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The ViKTORIES trial: A randomized, double-blind, placebo-controlled trial of vitamin K supplementation to improve vascular health in kidney transplant recipients

Jennifer S. Lees[1,2] | Alastair J. Rankin[1,2] | Keith A. Gillis[1,2] | Luke Y. Zhu[1] | Kenneth Mangion[1,2] | Elaine Rutherford[1] | Giles H. Roditi[1,2] | Miles D. Witham[3] | Donna Chantler[4] | Maurizio Panarelli[4] | Alan G. Jardine[1] | Patrick B. Mark[1,2]

[1]Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

[2]Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Glasgow, UK

[3]AGE Research Group, NIHR Newcastle Biomedical Research Centre, 3rd Floor Biomedical Research Building, Campus for Ageing and Vitality, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust Newcastle upon Tyne, Glasgow, UK

[4]Department of Clinical Biochemistry, Glasgow Royal Infirmary, NHS Greater Glasgow and Clyde, Glasgow, UK

Correspondence
Jennifer S. Lees, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Avenue, Glasgow, G12 8TA, UK.
Email: jennifer.lees@glasgow.ac.uk

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Premature cardiovascular disease and death with a functioning graft are leading causes of death and graft loss, respectively, in kidney transplant recipients (KTRs). Vascular stiffness and calcification are markers of cardiovascular disease that are prevalent in KTR and associated with subclinical vitamin K deficiency. We performed a single-center, phase II, parallel-group, randomized, double-blind, placebo-controlled trial (ISRCTN22012044) to test whether vitamin K supplementation reduced vascular stiffness (MRI-based aortic distensibility) or calcification (coronary artery calcium score on computed tomography) in KTR over 1 year of treatment. The primary outcome was between-group difference in vascular stiffness (ascending aortic distensibility). KTRs were recruited between September 2017 and June 2018, and randomized 1:1 to vitamin K (menadiol diphosphate 5 mg; $n = 45$) or placebo ($n = 45$) thrice weekly. Baseline demographics, clinical history, and immunosuppression regimens were similar between groups. There was no impact of vitamin K on vascular stiffness (treatment effect −0.23 [95% CI −0.75 to 0.29] × 10^{-3} $mmHg^{-1}$; $p = .377$), vascular calcification (treatment effect −141 [95% CI − 320 to 38] units; $p = .124$), nor any other outcome measure. In this heterogeneous cohort of prevalent KTR, vitamin K supplementation did not reduce vascular stiffness or calcification over 1 year. Improving vascular health in KTR is likely to require a multifaceted approach.

KEYWORDS
cardiovascular disease, clinical research / practice, clinical trial, diagnostic techniques and imaging: computed tomography, diagnostic techniques and imaging: magnetic resonance imaging, kidney disease, kidney transplantation / nephrology

Abbreviations: AE, adverse event; CACS, coronary artery calcium score; CKD, chronic kidney disease; CT, computed tomography; dp-ucMGP, desphospho-undercarboxylated Matrix Gla Protein; ESKD, end-stage kidney disease; KTR, kidney transplant recipient; MRI, magnetic resonance imaging; SAE, serious adverse event; SUSAR, suspected unexpected serious adverse reaction.

1 | INTRODUCTION

Cardiovascular disease is a major cause of morbidity in patients with chronic kidney disease (CKD) and is most pronounced in those with end-stage kidney disease (ESKD). The risk of cardiovascular disease is attenuated by kidney transplantation, but cardiovascular risk remains elevated compared with the general population,[1] progresses with declining transplant function[2] and is a major cause of death with a functioning graft.[3]

In CKD, cardiovascular risk can be partly attributed to atherosclerotic risk factors seen in the general population, such as smoking, dyslipidemia, and hypertension. However, secondary prevention strategies for cardiovascular disease (including antiplatelet and statins) are inadequate to address the excess cardiovascular risk seen in kidney transplant recipients (KTRs).[4-8] People with advanced CKD including KTR exhibit markers of cardiovascular aging that are more CKD-specific, and disproportionate for age and gender, such as vascular stiffness and calcification.[9-11] These markers are independently and significantly associated with cardiovascular disease and mortality among KTRs,[12-14] and there are no specific treatments available to improve vascular stiffness and calcification.

Vascular calcification impairs the ability of a vessel to stretch and relax, resulting directly in vascular stiffness, increased afterload, hypertension, and left ventricular hypertrophy.[15] Vascular calcification in CKD results from a relative excess of calcification promoters (e.g., CKD mineral and bone disorder, dyslipidemia, and diabetes) compared with inhibitors (including vitamin K–dependent proteins and magnesium).[16] Vitamin K is an essential cofactor for posttranslational carboxylation (activation) of a number of calcification inhibitors, such as Matrix Gla protein, osteocalcin, and Gla-rich protein.[17] In subclinical vitamin K deficiency, these calcification inhibitors are incompletely activated, and vascular calcification can progress unopposed.[18] Activity of these calcification inhibitors, and thus vitamin K status, can be estimated by measuring the levels of undercarboxylated enzyme in the blood.[19,20] Of these, desphospho-undercarboxylated Matrix Gla Protein (dp-ucMGP) may be the most sensitive for detecting changes in vitamin K status.[21]

Vitamin K deficiency is common among KTRs (at least in part due to suboptimal dietary intake[22]) and is associated with cardiovascular disease and increased mortality in this population.[23] Vitamin K supplementation may provide an inexpensive and low-risk treatment to attenuate progression of vascular stiffness and calcification in KTR by optimizing the function of vitamin K–dependent calcification inhibitors.

Trials of vitamin K to improve vascular stiffness and calcification show promising results in various populations.[24] We designed the ViKTORIES trial (Vitamin K in kidney Transplant Organ Recipients: Investigating vEssel Stiffness) to investigate the hypothesis that vitamin K supplementation improves vascular stiffness and calcification over 1 year in prevalent KTR.

2 | MATERIALS AND METHODS

The full ViKTORIES methods have been published previously.[25]

2.1 | Trial design and participants

This was a single-center, phase II, parallel-group, randomized, double-blind, placebo-controlled trial in prevalent KTR. Adult participants (18 years or over) who had a functioning kidney transplant for a year or more (eGFR >15 ml/min/1.73 m^2 by CKD-EPI[26]) were included. There was no minimum threshold for vascular stiffness or calcification. We excluded participants with the following: permanent or paroxysmal atrial fibrillation (known or identified at screening), warfarin use, taking vitamin K or indication for vitamin K, allergies to constituent ingredients of the study interventions (gelatin, lactose, or cellulose), breastfeeding or of childbearing potential, known glucose-6-phosphate dehydrogenase deficiency, life expectancy <12 months, standard contraindications to magnetic resonance imaging (MRI),[27] or inability to provide written informed consent in English.

