which range from significantly reducing markers for VC in some groups, with the others reporting unchanged findings or modest therapeutic effects.^[9] Meta-analysis among non-CKD patients has indicated benefits with Vitamin K2 for the reduction of atherosclerosis risk, but in CKD, its role has not been properly established and, therefore, needs a more refined synthesis of evidence.^[10-12]

Given the pathophysiologic role of Vitamin K2 deficiency in CKD and its therapeutic application in lowering cardiovascular risk, a comprehensive systematic review and meta-analysis were conducted to critically evaluate its role in arterial stiffness, coronary and abdominal aortic calcification, cardiovascular mortality and vascular well-being in patients with CKD and ESKD. Through the combination of evidence from randomised controlled trials (RCTs) and cohort studies, the present study aimed to derive a quantitative estimate of the impact of Vitamin K supplementation on cardiovascular events in patients with kidney disease.

MATERIALS AND METHODS

Eligibility criteria

A PECOS framework was used to establish inclusion and exclusion criteria, in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses reporting guidelines.^[13] Studies were included if they were patient studies of CKD or ESKD (Population), supplemented with Vitamin K (menaquinone forms: MK-4, MK-7 or MK-9) (Exposure), compared with placebo or no treatment (Comparator) and measured cardiovascular health outcomes such as arterial stiffness (pulse wave velocity), CAC (Agatston Score), all-cause and cardiovascular mortality and vascular function markers (Outcome). RCTs, prospective cohorts and case-control studies in isolation were included for analysis, but cross-sectional studies, reviews, animal studies and

studies with poor control groups were excluded from the study.

Search strategy

A systematic review of the existing literature was carried out using various databases such as PubMed, Embase, Cochrane Library, Web of Science and Scopus using a strategic combination of MeSH terms and Boolean operators [Table 1]. The specific search terms utilised were 'Vitamin K2' OR 'menaquinone' AND 'chronic kidney disease' OR 'end-stage renal disease' AND 'cardiovascular disease' OR 'arterial stiffness' OR 'vascular calcification' OR 'mortality'. The search was restricted to peer-reviewed articles published in English from the inception of the databases until the completion date of the final search (February 2025).

Study selection and data extraction

Two independent reviewers screened titles and abstracts, and subsequently full texts for assessment of study eligibility. Disagreements were settled by discussion with a third reviewer. Data extraction was performed using a standard data collection form, extracting information such as study design, sample size, description of participants, Vitamin K2 dose and duration, control interventions and cardiovascular health outcomes.

Risk of bias evaluation

ROBINS-I tool^[14] for the non-randomised trials and Cochrane Risk of Bias 2.0 assessment tool^[15] for the RCTs were applied, respectively to assess the risk of bias across the included trials. We based the studies on methodological quality as low risk of bias, moderate risk of bias or high risk of bias.

Statistical analysis

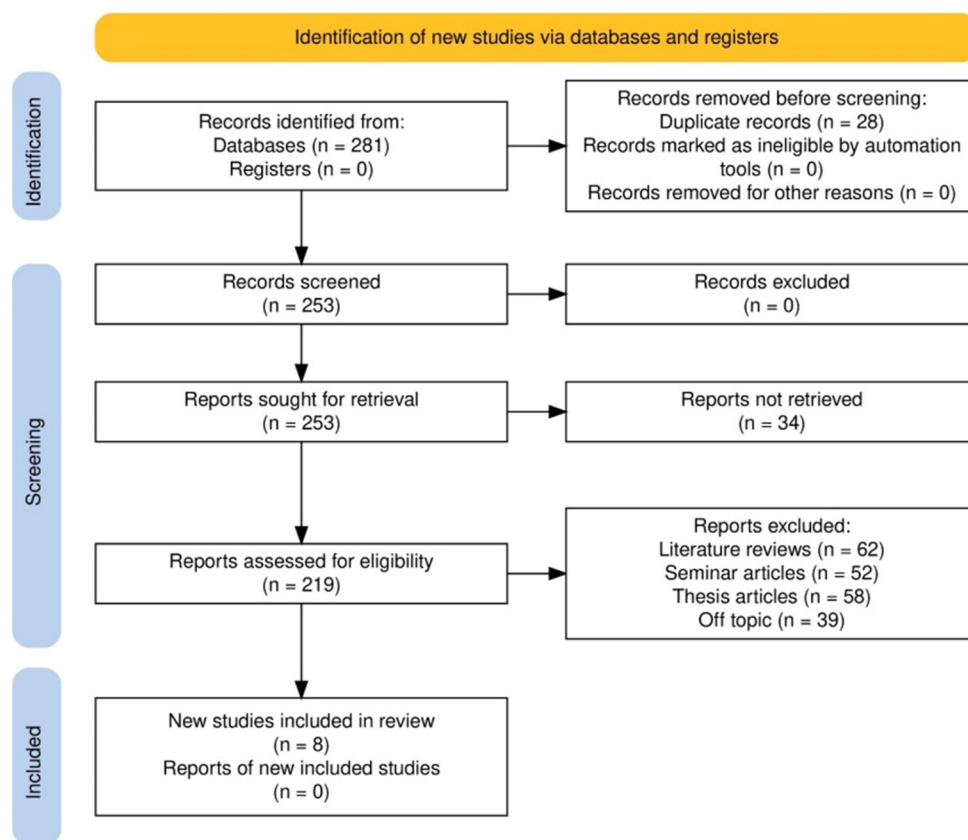
Meta-analysis was conducted with Review Manager (RevMan 5.4) and Stata 17. Continuous variables such as pulse wave velocity and CAC were pooled through mean differences (MDs) with 95% confidence intervals (CIs), while binary outcomes such as all-cause mortality and cardiovascular mortality were calculated as odds ratios (ORs) or risk ratios (RR). Random-effects models were used to account for heterogeneity, and heterogeneity size was calculated through the I^2 statistic. The study selection process is shown in Figure 1 (PRISMA flowchart).

RESULTS

Two hundred and eighty-one records were retrieved from electronic databases, of which 28 duplicates were removed before screening. After removing duplicates, 253 records were screened, of which none were removed at this level. Attempts

Table 1: Search strings utilised across the databases.