2.2 | Interventions

Full details of the choice and preparation of interventions have been detailed previously.[25] In brief, participants were randomized to menadiol diphosphate 5 mg or a matching placebo, administered orally three times per week (Monday, Wednesday, Friday) for 12 months. Menadiol diphosphate has not been used previously for this indication; however, it is a licensed preparation to correct vitamin K deficiency and has demonstrated similar biological activity to phytomenadione (vitamin K1) for correction of coagulopathy associated with liver disease.[28] This preparation was selected as it facilitated production of a matching placebo. Daily requirement of vitamin K is around 1 μg/kg.[29] The dose of 5 mg thrice weekly was, therefore, considered adequate to ensure saturation of vitamin K stores.

2.3 | Randomization sequence generation

A computer-generated code list was provided by Sealed Envelope (Sealed Envelope Ltd) in a password-protected file to the drug manufacturer (Tayside Pharmaceuticals) to produce identical, sequentially numbered bottles containing either vitamin K or placebo. The code list was organized in random permuted blocks to facilitate 1:1 unstratified allocation ratio.

2.4 | Allocation concealment mechanism

Randomization was conducted by study investigators using a custom-built, password-protected, web-based system, created

and maintained by a third party not otherwise involved in the trial (Sealed Envelope Ltd).

2.5 | Implementation

Participants were recruited (J.S.L.) from routine outpatient transplant clinic appointments in the west of Scotland (NHS Greater Glasgow and Clyde with a Patient Identification Centre in NHS Lanarkshire [Scotland, UK]) and enrolled into the study, including obtaining informed consent and randomizing according to methods detailed above.

2.6 | Blinding

Local investigators, research nurses, pharmacy staff, and participants were blinded to treatment allocation by use of numbered but otherwise identical medication bottles. Investigations including laboratory analysis of blood and urine samples, pulse wave velocity measurements, and quality of life questionnaires were conducted by blinded study investigators or laboratory staff. After enrollment in the study, participants were given a five-digit study ID (two-digit site code "01" followed by three-digit sequential screening code).

2.7 | Data capture

A custom-designed electronic case report form was used, designed (by J.S.L.) using Castor Electronic Data Capture (www.castoredc.com; Amsterdam, the Netherlands).

2.8 | Outcomes

The primary outcome was between-group difference measured by MRI-based ascending aortic distensibility at 12 months. All secondary outcomes were assessed as between-group differences at 12 months and were tested hierarchically in the following order: coronary artery calcification score (CACS) by non-contrast computed tomography (CT), carotid-femoral pulse wave velocity and augmentation index (SphygmoCor XCEL PWA and PWV software, AtCor Medical Pty Ltd), MRI measures of cardiac structure and function (descending aortic distensibility, left/right ventricular mass, function and peak systolic strain, T1 and T2 relaxation times), office blood pressure, electrocardiogram (ECG), calcium metabolism and bone turnover markers (calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D), transplant function, proteinuria, and quality of life (EuroQol EQ-5D-5L instrument[30]).

2.9 | Vitamin K status

dp-ucMGP was used as a marker of vitamin K status to confirm biological effect of supplementation. dp-ucMGP was measured in thawed plasma samples using an automated chemiluminescence sandwich immunoassay (InaKtifMGP) provided by ImmunoDiagnosticSystems (IDS PLC, Tyne and Wear) and processed on an IDS-iSYS instrument in the biochemistry laboratory at Glasgow Royal Infirmary, NHS Greater Glasgow and Clyde. During assay verification, there were concerns about linearity due to problems with variable recovery particularly at the lower end of the assay (<900 pmol/L). Reporting of absolute values of dp-ucMGP was possible above 900 pmol/L, but not below, and dp-ucMGP values <900 pmol/L were, therefore, considered to be equal to 900 pmol/L.

2.10 | Imaging acquisition and assessment

Full details of the MRI and CT image acquisition sequences and analysis are available in the published protocol.[25] Participants underwent ECG-gated, non-contrast cardiac MRI on a Siemens Prisma 3 T scanner (Siemens Healthineers). CACS was obtained using an Aquilion ONE Vision Edition CT scanner (Canon Medical Systems Ltd.).

Aortic volumes were obtained from MRI cine images, with simultaneous blood pressure measurements. Aortic distensibility ($mmHg^{-1}$) in ascending and descending aorta was then calculated from the following equation[31-33]:

$$AD = \frac{[\text{Maximum aortic volume (ml)}] - [\text{Minimum aortic volume (ml)}]}{[\text{Minimum aortic volume (ml)}] \times [\text{Pulse pressure (mmHg)}]}$$

MRI outcomes were assessed on dedicated software (CVi42, Circle Cardiovascular Imaging) by a single observer blinded to treatment allocation (J.S.L.), with blinded re-analysis of $n = 20$ randomly selected data sets, in random order, for intra- and inter-observer (L.Y.Z.) variability for all primary and secondary imaging outcomes. CACS was calculated by the Agatston method[34] using Vitrea Advanced Visualization software (Vital Images Inc.) by a consultant radiologist blinded to treatment allocation (G.H.R.), excluding segments with previous coronary artery stents in situ.

2.11 | Analysis and statistical considerations

ViKTORIES was analyzed in line with CONSORT guidelines, and the analysis plan was published in advance of locking the database (Data S1). The primary analysis was conducted by modified intention-to-treat (participants were included if they completed two scans irrespective of whether they stayed on study medication), except changes in dp-ucMGP, which were studied in participants who completed the study per-protocol. Outcomes were assessed as between-group difference at 12 months by two-way analysis of covariance (ANCOVA) adjusting for age, duration of ESKD, and the baseline value of the variable of interest. Plasma dp-ucMGP concentrations were log-transformed prior to analysis. Prespecified subgroup analysis was conducted in older (≥65 years) versus younger (<65 years) participants, testing for

multiplicative interaction effect between age and treatment group and heterogeneity of treatment effect.[35] Exploratory analyses by ANCOVA were conducted to assess the impact of baseline dp-ucMGP on vascular outcomes of interest, and ANCOVA repeated as for main outcomes in a subgroup of participants considered to be vitamin K deficient at baseline (dp-ucMGP >900 pmol/L). We conducted multiple imputation for missing data (using the average of five separately imputed data sets) for the main outcomes where the assumption of missing at random was met.[36] The number and characteristics of adverse events (AEs) were summarized as a whole and by study arm. Results from the ViKTORIES trial were combined with other published reports in an updated meta-analysis (using a random effects model) according to methods described previously.[24] Analyses were conducted using *stats*, *subgroup*, *mice*, and *meta* packages for R statistical software[37] (version 3.5.3 or higher).

2.12 | Sample size

The sample size was calculated to detect a 1.0×10^{-3} (SD 1.3×10^{-3}) $mmHg^{-1}$ improvement in ascending aortic distensibility in the intervention group relative to placebo at 12 months. This difference was shown to be the minimum meaningful difference associated with cardiovascular outcomes in a historical cohort of hemodialysis patients from our own center.[31] To achieve a power of 90% with alpha = 0.05 required 37 patients per group (74 in total). We anticipated 20% dropout over 12 months of follow-up and, therefore, recruited 90 participants.

2.13 | Follow-up and timetable

Randomized participants completed visits at baseline and 12 months for all relevant clinical, biochemical, and radiological data, with monitoring visits at 1 and 6 months. The study duration was selected by extrapolating the duration from other studies where a positive result was obtained (range 1–3 years),[24] but there was an influence of trial cost and feasibility on the duration selected. We considered that if no significant impact was demonstrated on surrogate markers at 1 year, the influence on hard cardiovascular outcomes over the longer term was likely to be minimal.

2.14 | Safety

AEs were recorded from the time a participant consented until the last study visit. Several events were classed as expected due to high levels of comorbidity in this patient cohort: death or hospitalization due to new cardiovascular event, new diagnosis or treatment of cancer, fall, fracture, infection, exacerbation of an existing medical condition, deteriorating kidney function, high or low potassium

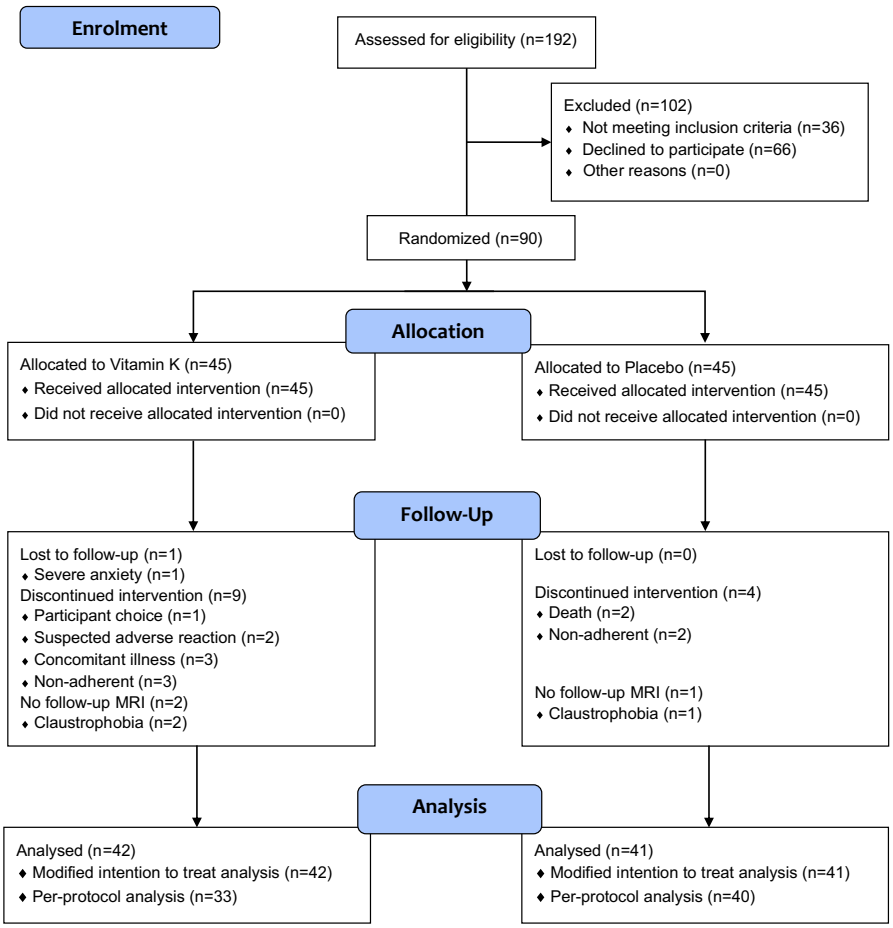

FIGURE 1 CONSORT diagram of included and excluded participants [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline clinical demographics