Database	Search String
PubMed	('Vitamin K2' OR 'menaquinone' OR 'MK-4' OR 'MK-7' OR 'MK-9') AND ('chronic kidney disease' OR 'CKD' OR 'end-stage renal disease' OR 'ESRD' OR 'hemodialysis' OR 'peritoneal dialysis') AND ('cardiovascular disease' OR 'CVD' OR 'arterial stiffness' OR 'vascular calcification' OR 'coronary artery calcification' OR 'pulse wave velocity' OR 'vascular health' OR 'cardiovascular mortality' OR 'all-cause mortality')
Embase	('Vitamin K2 supplementation' OR 'menaquinone intervention' OR 'MK-4 supplementation' OR 'MK-7 supplementation' OR 'MK-9 intervention') AND ('chronic renal disease' OR 'kidney failure' OR 'end-stage kidney disease' OR 'stage 3 CKD' OR 'stage 4 CKD' OR 'stage 5 CKD' OR 'dialysis-dependent CKD') AND ('arterial compliance' OR 'vascular function' OR 'coronary artery calcification score' OR 'cardiovascular mortality risk' OR 'total mortality')
Cochrane Library	('Vitamin K-dependent proteins' OR 'matrix Gla protein' OR 'Gla proteins' OR 'uncarboxylated MGP' OR 'dp-ucMGP' OR 'phylloquinone') AND ('chronic kidney insufficiency' OR 'advanced CKD' OR 'renal impairment' OR 'glomerular filtration rate decline' OR 'eGFR reduction') AND ('cardiovascular health' OR 'vascular elasticity' OR 'aortic calcification' OR 'cardiovascular events' OR 'stroke risk' OR 'heart failure incidence')
Web of Science	('Vitamin K intake' OR 'Vitamin K deficiency' OR 'menaquinone-rich diet' OR 'vitamin K antagonism' OR 'oral vitamin K') AND ('renal disease progression' OR 'CKD progression' OR 'renal replacement therapy' OR 'CKD stages 3-5') AND ('vascular calcification index' OR 'carotid-femoral pulse wave velocity' OR 'arterial stiffness index' OR 'cardiac mortality' OR 'ischemic heart disease')
Scopus	('Vitamin K analogues' OR 'Vitamin K therapy' OR 'synthetic menaquinones' OR 'Vitamin K metabolic pathways') AND ('end-stage renal failure' OR 'stage 4-5 CKD' OR 'patients on dialysis' OR 'kidney transplant recipients') AND ('vascular inflammation' OR 'atherosclerosis progression' OR 'myocardial infarction risk' OR 'hypertension-related CVD' OR 'all-cause cardiovascular mortality')

**Figure 1:** PRISMA flowchart representing the study selection process for the review. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

were then made to retrieve full text for 253 reports, of which 34 could not be retrieved due to non-availability. Eligibility assessment was done on 219 full-text reports, of which 62 were found to be literature reviews, 52 seminar articles, 58 thesis articles and 39 off-topic, leading to their exclusion. Eight studies^[16-23] were included in the systematic review, of which no new studies were reported to be included.

Bias assessment observations

Among the RCTs included [Figure 2], De Vriese *et al.*^[16] Lees *et al.*^[19] and Eelderink *et al.*^[17] had some issues in some domains, notably D1 (process of randomisation) and D4 (measurement of the outcome), but were at low risk in other domains. Kurnatowska *et al.*^[18] and Levy-Schousboe *et al.*^[20] were at low risk of bias in most domains but had some issues in D3 (missing outcome data) and D5 (selection of reported results). Witham *et al.*^[23] had issues in D2 (deviations from intended interventions) but otherwise had a low overall risk of bias.

For non-randomised trials, as evaluated by ROBINS-I [Figure 3], Palmer *et al.*^[21] had a general moderate risk of bias, mainly due to moderate risk in D1 (confounding), D4 (outcome measurement) and D6 (intervention classification), whereas in all the other domains, low risk was present. Shea *et al.*^[22] had low risk in most of the domains, whereas only in D6 (intervention classification), it was moderate, and in general, it was low.

Demographic attributes

The trials in this review were a broad range of RCTs and observational cohort studies, varying by sample size, follow-up duration and demographic profile of the participants. The RCTs by De Vriese *et al.*^[16] Eelderink *et al.*^[17] Kurnatowska *et al.*^[18] Lees *et al.*^[19] Levy-Schousboe *et al.*^[20] and Witham *et al.*^[23] mainly examined the effect of interventional Vitamin K2 supplementation. The prospective cohort studies by Palmer *et al.*^[21] and Shea *et al.*^[22] aimed to examine dietary Vitamin K intake as well as biomarker-related correlations with cardiovascular events.

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	De Vriese et al. [16]	-	+	+	-	+	+
	Eelderink et al. [17]	+	-	+	+	+	-
	Kurnatowska et al. [18]	+	+	-	+	+	+
	Lees et al. [19]	-	+	+	-	+	-
	Levy-Schousboe et al. [20]	+	-	+	+	-	+
	Witham et al. [23]	+	-	+	+	+	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
- Some concerns
+ Low

Figure 2: Bias assessment using the RoB 2.0 tool.

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Palmer et al. [21]	-	+	+	-	+	-	+	-
	Shea et al. [22]	-	+	+	+	+	-	+	+

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
- Moderate
+ Low

Figure 3: Bias assessment using the ROBINS-I tool.

Sample sizes were extremely heterogeneous, ranging from a large study by Palmer *et al.*^[21] ($n = 56,048$, follow-up time: 23 years) to a very small RCT by Eelderink *et al.*^[17] ($n = 40$, follow-up time: 12 weeks). Mean age of the participants varied from 57 years (Eelderink *et al.*^[17]) to 66 years (Witham *et al.*^[23]), which implies that the population was largely middle-aged to elderly.

Sex distribution among participants was variably presented, with Kurnatowska *et al.*^[18] presenting a precise male-to-female ratio (22 M:20 F), while other studies presented approximate percentage females (e.g., Witham *et al.*^[23]: 39% female; Eelderink *et al.*^[17]: 35% female). Sex distribution was not presented by some studies (De Vriese *et al.*^[16], Lees *et al.*^[19] and Levy-Schousboe *et al.*^[20]), which may limit the possibility of conducting gender-specific outcome analyses [Table 2].