Baseline data	Vitamin K *N* = 45	Placebo *N* = 45	All *N* = 90
Male: n (%)	32 (71.1)	31 (68.9)	63 (70.0)
Age (years)	56.3 (11.1)	58.9 (7.8)	57.6 (9.6)
Ethnicity			
Caucasian: n (%)	44 (97.8)	44 (97.8)	88 (97.8)
Asian: n (%)	1 (2.2)	1 (2.2)	2 (2.2)
Deprivation: median (IQR)[a]	4 (2–5)	4 (2–5)	4 (2–5)
Transplant age (years): median (IQR)	8.7 (3.5–16.9)	6.3 (3.5–11.7)	7.8 (3.5–13.9)
Duration of ESKD (years): median (IQR)	12.0 (6.2–22.5)	10.5 (6.3–13.7)	11.2 (6.2–21.0)
Primary renal disease			
Diabetes mellitus: n (%)	4 (8.9)	1 (2.2)	5 (5.6)
Hypertension: n (%)	0 (0.0)	2 (4.4)	2 (2.2)
Glomerulonephritis: n (%)	11 (24.4)	12 (26.7)	23 (25.6)
Polycystic kidney disease: n (%)	10 (22.2)	11 (24.4)	21 (23.3)
Vascular disease: n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other: n (%)	15 (33.3)	16 (35.6)	31 (34.4)
Not known: n (%)	5 (11.1)	3 (6.7)	8 (8.9)
Other medical history			
Ischemic heart disease: n (%)[b]	17 (37.8)	12 (26.7)	29 (32.2)
Heart failure: n (%)	3 (6.7)	0 (0.0)	3 (3.3)
Transient ischemic attack or stroke: n (%)	2 (4.4)	1 (2.2)	3 (3.3)
Peripheral vascular disease: n (%)	3 (6.7)	0 (0.0)	3 (3.3)
Hypertension: n (%)	42 (93.3)	44 (97.8)	86 (95.6)
Diabetes: n (%)	13 (28.9)	7 (15.6)	20 (22.2)
Liver disease: n (%)	1 (2.2)	2 (4.4)	3 (3.3)
Anthropometric data			
Systolic blood pressure (mmHg)	150 (19)	146 (18)	148 (19)
Diastolic blood pressure (mmHg)	87 (13)	84 (10)	86 (12)
Mean arterial pressure (mmHg)	108 (13)	105 (10)	107 (12)
Pulse pressure (mmHg)	63 (16)	62 (17)	63 (17)
Body mass index (kg/m^2)	28.4 (6.2)	28.1 (6.8)	28.3 (6.5)
Smoking history			
Current smoker (within 6 months)	1 (2.2)	6 (13.3)	7 (7.8)
Previous smoker (>6 months)	14 (31.1)	12 (26.7)	36 (40.0)
Never smoked	30 (66.7)	27 (60.0)	57 (63.3)
Alcohol			
Never or rarely	19 (42.2)	20 (44.4)	39 (43.3)
Less than once a week	9 (20.0)	7 (15.6)	16 (17.8)
Once a week or more	17 (37.8)	18 (40.0)	35 (38.9)
Quality of life (overall health: %)	82.6 (18.1)	72.6 (31.5)	77.6 (26.0)

[a]Deprivation measured by Scottish Index of Multiple Deprivation quintiles (1–5: 1 = most deprived).

[b]Ischemic heart disease = angina, previous myocardial infarction, previous percutaneous coronary intervention, or coronary artery bypass grafting.

Abbreviations: IQR, interquartile range; ESKD, end-stage kidney disease.

levels, nausea, vomiting, constipation, diarrhea, and admission for elective or planned investigation or treatment. Only suspected unexpected serious adverse reactions (SUSARs) were collected in an expedited manner (within 24 hours of the site becoming aware of the event) and reported to the sponsor via the Pharmacovigilance Office. Participants with unresolved AEs at the last study visit were followed up until resolution or 30 days (whichever was sooner).

2.15 | Registration

ViKTORIES was prospectively registered with ISRCTN Registry on 26/09/2017 (ISRCTN22012044).

2.16 | Ethics

The study was conducted according to the Declaration of Helsinki (1964) and its revisions. The trial was approved by the West of Scotland Research Ethics Committee 4 (Ref: 17/WS/0101 on 22/06/2017) and was sponsored by NHS Greater Glasgow and Clyde Research and Development Department (Ref: GN16RE696 on 22/09/2017). The study followed standard operating procedures of the trial Sponsor (https://www.glasgowctu.org/sops.aspx; NHS Greater Glasgow and Clyde, Scotland, UK as part of Glasgow Clinical Trials Unit). Trial progress was monitored by Sponsor representatives from pharmacy, research, and development and by the Clinical Trials Manager (K.B.); routine audit was conducted by Sponsor in 2018. An annual report was issued to the Research Ethics Committee and to the funder (Kidney Research UK). The study followed CONSORT guidelines (http://www.consort-statement.org).

3 | RESULTS

3.1 | Study participants and recruitment

Of 192 potential participants assessed for eligibility, 90 were recruited (September 2017 to June 2018 with follow-up to July

TABLE 2 Baseline biochemical and imaging data for all participants in ViKTORIES

Baseline data	Vitamin K *N* = 45	Placebo *N* = 45	All N = 90
Vitamin K status			
dp-ucMGP (pmol/L)	1173 (1108)	1084 (454)	1127 (836)
Transplant function			
eGFR (ml/min/1.73 m^2)[a]	52.4 (21.6)	52.6 (20.7)	52.5 (21.0)
Urinary PCR (mg/mmol): median (IQR)	12 (<3–130)	<3 (<3–40)	5 (<3–63)
Immunosuppression			
Tacrolimus: n (%) Trough level: ng/mL	32 (71.1) 6.5 (1.6)	35 (77.8) 6.5 (1.9)	67 (74.4) 6.5 (1.8)
Ciclosporin: n (%) Trough level: ng/mL	11 (24.4) 65 (15)	7 (15.6) 59 (21)	18 (20.0) 63 (17)
Sirolimus: n (%) Trough level: ng/mL	0 (0.0) n/a	1 (2.2) 2.9	1 (1.1) 2.9
Steroid only: n (%)	2 (4.4)	2 (4.4)	4 (4.4)
Steroid free: n (%)	2 (4.4)	5 (11.1)	7 (7.8)
Biochemical data			
Hemoglobin (g/L)	131 (19)	133 (19)	132 (19)
Platelets (×10^9/L)	234 (60)	220 (59)	227 (60)
Urea (mmol/L)	10.8 (5.4)	10.3 (5.6)	10.5 (5.5)
Creatinine (mg/dL)	1.6 (0.6)	1.5 (0.7)	1.6 (0.7)
Sodium (mmol/L)	139 (2)	137 (19)	138 (13)
Potassium (mmol/L)	4.5 (0.3)	4.4 (0.5)	4.5 (0.4)
Calcium (mmol/L)	2.42 (0.12)	2.42 (0.16)	2.42 (0.14)
Phosphate (mmol/L)	0.97 (0.23)	0.97 (0.24)	0.97 (0.24)
Parathyroid hormone (pmol/L)	17.9 (21.2)	20.1 (21.3)	19.0 (21.1)
Magnesium (mmol/L)	0.71 (0.10)	0.71 (0.08)	0.71 (0.09)
Albumin (g/L)	36 (4)	37 (3)	37 (4)
Cholesterol (mmol/L)	4.8 (1.2)	4.9 (1.2)	4.9 (1.2)
High-density lipoprotein (mmol/L)	1.3 (0.5)	1.4 (0.4)	1.4 (0.4)
Low-density lipoprotein (mmol/L)	2.7 (1.1)	2.8 (1.0)	2.7 (1.0)
Triglycerides (mmol/L)	1.8 (0.9)	1.5 (0.6)	1.7 (0.8)
25-hydroxyvitamin D (nmol/L)	30 (16)	32 (21)	31 (19)
Vascular stiffness			
Aortic distensibility (ascending): (×10^{-3} $mmHg^{-1}$)	2.7 (1.6)	2.9 (1.7)	2.8 (1.6)
Aortic distensibility (descending): (×10^{-3} $mmHg^{-1}$)	4.1 (1.7)	4.1 (1.8)	4.1 (1.7)
Carotid-femoral PWV (m/s)	8.4 (2.2)	8.3 (1.7)	8.4 (1.9)
Augmentation index (%)	18.8 (14.4)	21.6 (10.0)	19.7 (12.4)
Vascular calcification			
CACS (units)	330 (28–1389)	450 (54–1323)	388 (38–1323)
CACS: % for age/gender	94 (64–99)	88 (63–99)	92 (66–99)
Cardiac structure and function			
LV mass index (g/m^2)	64.0 (14.1)	62.0 (14.4)	63.0 (14.2)
LV ejection fraction (%)	65.6 (10.0)	69.0 (7.2)	67.3 (8.8)
LV global longitudinal strain (%)	−15.1 (3.3)	−16.7 (3.0)	−15.9 (3.2)
RV global longitudinal strain (%)	−19.1 (7.1)	−21.2 (4.8)	−20.1 (6.1)
Left atrial area (mm^2)	67.2 (24.9)	70.1 (24.8)	68.6 (24.7)
Right atrial area (mm^2)	67.4 (24.1)	69.3 (23.9)	68.3 (23.8)
Global myocardial T1 time (ms)	1259 (45)	1255 (42)	1257 (43)
Global myocardial T2 time (ms)	41 (3)	42 (2)	42 (3)

Note: Data are displayed as mean (standard deviation) or median (interquartile range) as appropriate. *p values expressed are for Chi-square, Student's t test or Mann–Whitney U test as appropriate.*

[a]eGFR measured by CKD-EPI equation.

Abbreviations: CACS, coronary artery calcium score; Dp-ucMGP, desphospho-undercarboxylated Matrix Gla Protein; LV, left ventricular; PCR, protein:creatinine ratio; PWV, pulse wave velocity; RV, right ventricular.

2019) and randomized to vitamin K (*n* = 45) or placebo (*n* = 45). Participants who had baseline and follow-up MRI for the primary outcome measure were included in the modified intention-to-treat analysis (vitamin K *n* = 42 and placebo *n* = 41); *n* = 79 (87.8%) completed the study per-protocol. Reasons for withdrawal, discontinuation of study intervention, or lack of availability of follow-up MRI data are detailed in Figure 1. Median duration of follow-up was similar between treatment groups: vitamin K 11.6 (IQR 11.5–11.7) versus placebo 11.6 (IQR 11.5–11.7) months; *p* = .919.

3.2 | Baseline data

Baseline data for all randomized participants are illustrated in Tables 1 and 2. Age, sex, ethnicity, duration of kidney transplant,

TABLE 3 Primary outcome by intention-to-treat analysis: aortic distensibility

Baseline data		Vitamin K *N* = 42	Placebo *N* = 41	*p* value[a]
Primary outcome Aortic distensibility (ascending - $\times 10^{-3}$ mmHg^{-1})	12 months	2.5 (1.5)	2.7 (1.4)	
	Difference from baseline	−0.2 (1.2)	−0.2 (1.4)	
	Adjusted difference from baseline[a]	−0.3 (−0.6 to 0.1)	−0.1 (−0.4 to 0.3)	.596
	Adjusted treatment effect[a]	−0.23 (−0.75 – 0.29)		.377
	Adjusted treatment effect[a] with multiple imputations[b]	−0.19 (−0.71 – 0.32)		.458
Secondary outcome Aortic distensibility (descending - $\times 10^{-3}$ mmHg^{-1})	12 months	3.9 (1.8)	3.6 (1.3)	
	Difference from baseline	−0.2 (1.5)	−0.5 (1.5)	
	Adjusted difference from baseline[a]	−0.2 (−0.6 to 0.2)	−0.5 (−0.9 to −0.1)	.385
	Adjusted treatment effect[a]	0.23 (−0.32 to 0.78)		.407
	Adjusted treatment effect[a] with multiple imputation[b]	−0.14 (−0.39 to 0.67)		.598

Note: Data are displayed as mean (SD) or mean (95% confidence interval) as appropriate.

[a]ANCOVA adjusted for covariates of age, duration of end-stage kidney disease, and baseline value of ascending aortic distensibility.

[b]Multiple imputation for *n* = 88 participants excluding two participants who died during follow-up.

and ESKD were similar across treatment groups, as were baseline levels of vascular stiffness, calcification, and dp-ucMGP.

3.3 | Outcomes and estimation

3.3.1 | Primary outcome

There was no difference in ascending aortic distensibility between groups (adjusted treatment effect −0.23 [95% CI −0.75 to 0.29] $\times 10^{-3}$ mmHg^{-1}; p = .377: Table 3). Data for descending aortic distensibility are also displayed in Table 3.

3.3.2 | Secondary outcomes

Analyses were conducted hierarchically as described but displayed in full for completeness. There was no significant difference in any clinical, biochemical (Table 4), or imaging measure (Table 5).

3.3.3 | Vitamin K status and biological effect

Vitamin K status was similar in treatment groups at baseline. Vitamin K deficiency was evident in 15 (33.3%) versus 14 (31.1%) participants (p = .881) in vitamin K and placebo groups respectively. In n = 72 participants who completed the study per-protocol and had available dp-ucMGP measurements, vitamin K caused a reduction in dp-ucMGP (i.e., improved vitamin K availability and activity) compared with placebo (mean difference −186 [95% CI −294 to −78] vs. −12 [95% CI −109 to 84] pmol/L; p = .020). There remained no significant effect on vascular stiffness or calcification in this group. Individual changes in dp-ucMGP values are illustrated in Figure 2.

3.3.4 | Inter- and intra-observer consistency of agreement for magnetic resonance imaging outcome measures

On blinded repeat analysis of 20% of randomly selected data sets in random order, there was good or excellent inter- and intra-consistency of agreement on most outcome measures (Table S1).