Vitamin K2 supplementation and study interventions

The research included mainly Vitamin K2 supplementation, mainly in the form of menaquinone-7 (MK-7), varying in dose and frequency of administration. De Vriese *et al.*^[16] used 2000 mcg of MK-7 3 times a week together with rivaroxaban, while Eelderink *et al.*^[17] gave 360 mcg MK-7 daily. Kurnatowska *et al.*^[18] used 90 mcg MK-7/day co-administered with Vitamin D, while Witham *et al.*^[23] gave 400 mcg MK-7/day. A different approach was taken in Lees *et al.*^[19] which used Menadiol diphosphate (Vitamin K3) at 5 mg 3 times a week, differing from the MK-7 form mainly used. Control groups used were placebo or standard treatment, except in Kurnatowska *et al.*^[18] where Vitamin D was used as the control. The population targeted was varied, with post-transplant patients being included in Eelderink *et al.*^[17] and Lees *et al.*^[19] but dialysis patients were studied solely in De Vriese *et al.*^[16] and Levy-Schousboe *et al.*^[20]. The estimated glomerular filtration rate (eGFR) was varied in range, with Witham *et al.*^[23] using patients with eGFR 15–45 mL/min/1.73 m², while other trials had more severe CKD or dialysis-dependent patients [Table 3].

Impact on vascular health and calcification markers

Several studies have also looked at vascular stiffness and arterial calcification by measuring parameters such as pulse wave velocity (PWV), carotid intima-media thickness (CCA-IMT), CAC and abdominal aortic calcification (AAC). Eelderink *et al.*^[17] reported a significant reduction in PWV (-0.06 ± 0.26 m/s) in comparison to the placebo group ($+0.27 \pm 0.43$ m/s, $P = 0.010$), demonstrating increased arterial elasticity following Vitamin K2 supplementation. On the contrary, Witham *et al.*^[23] did not see statistically significant changes in PWV (-0.1 m/s, 95% CI: $-0.9-0.7$, $P = 0.77$), indicating the vascular response may be dose-dependent or based on the severity of CKD. Kurnatowska *et al.*^[18] documented a significant reduction in CCA-IMT (0.06 ± 0.08 mm) in comparison to the control group (0.136 ± 0.05 mm, $P = 0.005$), indicating the beneficial effect of Vitamin K2 on arterial remodelling. On the contrary, Lees *et al.*^[19] and Levy-Schousboe *et al.*^[20] noted no significant changes in aortic distensibility, CAC or AAC despite documenting a measurable decrease in dp-ucMGP (-1380 pmol/L, $P < 0.05$ as per Levy-Schousboe *et al.*^[20]), the marker of Vitamin K status. These findings indicate that even though Vitamin K2 has been linked with benefits in biomarkers of VC, the clinical significance of arterial stiffness and plaque formation remains uncertain.

Effects on cardiovascular and overall mortality rates

Longitudinal cohort studies have clarified the associations of Vitamin K status and risk of mortality. Palmer *et al.*^[21] found a robust inverse association between dietary Vitamin K and all-cause mortality (HR: 0.76, 95% CI: 0.72–0.79, $P < 0.001$) with a protective effect. Similarly, Shea *et al.*^[22] noted reduced risk of all-cause mortality with lower levels of dp-ucMGP (HR: 0.71, 95% CI: 0.61–0.83, $P < 0.001$). In RCTs, De Vriese *et al.*^[16] noted a significant reduction in fatal and nonfatal cardiovascular events (HR: 0.34,

Table 2: Demographic variables assessed across the included papers.

Author ID	Year	Location	Study design	Sample size	Mean age (in years)	Male: Female ratio	Follow-up period
De Vriese <i>et al.</i> ^[16]	2021	Belgium	RCT	132	Not reported	Not reported	1.88 years
Eelderink <i>et al.</i> ^[17]	2023	Netherlands	RCT	40	57	35% Female	12 weeks
Kurnatowska <i>et al.</i> ^[18]	2015	Poland	RCT	42	60 (M), 56 (F)	22 M: 20 F	270 days
Lees <i>et al.</i> ^[19]	2021	UK	RCT, Double-blind	90	Not reported	Not reported	1 year
Levy-Schousboe <i>et al.</i> ^[20]	2021	Denmark	RCT, Double-blind	48	Not reported	Not reported	2 years
Palmer <i>et al.</i> ^[21]	2021	Denmark	Prospective cohort	56048	56	47.6% male	23 years
Shea <i>et al.</i> ^[22]	2022	USA	Cohort Study	3066	61	45% female	12.8 years
Witham <i>et al.</i> ^[23]	2020	UK	RCT	159	66	39% Female	12 months

RCT: Randomised controlled trials

Table 3: Technical characteristics of the included papers.

Author ID	Groups assessed	Intervention (Vitamin K2 form and dosage)	Control (Placebo/ Standard care)	eGFR range (mL/min/1.73m ²)	CKD stage (1–5 or dialysis)
De Vriese et al. ^[16]	Rivaroxaban+K2 vs. Rivaroxaban vs. VKA	MK-7, 2000 mg thrice weekly	VKA	Dialysis	Dialysis
Eelderink et al. ^[17]	Vitamin K2 vs. Placebo	MK-7, 360 mcg/day	Placebo	>20	Post-transplant
Kurnatowska et al. ^[18]	Vitamin K2+D vs. Vitamin D	MK-7, 90 mcg/day	Vitamin D	<60	03-May
Lees et al. ^[19]	Vitamin K vs. Placebo	Menadiol diphosphate, 5 mg thrice weekly	Placebo	eGFR>15	Kidney transplant recipients
Levy-Schousboe et al. ^[20]	Vitamin K2 vs. Placebo	MK-7, 360 µg/day	Placebo	Dialysis	CKD stage 5
Palmer et al. ^[21]	Vitamin K1 intake assessed	Dietary intake	Standard diet	Various	General population
Shea et al. ^[22]	Vitamin K biomarkers	Endogenous levels measured	None	41 mL/min/1.73m ²	CKD stages 3-5
Witham et al. ^[23]	Vitamin K2 vs. Placebo	MK-7, 400 mcg/day	Placebo	15-45	3b-4
Author ID	Primary cardiovascular outcome	Secondary cardiovascular outcomes	Anticoagulation therapy use	Statistical effect measure	Inference observed
De Vriese et al. ^[16]	Fatal and nonfatal cardiovascular events	Bleeding risk, Stroke	Warfarin	Not reported	HR: 0.34 (95% CI: 0.19–0.61, P=0.0003)
Eelderink et al. ^[17]	Pulse wave velocity	dp-ucMGP, ucOC	None	dp-ucMGP, ucOC	Change in PWV (–0.06±0.26 m/s) vs. placebo (+0.27±0.43 m/s, P=0.010)
Kurnatowska et al. ^[18]	Carotid IMT	CACS, dp-ucMGP, OC, OPG	None	dp-ucMGP, OC, OPG	CCA-IMT: 0.06±0.08 vs. 0.136±0.05 mm, P=0.005
Lees et al. ^[19]	Aortic distensibility, CAC	dp-ucMGP	None	No significant changes observed	No effect on vascular stiffness or calcification
Levy-Schousboe et al. ^[20]	CAC, AAC, PWV	dp-ucMGP, PIVKA-II	None	HR: –1380 pmol/L dp-ucMGP (P<0.05)	No effect on arterial calcification
Palmer et al. ^[21]	All-cause and CVD mortality	None	None	HR: 0.76 (0.72, 0.79) for all-cause mortality	Higher intake linked to lower mortality
Shea et al. ^[22]	All-cause and CVD mortality	dp-ucMGP, Phylloquinone	None	HR: 0.71 (0.61, 0.83) for all-cause mortality	Lower dp-ucMGP linked to reduced mortality
Witham et al. ^[23]	Pulse wave velocity	AIx, BP, BNP	None	dp-ucMGP	Adjusted treatment effect (–0.1 m/s, 95% CI: –0.9–0.7, P=0.77)

eGFR: Estimated glomerular filtration rate, CKD: Chronic kidney disease, MK: Menaquinone, VKA: Vitamin K antagonists, dp-ucMGP: dephosphorylated-uncarboxylated matrix Gla protein, OGP: Osteoprotegerin, OC: Osteocalcin, PWV: Pulse wave velocity, CCA-IMT: Carotid intima-media thickness, CAC: Coronary artery calcification, AAC: aortic calcification, CVD: Cardiovascular disease, AIx: Augmentation index, BP: Blood pressure, VKDP: Vitamin K-dependent proteins, BNP: B-type natriuretic peptide, vs.: Versus, CI: Confidence interval, HR: Hazard ratio

95% CI: 0.19–0.61, P = 0.0003) in dialysis patients treated with Vitamin K2 supplementation. Conversely, Witham

et al.^[23] and Lees et al.^[19] did not find statistically significant differences in all-cause mortality or cardiovascular events

and noted heterogeneity of Vitamin K2 effects in different subpopulations with CKD.

Biochemical markers and follow-up results

Several studies have compared biomarkers of Vitamin K to assess the efficacy of supplementation. Eelderink *et al.*^[17] and Levy-Schousboe *et al.*^[20] both indicated significant decreases in dp-ucMGP levels, with Levy-Schousboe *et al.*^[20] finding a mean decrease of 1380 pmol/L ($P < 0.05$). Kurnatowska *et al.*^[18] also assessed OC and osteoprotegerin, indicating significant reductions after Vitamin K2 supplementation. Witham *et al.*^[23] assessed markers of arterial stiffness, such as augmentation index (AIx) and blood pressure (BP), but indicated no significant changes in these measurements. Overall, these results suggest that although Vitamin K2 universally increases biochemical markers that are predictive of vascular health, the direct clinical significance for cardiovascular outcomes is uncertain.

Arterial stiffening and VC

The carotid-femoral pulse wave velocity analysis [Figure 4] showed a pooled MD of 0.05 [-0.34, 0.45], no statistically significant difference being found by Vitamin K supplementation versus controls ($Z = 0.27$, $P = 0.79$). Low heterogeneity ($I^2 = 0\%$) existed, with homogenous results

being reported in studies (Eelderink *et al.*,^[17] Lees *et al.*,^[19] Levy-Schousboe *et al.*^[20] and Witham *et al.*^[23]).

Likewise, coronary arterial calcification (Agatston Score) [Figure 5] yielded a pooled MD of 25.05 [-57.05, 107.14] with no statistically significant difference between the Vitamin K and control groups ($Z = 0.60$, $P = 0.55$). The heterogeneity was very low in the analysis ($I^2 = 0\%$), in support of the consistency of the results. The same trend was noted in abdominal aortic calcification (Agatston Score) [Figure 6] with the pooled effect size of 10.35 [-30.76, 51.45], with no significant reduction in VC ($Z = 0.49$, $P = 0.62$).

Mortality outcomes

The combined OR for all-cause mortality [Figure 7] was calculated as 0.96 [0.93, 0.98], showing a small but statistically significant reduction in mortality in those cohorts treated with Vitamin K ($Z = 3.31$, $P = 0.0009$). The biggest share of this effect was provided by cohort studies (Palmer *et al.*,^[21] Shea *et al.*,^[22]), whereas RCTs (Eelderink *et al.*,^[17] Witham *et al.*,^[23]) provided non-significant results (OR = 0.81 [0.45, 1.47], $Z = 0.69$, $P = 0.49$).

For cardiovascular mortality [Figure 8], the global OR was 0.98 [0.94, 1.02], which did not indicate any protective effect

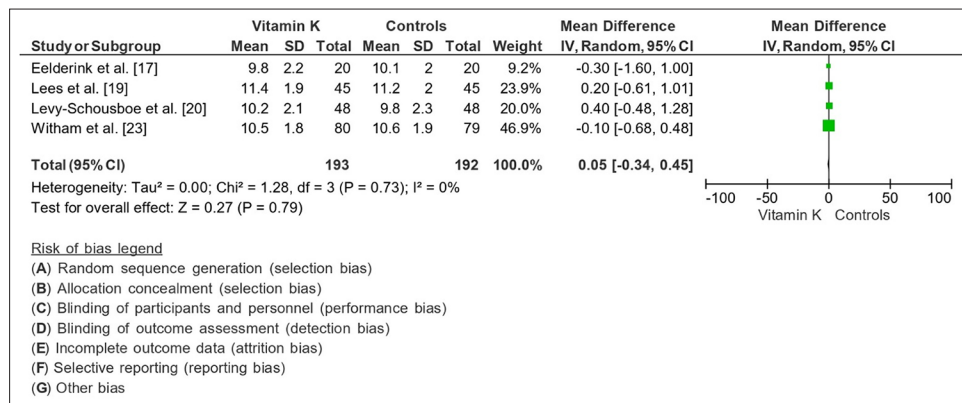


Figure 4: Carotid-femoral pulse wave velocity (Vitamin K vs. controls). The bold value represents the mean difference (MD) in pulse wave velocity (PWV) between the Vitamin K2 supplementation and control groups. SD: Standard deviation, IV: Inverse variance, CI: Confidence interval.