3.4 | Adverse events

AEs were common in both treatment arms, although relatively less common in the group treated with vitamin K (57.8% vs. 80.0%): Table 6). Specifically, there was a lower incidence of infections (15.6% vs. 40%; p = .018) and musculoskeletal AEs (8.9% vs. 31.1%; p = .016). The latter predominantly consisted of nonspecific joint/muscle aches. All serious AE were characterized as expected.

There were no SUSAR during the study. One participant in the vitamin K arm had a suspected adverse reaction (rash), classed as moderate. Two patients died during the study: one had a hemorrhagic stroke, complicated by sepsis, a seizure, and death. A second patient had recurrence of known posttransplant lymphoproliferative disease and was admitted to hospital with neutropenic sepsis due to community-acquired pneumonia, multi-organ failure, and death. Both had been randomized to placebo.

TABLE 4 Clinical and biochemical secondary outcomes by intention-to-treat analysis

Outcome		Vitamin K N = 42	Placebo N = 41	p value[a]
Anthropometric data				
Systolic blood pressure (mmHg)	12 months	149 (23)	146 (16)	
	Difference from baseline	−2 (20)	0 (17)	
	Adjusted treatment effect[a]	0 (−8 to 7)		.901
Diastolic blood pressure (mmHg)	12 months	85 (12)	82 (12)	
	Difference from baseline	−2 (10)	−2 (11)	
	Adjusted treatment effect[a]	1 (−4 to 5)		.750
Mean arterial pressure (mmHg)	12 months	134 (17)	131 (15)	
	Difference from baseline	26 (14)	26 (15)	
	Adjusted treatment effect[a]	1 (−5 to 7)		.762
Pulse pressure (mmHg)	12 months	64 (21)	64 (15)	
	Difference from baseline	0 (15)	2 (12)	
	Adjusted treatment effect[a]	0 (−1 to 0)		.521
Transplant function				
eGFR (ml/min/1.73 m^2)	12 months	49.4 (22.0)	52.4 (22.8)	
	Difference from baseline	−1.6 (10.9)	−0.2 (8.0)	
	Adjusted treatment effect[a]	−0.2 (−4.3 to 3.9)		.937
Urinary PCR (mg/mmol)	12 months	20 (<3–131)	<3 (<3–1121)	
	Difference from baseline	7 (102)	−3 (88)	
	Adjusted treatment effect[a]	28 (−13 to 68)		.175
Quality of life (overall health: %)	12 months	82.0 (16.2)	76.6 (16.3)	
	Difference from baseline	−0.2 (20.0)	3.5 (30.5)	
	Adjusted treatment effect[a]	3.5 (−3.3 to 10.2)		.310
Vascular stiffness				
Carotid-femoral PWV (m/s)	12 months	9.4 (2.1)	9.6 (2.0)	
	Difference from baseline	0.8 (1.9)	1.3 (1.4)	
	Adjusted treatment effect[a]	−0.1 (−0.8 to 0.6)		.746
Augmentation index (%)	12 months	19.6 (13.9)	22.1 (9.5)	
	Difference from baseline	0.1 (14.7)	1.6 (9.4)	
	Adjusted treatment effect[a]	0.1 (−4.8 to 4.9)		.979

Abbreviations: eGFR, estimated glomerular filtration rate; PCR, protein:creatinine ratio; PWV, pulse wave velocity.
[a]ANCOVA adjusted for age, duration of end-stage kidney disease, and baseline value of the variable under test.

3.5 | Secondary analyses

3.5.1 | Prespecified subgroup analysis in older versus younger participants

Prespecified subgroup analysis was conducted in participants who were older (age ≥65 years; $n = 20$) or younger (age <65 years; $n = 70$) at randomization, based on a known positive association between vascular stiffness, calcification, and increasing age. There was no evidence of multiplicative interaction effect between treatment group and age for ascending aortic distensibility ($p = .892$) nor for CACS ($p = .981$). Subgroup analysis in older versus younger participants shows no heterogeneity of treatment effect that cannot be explained by chance ($p = .480$). Those who were older at randomization displayed more progression in CACS when treated with vitamin K, although there was a significant interaction between age, duration of ESKD, and baseline CACS ($p = .003$) in these participants, which are all likely to be predictive of progressive calcification. There were no differences in any of the imaging outcomes by treatment group in younger participants.

3.5.2 | Exploratory analysis: baseline vitamin K status

Baseline dp-ucMGP had no impact on any vascular outcome (aortic distensibility: ascending and descending, CACS, and pulse wave velocity) by ANCOVA. In $n = 29$ participants with vitamin K deficiency at baseline, vitamin K treatment was associated with a reduction (i.e., increased stiffening) in ascending aortic distensibility (adjusted

TABLE 5 Imaging secondary outcomes by intention-to-treat analysis

Outcome		Vitamin K N = 42	Placebo N = 41	p value[a]
Vascular calcification				
CACS (units)	12 months	460 (53–1626)	412 (71–1663)	
	Difference from baseline	28 (0–65)	33 (0–87)	
	Adjusted treatment effect[a]	−141 (−320 to 38)		.120
	Adjusted treatment effect[a] with multiple imputation[b]	−155 (−330 to 20)		.082
CACS: % for age/gender	12 months	96 (75–99)	90 (63–99)	
	Difference from baseline	0 (0–0)	0 (0–1)	
	Adjusted treatment effect[a]	2 (−3 to 7)		.458
Cardiac structure and function				
LV mass index (g/m^2)	12 months	65.9 (16.3)	63.2 (16.8)	
	Difference from baseline	1.4 (10.5)	0.8 (7.6)	
	Adjusted treatment effect[a]	2.1 (−2.3 to 6.4)		.348
LV ejection fraction (%)	12 months	65.6 (8.9)	67.9 (7.9)	
	Difference from baseline	0.4 (8.9)	−1.1 (6.3)	
	Adjusted treatment effect[a]	0.0 (−3.2 to 3.1)		.986
LV Global longitudinal strain (%)	12 months	−15.4 (3.1)	−16.3 (2.2)	
	Difference from baseline	−0.3 (2.6)	0.3 (2.6)	
	Adjusted treatment effect[a]	−1.2 (−6.1 to 3.7)		.630
RV Global longitudinal strain (%)	12 months	−20.1 (4.6)	−21.0 (4.8)	
	Difference from baseline	0.4 (5.3)	−0.0 (4.9)	
	Adjusted treatment effect[a]	0.8 (−1.4 to 3.0)		.482
Left atrial max area (mm^2)	12 months	69.7 (24.7)	70.1 (27.1)	
	Difference from baseline	2.1 (19.2)	0.4 (14.3)	
	Adjusted treatment effect[a]	3.1 (−5.5 to 11.7)		.473
Right atrial max area (mm^2)	12 months	71.5 (23.3)	73.3 (24.5)	
	Difference from baseline	3.0 (22.6)	3.6 (18.5)	
	Adjusted treatment effect[a]	−1.4 (−12.0 to 9.2)		.790
Global myocardial T1 time (ms)	12 months	1251 (58)	1264 (40)	
	Difference	−10 (48)	9 (33)	
	Adjusted treatment effect[a]	−16 (−35 to 2)		.084
Global myocardial T2 time (ms)	12 months	43 (3)	43 (3)	
	Difference from baseline	1 (3)	0 (2)	
	Adjusted treatment effect[a]	1 (0 to 1.7)		.135

[a]ANCOVA adjusted for age, duration of end-stage kidney disease, and baseline value of the variable under test.

[b]Multiple imputation for n = 88 participants excluding two participants who died during follow-up.

Abbreviations: CACS, coronary artery calcium score; LV, left ventricular; RV, right ventricular.

treatment effect −1.2 [95% CI −2.2 to −0.2] $\times 10^{-3}$ mmHg^{-1}; p = .018). There was no significant treatment effect on descending aortic distensibility, CACS, or pulse wave velocity.

3.6 | Sensitivity analysis: multiple imputation

Multiple imputation was conducted for missing outcome data for n = 88 participants (excluding n = 2 patients who died). The proportion of data missing at random for aortic distensibility (ascending and descending) was 5.7%; CACS 3.4%; left ventricular mass index 6.8%; pulse wave velocity 5.7%; and augmentation index 3.4%. Multiple imputation had no meaningful impact on the results of these selected endpoints (Tables 3 and 5).

3.7 | Update of meta-analysis

Among published reports across various populations, and including results from ViKTORIES, vitamin K supplementation does not

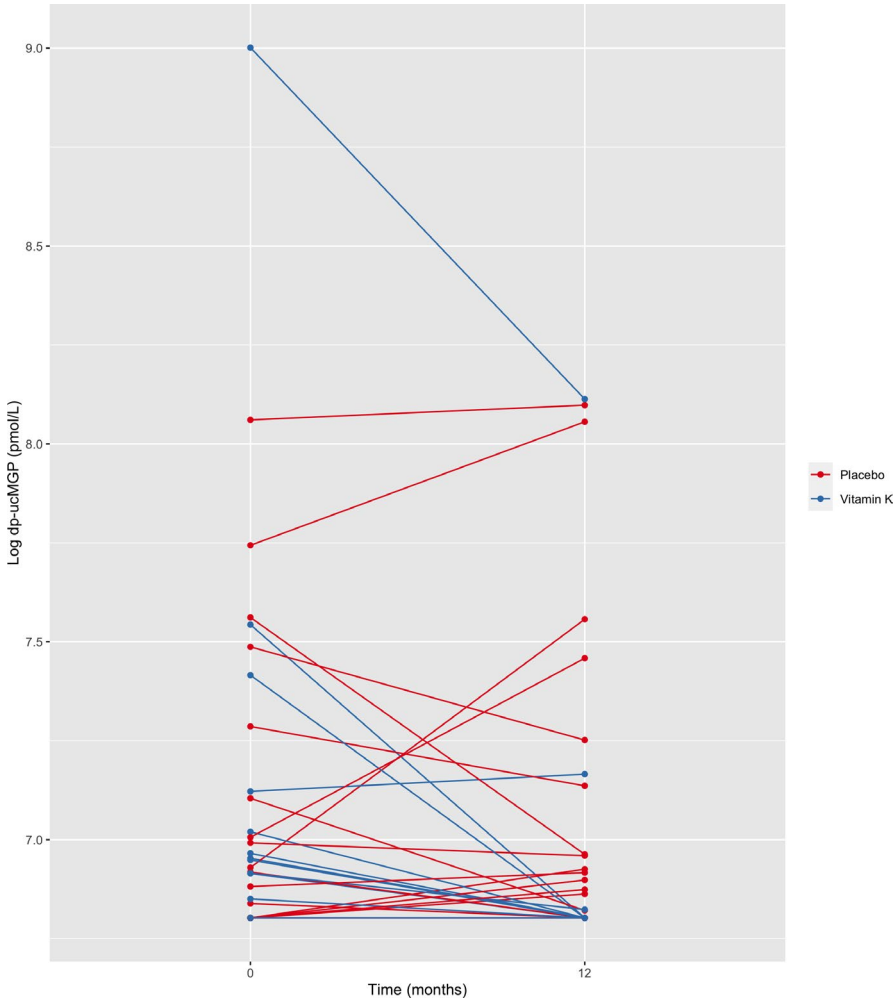

FIGURE 2 Individual change in log dp-ucMGP (pmol/L) by treatment group from baseline to 12 months for $n = 72$ participants who completed the study per-protocol with quantifiable dp-ucMGP at baseline and 12 months. Values <900 pmol/L could not be measured reliably and were considered to be equal to 900 pmol/L. Data have been log-transformed for ease of viewing values at the lower end of the scale [Color figure can be viewed at wileyonlinelibrary.com]

improve vascular stiffness (mean difference −2.74 [95% CI −6.25–0.77]%, $p = .126$; Figure 3A) or vascular calcification (mean difference −4.57 [95% CI −11.05–1.91]; $p = .167$; Figure 3B). Details of the trials included in this updated meta-analysis are available in Table S2.

4 | DISCUSSION

The ViKTORIES trial showed no evidence that treatment with a synthetic form of vitamin K improves vascular stiffness or calcification in a heterogeneous group of KTRs. When these results were combined with other published reports in meta-analyses, there was no observed impact of vitamin K supplementation on vascular stiffness or calcification across varying populations.

In CKD, vitamin K deficiency is associated with reduced activity of calcification inhibitors and vascular calcification[38,39] and may be associated with cardiovascular disease and early mortality.[24] There are several reasons why supplementation may not have induced clinical benefit in this trial.