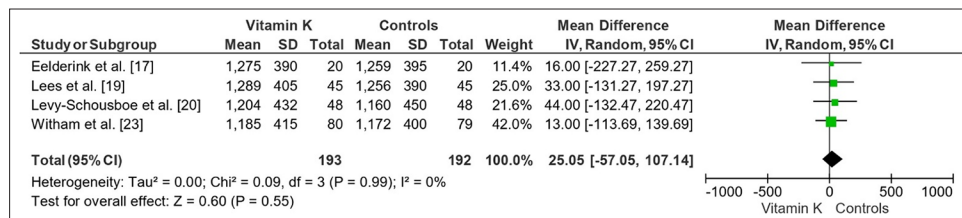


Figure 5: Coronary arterial calcification - Agatston score (Vitamin K vs. controls). The bold value represents the mean difference (MD) in pulse wave velocity (PWV) between the Vitamin K2 supplementation and control groups. SD: Standard deviation, IV: Inverse variance, CI: Confidence interval.

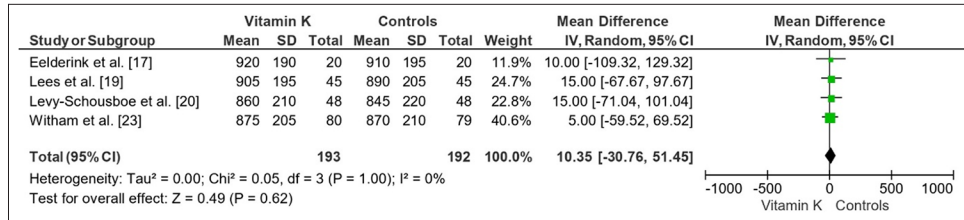


Figure 6: Abdominal aortic calcification – Agatston score (Vitamin K vs. controls). The bold value represents the mean difference (MD) in pulse wave velocity (PWV) between the Vitamin K2 supplementation and control groups. SD: Standard deviation, IV: Inverse variance, CI: Confidence interval.

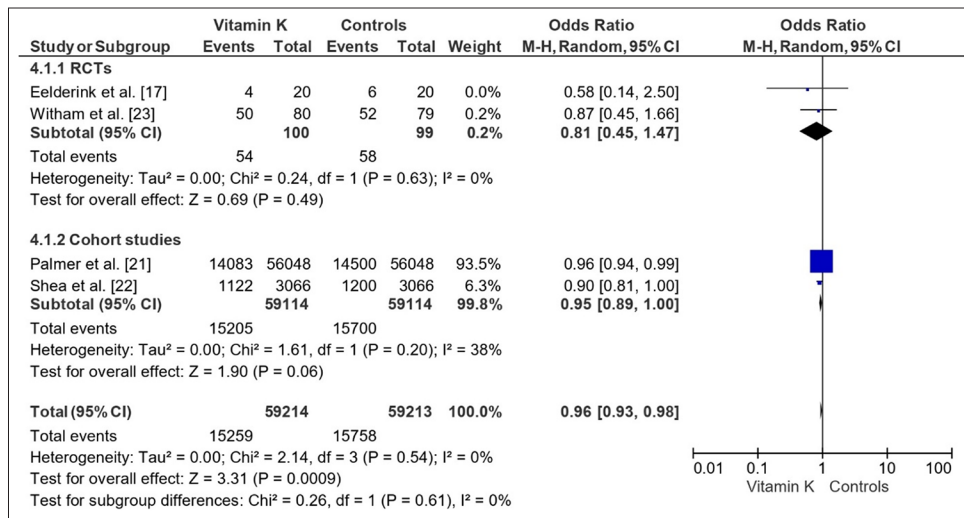


Figure 7: All-cause mortality across randomised controlled trials and cohort studies (Vitamin K vs. controls). The bold value represents the mean difference (MD) in pulse wave velocity (PWV) between the Vitamin K2 supplementation and control groups. SD: Standard deviation, IV: Inverse variance, CI: Confidence interval.

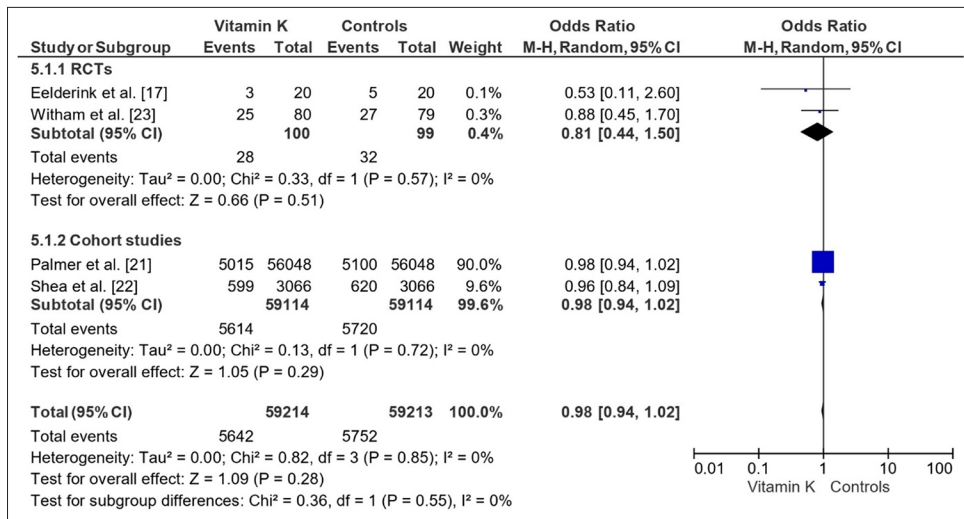


Figure 8: Cardiovascular mortality across randomised controlled trials (RCT) and cohort studies (Vitamin K vs. controls). The bold value represents the mean difference (MD) in pulse wave velocity (PWV) between the Vitamin K2 supplementation and control groups.

of Vitamin K ($Z = 1.09$, $P = 0.28$). RCT and cohort studies revealed comparable findings, with low heterogeneity ($I^2 = 0\%$).

DISCUSSION

Comparative assessment of analysed evidence

The results across the included trials varied with regard to the impact of Vitamin K2 supplementation on cardiovascular events in CKD and ESKD patients. Eelderink *et al.*,^[17] Kurnatowska *et al.*^[18] and De Vriese *et al.*^[16] reported improved vascular function and a decrease in cardiovascular events, while Lees *et al.*^[19] Levy-Schousboe *et al.*^[20] and Witham *et al.*^[23] had no significant effects on arterial stiffness or VC. Palmer *et al.*^[21] and Shea *et al.*^[22] the long-term cohort studies, described that increased Vitamin K intake was related to decreased mortality, partly in agreement with the interventional result of De Vriese *et al.*^[16] but in disagreement with the null results in the RCTs of Lees *et al.*^[19] and Witham *et al.*^[23]

Vitamin K status and cardiovascular risk in CKD

Insufficient consumption of both phylloquinone (Vitamin K1) and menaquinone (Vitamin K2) has been correlated with a heightened risk of cardiovascular mortality as well as overall mortality in patients diagnosed with CKD.^[24] The inadequacy of Vitamin K has been identified as an independent risk factor for CVD, with research indicating its involvement in the processes that lead to VC and arterial stiffness.^[25] Low levels of Vitamin K2, or the pharmacological blockade of Vitamin K function through warfarin administration, have been associated with an augmented accumulation of vascular calcium deposits, thereby exacerbating arterial injury in CKD populations.^[12] Some investigations have indicated that Vitamin K2 supplementation may lead to a modest increase in high-density lipoprotein cholesterol levels while concurrently reducing systemic inflammation.^[26,27] In light of its possible impacts on vascular health, it has been suggested that Vitamin K2 supplementation could decelerate the progression of VC and lower the risk of atherosclerosis, CVD and stroke.^[28-31] Observational evidence derived from dietary intake analyses has indicated an inverse association between menaquinone intake exceeding 21.6 $\mu\text{g}/\text{day}$ and mortality associated with coronary heart disease and aortic calcification; however, such an association has not been observed with phylloquinone intake.^[32-34] Results from the PREVENT study indicated that 31% of participants demonstrated functional Vitamin K deficiency, with a markedly higher prevalence among older individuals, those afflicted by hypertension, type 2 diabetes, CKD and pre-existing cardiovascular conditions.^[35] Active RCTs are ongoing as well to evaluate the efficacy of Vitamin K1 and K2

supplementation for reducing VC in CKD, though optimal dose and clinical efficacy remain under investigation.^[36,37]

Guidelines pertaining to Vitamin K supplementation in CKD

International clinical practice guidelines suggest arterial BP below 130/80 mmHg in CKD patients with comorbid cardiovascular risk factors, in an attempt to avoid cardiorenal complications.^[38] Recent studies have envisioned that Vitamin K2 supplementation could have a role in the modulation of BP, particularly in primary hypertension.^[39,40] Mechanistic studies have employed 16S ribosomal RNA (rRNA) sequencing to examine the theoretical mechanisms by which Vitamin K2 modulates vascular function and BP homeostasis.^[41] Their results demonstrated interaction between Vitamin K2, the complement system, calcium signalling pathways and the renin-angiotensin-aldosterone system (RAAS) in an experimental model of salt-sensitive hypertension.^[41] The study proved RAAS participation in salt-induced hypertension, but also demonstrated Vitamin K2 administration blocked RAAS-mediated signals, and thus suggests a potential regulatory function in hypertension pathophysiology. In addition, microbial analysis demonstrated some gut bacteria, such as *Dubosiella* and *Ileibacterium*, were associated with beneficial modulation of RAAS, and thus suggest a potential connection between the composition of intestinal microbiota, Vitamin K2 metabolism and vascular homeostasis.^[42] These findings have prompted speculations that probiotic supplementation with bacterial strains enhancing Vitamin K2 production is implicated in vascular endothelium protection through immune and metabolic pathway regulation.^[25-42] Clinical trials are, however, needed to establish the long-term effect of Vitamin K2 supplementation on hypertension and vascular function in CKD populations.

Vitamin K deficiency and its significance in CKD

Our findings concurred with the postulations of Bellone *et al.*^[43] who emphasised that Vitamin K deficiency is an ubiquitous and potentially modifiable risk factor in CKD that is responsible for VC as well as bone fragility. In line with their study, our research confirmed that CKD patients with a low Vitamin K diet were at increased risk of all-cause mortality, as revealed by the pooled OR of 0.96 [0.93, 0.98] ($Z = 3.31$, $P = 0.0009$, $I^2 = 0\%$). However, while Bellone *et al.*^[43] theorised that Vitamin K supplementation needs to be added to treatment strategies for CKD to prevent cardiovascular and skeletal complications, our meta-analysis was unable to identify any significant reduction in vascular stiffness or calcification biomarkers with such supplementation. This finding suggests that while Vitamin K deficiency is undoubtedly associated with unfavourable outcomes in the

context of cardiovascular and bone morbidity, the immediate effect of supplementation is uncertain.

In addition, Bellone *et al.*^[43] suggested that Vitamin K status could serve as a biomarker of renal and cardiovascular well-being, a notion indirectly validated by our findings of reductions in dp-ucMGP within some of the trials (e.g., Levy-Schousboe *et al.*,^[20]) even without the attendant clinical benefits. This suggests that while Vitamin K-dependent proteins can be employed as a marker of vascular well-being, their alteration with supplementation does not necessarily equate to improved clinical results.

VC and activation of MGP

Our evidence supports Roumeliotis *et al.*^[44] who emphasised that VC is a progressive complication of CKD and ESRD and is mediated by a pro-calcific/anti-calcific imbalance, with MGP involved. Roumeliotis *et al.*^[44] further claimed that the inactive dp-ucMGP form of MGP, reflecting Vitamin K deficiency, is strongly associated with cardiovascular events and mortality in CKD patients. Our research also showed that cohort studies had a negative correlation between Vitamin K intake and all-cause mortality, which agrees with their evidence.

However, Roumeliotis *et al.*^[44] suggested that Vitamin K-dependent proteins can actively induce the reversal of VC by removing calcium deposits from arterial walls. The above suggestion conflicts with our findings, which revealed that MDs for carotid-femoral pulse wave velocity (0.05 [-0.34, 0.45], $Z = 0.27$, $P = 0.79$) and CAC (25.05 [-57.05, 107.14], $Z = 0.60$, $P = 0.55$) showed no significant improvement with Vitamin K2 supplementation. Such differences can be explained by differences in study populations, follow-up periods or suboptimal dosing of Vitamin K2 in the performed interventional trials. While mechanistic studies suggest that Vitamin K can have a protective advantage to vascular health, our evidence suggests that such an effect is not necessarily translatable to clinical significance in all CKD populations.

Vitamin K subclinical deficiency in CKD

The results shown by Cozzolino *et al.*^[45] concurred with our observation of prevalent subclinical Vitamin K deficiency among CKD patients. Their experiment demonstrated increased Vitamin K requirements upon activation of Vitamin K-dependent proteins involved in the regulation of calcification, which fact is consistent with increased dp-ucMGP levels reported among CKD patients in our considered studies (e.g., Levy-Schousboe *et al.*^[20]). Yet, while Cozzolino *et al.*^[45] indicated that the deficiency would increase the risk of cardiovascular complications in CKD patients, our research did not identify a lasting benefit of Vitamin K2 supplementation to reduce vascular stiffness or calcification of arteries. One of the key areas of contention

is that Cozzolino *et al.*^[45] indicated that Vitamin K depletion is a direct stimulus to VC, whereas our study revealed that even with Vitamin K2 supplementation, no appreciable improvement in VC outcomes was evident (MD for AAC: 10.35 [-30.76, 51.45], $Z = 0.49$, $P = 0.62$). This indicates that although Vitamin K deficiency may be a causative factor for the phenomenon, it is doubtful that it is the only factor for VC in patients with CKD, and other pathophysiological mechanisms may be involved.

Limitations

This study was also faced with numerous limitations that influenced the interpretation of its results. Variability in the study design, Vitamin K2 dosing, follow-up periods and CKD stages led to heterogeneity of the reported effects. While improved biomarkers were documented, whether these changes have clinical significance which is uncertain, since there were no reported long-term decreases in arterial stiffness and VC. Most of the significant results relied on observational cohort studies, which are prone to residual confounding, and were thus precluded from making claims of causality. In addition, the relatively modest sizes of a number of the RCTs might have diluted the statistical power necessary to show significant differences between cardiovascular outcomes. Heterogeneity of the control interventions, which involved placebo and standard care, also made study comparisons difficult in a direct manner. Finally, the follow-up periods in a number of studies might not have been long enough to ascertain the long-term effects of Vitamin K2 on CVD.

Future implications

Larger controlled trials with controlled dosing of Vitamin K2, control interventions and follow-up times should be carried out in future research to determine its role in cardiovascular risk reduction in CKD and ESKD patients. Long-term follow-up studies will be required to determine the long-term effect of supplementation on VC and clinical outcomes. Investigation of potential interactions between Vitamin K2 and other cardiovascular risk modifiers, including anticoagulants and mineral metabolism regulators, may further determine its therapeutic role. Patient subgroups defined by CKD severity, dialysis status and baseline Vitamin K status should be studied to determine populations most likely to benefit from supplementation. Standardised reporting of arterial stiffness and VC outcomes will be required to maximise between-study comparability and to construct the evidence base to inform clinical recommendations.

CONCLUSION

This review points to the fact that Vitamin K2 supplementation increased biomarkers for VC but failed

to consistently produce significant decreases in arterial stiffness, coronary or aortic calcification or cardiovascular mortality in CKD and ESKD patients. All-cause mortality decreased marginally and significantly in observational studies, but RCTs were heterogeneous. The findings indicated that although Vitamin K2 could have a part to play in the modulation of vascular health markers, its definitive clinical effect on cardiovascular events was unclear. Due to heterogeneity of results, well-performed trials with long-term follow-up and increased numbers are required to determine the probable benefit of Vitamin K2 supplementation in CKD patients.

Ethical approval: The Institutional Review Board approval is not required.

Declaration of Patient Consent: Patient's consent was not required as there are no patients in this study.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

REFERENCES

- Zhang T, O'Connor C, Sheridan H, Barlow JW. Vitamin K2 in health and disease: A clinical perspective. *Foods* 2024;13:1646.
- Kaesler N, Schurgers LJ, Floege J. Vitamin K and cardiovascular complications in chronic kidney disease patients. *Kidney Int* 2021;100:1023-36.
- Fusaro M, Cosmai L, Evenepoel P, Nickolas TL, Cheung AM, Aghi A, *et al.* Vitamin K and kidney transplantation. *Nutrients* 2020;12:2717.
- Palmer CR, Blekkenhorst LC, Lewis JR, Ward NC, Schultz CJ, Hodgson JM, *et al.* Quantifying dietary vitamin K and its link to cardiovascular health: A narrative review. *Food Funct* 2020;11:2826-37.
- Bellinge JW, Dalgaard F, Murray K, Connolly E, Blekkenhorst LC, Bondonno CP, *et al.* Vitamin K intake and atherosclerotic cardiovascular disease in the danish diet cancer and health study. *J Am Heart Assoc* 2021;10:e020551.
- Kaesler N, Schreiber F, Speer T, De la Puente-Secades S, Rapp N, Drechsler C, *et al.* Altered vitamin K biodistribution and metabolism in experimental and human chronic kidney disease. *Kidney Int* 2022;101:338-48.
- Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andía JB, *et al.* Vertebral fractures and mortality in haemodialysis patients. *Nephrol Dial Transplant* 2009;24:239-46.
- Grzejszczak P, Kurnatowska I. Role of Vitamin K in CKD: Is its supplementation advisable in CKD patients? *Kidney Blood Press Res* 2021;46:523-30.
- Shea MK, O'Donnell CJ, Hoffmann U, Dallal GE, Dawson-Hughes B, Ordovas JM, *et al.* Vitamin K supplementation and progression of coronary artery calcium in older men and women. *Am J Clin Nutr* 2009;89:1799-807.
- Roumeliotis S, Roumeliotis A, Georgianos PI, Thodis E, Schurgers LJ, Maresz K, *et al.* Vitamin K In PERitoneal DIAlysis (VIKIPEDIA): Rationale and study protocol for a randomized controlled trial. *PLoS One* 2022;17:e0273102.
- Caluwé R, Verbeke F, De Vriese AS. Evaluation of vitamin K status and rationale for vitamin K supplementation in dialysis patients. *Nephrol Dial Transplant* 2020;35:23-33.
- Fusaro M, Cozzolino M, Plebani M, Iervasi G, Ketteler M, Gallieni M, *et al.* Sevelamer use, vitamin K levels, vascular calcifications, and vertebral fractures in hemodialysis patients: Results from the VIKI study. *J Bone Miner Res* 2021;36:500-9.
- Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;372:n160.
- Igelström E, Campbell M, Craig P, Katikireddi SV. Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) is frequently misapplied: A methodological systematic review. *J Clin Epidemiol* 2021;140:22-32.
- Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
- De Vriese AS, Caluwé R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: A multicenter randomized controlled trial. *J Am Soc Nephrol* 2021;32:1474-83.
- Eelderink C, Kremer D, Riphagen IJ, Knobbe TJ, Schurgers LJ, Pasch A, *et al.* Effect of vitamin K supplementation on serum calcification propensity and arterial stiffness in vitamin K-deficient kidney transplant recipients: A double-blind, randomized, placebo-controlled clinical trial. *Am J Transplant* 2023;23:520-30.
- Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, Kaczmarek M, Stefańczyk L, Vermeer C, *et al.* Effect of vitamin K2 on progression of atherosclerosis and vascular calcification in nondialyzed patients with chronic kidney disease stages 3-5. *Pol Arch Med Wewn* 2015;125:631-40.
- Lees JS, Rankin AJ, Gillis KA, Zhu LY, Mangion K, Rutherford E, *et al.* The VIKTORIES trial: A randomized, double-blind, placebo-controlled trial of vitamin K supplementation to improve vascular health in kidney transplant recipients. *Am J Transplant* 2021;21:3356-68.
- Levy-Schousboe K, Frimodt-Møller M, Hansen D, Peters CD, Kjærgaard KD, Jensen JD, *et al.* Vitamin K supplementation and arterial calcification in dialysis: Results of the double-blind, randomized, placebo-controlled RenaKvit trial. *Clin Kidney J* 2021;14:2114-23.
- Palmer CR, Bellinge JW, Dalgaard F, Sim M, Murray K, Connolly E, *et al.* Association between vitamin K1 intake and mortality in the Danish Diet, cancer, and health cohort. *Eur J Epidemiol* 2021;36:1005-14.
- Shea MK, Barger K, Booth SL, Wang J, Feldman HI, Townsend RR, *et al.* Vitamin K status, all-cause mortality, and cardiovascular disease in adults with chronic kidney disease: The chronic renal insufficiency cohort. *Am J Clin Nutr* 2022;115:941-8.

23. Witham MD, Lees JS, White M, Band M, Bell S, Chantler DJ, *et al.* Vitamin K supplementation to improve vascular stiffness in CKD: The K4 kidneys randomized controlled trial. *J Am Soc Nephrol* 2020;31:2434-45.
24. Vissers LE, Dalmeijer GW, Boer JM, Verschuren WM, Van Der Schouw YT, Beulens JW. The relationship between vitamin K and peripheral arterial disease. *Atherosclerosis* 2016;252:15-20.
25. Popa DS, Bigman G, Rusu M. The role of vitamin K in humans: Implication in aging and age-associated diseases. *Antioxidants (Basel)* 2021;10:566.
26. Mladěnka P, Macáková K, Kujovská Krčmová L, Javorská L, Mrštná K, Carazo A, *et al.* Vitamin K-sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. *Nutr Rev* 2022;80:677-98.
27. Beulens JW, Van der AD, Grobbee DE, Sluijs I, Spijkerman AM, Van der Schouw Y. Dietary phyloquinone and menaquinones intakes and risk of type 2 diabetes. *Diabetes Care* 2010;33:1699-705.
28. Harshman SG, Shea MK. The role of vitamin K in chronic aging diseases: Inflammation, cardiovascular disease, and osteoarthritis. *Curr Nutr Rep* 2016;5:90-8.
29. Braam LA, Hoeks AP, Brouns F, Hamulyák K, Gerichhausen MJ, Vermeer C. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: A follow-up study. *Thromb Haemost* 2004;91:373-80.
30. Vaccaro JA, Huffman FG. Phylloquinone (vitamin K1) intake and pulse pressure as a measure of arterial stiffness in older adults. *J Nutr Gerontol Geriatr* 2013;32:244-57.
31. Provenzano M, Coppolino G, Faga T, Garofalo C, Serra R, Andreucci M. Epidemiology of cardiovascular risk in chronic kidney disease patients: The real silent killer. *Rev Cardiovasc Med* 2019;20:209-20.
32. Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, Van Der Meer IM, *et al.* Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: The rotterdam study. *J Nutr* 2004;134:3100-5.
33. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Turck D, Bresson J, Burlingame B, Dean T, *et al.* Dietary reference values for vitamin K. *EFSA J* 2017;15:e04780.
34. Cundiff DK, Agutter PS. Cardiovascular disease death before age 65 in 168 countries correlated statistically with biometrics, socioeconomic status, tobacco, gender, exercise, macronutrients, and vitamin K. *Cureus* 2016;8:e748.
35. Riphagen IJ, Keyzer CA, Drummen NE, De Borst MH, Beulens JW, Gansevoort RT, *et al.* Prevalence and effects of functional vitamin K insufficiency: The PREVEND study. *Nutrients* 2017;9:1334.
36. Roumeliotis S, Duni A, Vaios V, Kitsos A, Liakopoulos V, Dounousi E. Vitamin K supplementation for prevention of vascular calcification in chronic kidney disease patients: Are we there yet? *Nutrients* 2022;14:925.
37. Krueger T, Schlieper G, Schurgers L, Cornelis T, Cozzolino M, Jacobi J, *et al.* Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): A rationale and study protocol. *Nephrol Dial Transplant* 2014;29:1633-8.
38. Li PK, Ma TK. Global impact of nephropathies. *Nephrology* 2017;22 Suppl S4:9-13.
39. Bertolani F, Pederzini A. Vitamin K in arterial hypertension. *Clin Nuova Rass Prog Med Int* 1948;6:169-79.
40. Bellini E. The treatment of essential arterial hypertension; vitamin K. *Minerva Med* 1948;39:56-9.
41. Liu TH, Chen MH, Tu WQ, Liang QE, Tao WC, Jin Z, *et al.* Network and 16S rRNA sequencing-combined approach provides insightful evidence of vitamin k2 for salt-sensitive hypertension. *Front Nutr* 2021;8:639467.
42. Liu TH, Tao WC, Liang QE, Tu WQ, Xiao Y, Chen LG. Gut microbiota-related evidence provides new insights into the association between activating transcription factor 4 and development of salt-induced hypertension in mice. *Front Cell Dev Biol* 2020;8:1283.
43. Bellone F, Cinquegrani M, Nicotera R, Carullo N, Casarella A, Presta P, *et al.* Role of vitamin K in chronic kidney disease: A focus on bone and cardiovascular health. *Int J Mol Sci* 2022;23:5282.
44. Roumeliotis S, Roumeliotis A, Dounousi E, Eleftheriadis T, Liakopoulos V. Vitamin K for the treatment of cardiovascular disease in end-stage renal disease patients: Is there hope? *Curr Vasc Pharmacol* 2021;19:77-90.
45. Cozzolino M, Mangano M, Galassi A, Ciceri P, Messa P, Nigwekar S. Vitamin K in chronic kidney disease. *Nutrients* 2019;11:168.

How to cite this article: Matreja PS, Awasthi S, Singh S, Jain SK. Impact of Vitamin K supplementation on cardiovascular health outcomes associated with kidney disease – A systematic review and meta-analysis. *Indian J Physiol Pharmacol*. doi: 10.25259/IJPP_169_2025