We assumed that vitamin K as menadiol diphosphate could function as a cofactor for carboxylation of vitamin K–dependent proteins. Menadiol diphosphate is effective in the treatment of coagulation abnormalities,[28] proving activity as a cofactor for carboxylation of vitamin K–dependent clotting factors. We tested the ability of menadiol diphosphate to facilitate carboxylation of Matrix Gla protein. Plasma dp-ucMGP testing is not routinely available in clinical laboratories; commercial companies (VitaK, the Netherlands) are no longer offering analysis. We used the only available dp-ucMGP assay, which demonstrated suboptimal performance at the lower end of the scale in our local laboratory, and we were unable to report accurate numerical values below 900 pmol/L. Griffin et al. suggested reference values for healthy Caucasian individuals from <300 to 532 pmol/L[40] (although no assay validation was offered for values below 900 pmol/L). We, therefore, assumed that those with dp-ucMGP >900 pmol/L were "deficient" and those ≤900 pmol/L "sufficient" (or mildly deficient). Only 29 included participants had dp-ucMGP >900 pmol/L, and it is possible that a substantial proportion of participants were not vitamin K deficient at baseline. However, there was a clear improvement in the absolute values of dp-ucMGP in those who were adherent with study medication, confirming biological activity of menadiol diphosphate. Our results are consistent with other studies in CKD using different preparations of vitamin K; thus, it is less likely that the null result was due to the choice of preparation alone. It was not possible to confirm vitamin K status in advance of inclusion due to the lack of a reliable biomarker. Consideration could be given to testing the utility of vitamin K supplementation

TABLE 6 Adverse events by treatment arm

System organ class	Number of participants with events: n (%)		
	Vitamin K (*n* = 45)	Placebo (*n* = 45)	All (*n* = 90)
Any event	26 (57.8)	36 (80.0)	62 (68.9)
Commenced dialysis	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	2 (4.4)	2 (2.2)
Blood and lymphatic	1 (2.2)	3 (6.7)	4 (4.4)
Cardiac	3 (6.7)	0 (0.0)	3 (3.3)
Congenital and genetic	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth	1 (2.2)	2 (4.4)	3 (3.3)
Endocrine	0 (0.0)	1 (2.2)	1 (1.1)
Eye	1 (2.2)	0 (0.0)	1 (1.1)
Gastrointestinal	7 (15.6)	8 (17.8)	15 (16.7)
General	1 (2.2)	1 (2.2)	2 (2.2)
Hepatobiliary	0 (0.0)	2 (4.4)	2 (2.2)
Immune system	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	7 (15.6)	18 (40.0)	25 (27.8)
Injury, poisoning, and procedural complications	1 (2.2)	1 (2.2)	2 (2.2)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition	1 (2.2)	0 (0.0)	1 (1.1)
Musculoskeletal	4 (8.9)	14 (31.1)	18 (20.0)
Neoplasms	1 (2.2)	0 (0.0)	1 (1.1)
Nervous system	2 (4.4)	3 (6.7)	5 (5.6)
Psychiatric	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary	3 (6.7)	9 (20.0)	12 (13.3)
Reproductive and breast	2 (4.4)	0 (0.0)	2 (2.2)
Respiratory	2 (4.4)	2 (4.4)	4 (4.4)
Skin	1 (2.2)	5 (11.1)	6 (6.7)
Surgical/medical procedure	2 (4.4)	3 (6.7)	5 (5.6)
Vascular	1 (2.2)	0 (0.0)	1 (1.1)

Note. Number of participants with adverse events by MedDRA System Order Class (SOC), number of deaths and participants who commenced renal replacement therapy. All participants who received at least one dose of study medication were included in safety analyses. All serious adverse events were characterized as expected according to the study protocol.

(either alone or in combination) in patients with confirmed vitamin K deficiency.

We used vascular stiffness (MR-based aortic distensibility) as the primary endpoint. Aortic distensibility is an accurate and highly reproducible measure of central vascular stiffness, that is strongly and inversely associated with cardiovascular risk.[31] Aortic distensibility has been shown to be modifiable in response to therapeutic interventions to reduce cardiovascular risk in CKD.[41] Vascular stiffness is modifiable over time, such as after kidney transplantation in patients with ESKD,[42] and after vitamin K supplementation in some,[43,44] but not all,[24] trials. We detected no signal that vitamin K altered vascular stiffness; it is unlikely that the choice of endpoint explained the null result.

Vascular stiffness and calcification develop alongside exposure to multiple risk factors and an imbalance of calcification promoters and inhibitors.[16] CKD-specific risk factors—like CKD mineral and bone disorder—begin early in the disease process, and the effects persist after correction of kidney function with transplantation. Vitamin K is primarily obtained from green vegetables, so vitamin K deficiency may serve as a marker of prolonged exposure to unhealthy diet and/or lifestyle. Vitamin K supplementation alone may be inadequate to reverse established effects of a lifetime of accumulated vascular damage. An earlier, multifaceted, preventative approach may have greater success.

In this trial, there was a lower rate of infections and joint/muscle pain in the vitamin K group. Vitamin K–dependent proteins (including osteocalcin, Matrix Gla Protein, and Gla-rich protein) play an important role in bone mineralization and mass,[45] and it is conceivable that this was a genuine effect of vitamin K supplementation. However, this outcome was not prespecified. Existing trial evidence is insufficient to support a role for vitamin K supplementation in improving musculoskeletal health including bone mineral density or fracture risk.[46]

This study has several limitations. First, due to the constraints on testing of vitamin K status detailed above, it was not possible to identify those with confirmed or severe vitamin K deficiency in advance of running the trial. It is possible that vitamin K supplementation may improve vascular health in cohorts with clear evidence of vitamin K deficiency. Second, ViKTORIES participants were a heterogeneous group with heavy baseline calcification, which may have limited the ability of vitamin K to exert any beneficial effect. Third, this population of KTRs has a lower burden of vascular disease and diabetes than the prevalent kidney transplant population in the United Kingdom and may not be representative of the population as a whole. Fourth, there was a slight male and heavy Caucasian preponderance among ViKTORIES participants, and the results may not be generalizable to other groups. Fifth, we tested vitamin K supplementation over only 1 year. It is possible that longer treatment is required to see a difference, particularly if used to reduce progression of vascular stiffness, rather than induce regression of existing disease. However, our impression is that if there is no impact on surrogate markers of vascular health over 1 year, long-term impact on hard cardiovascular outcomes is likely to be minimal.

In conclusion, we did not find any sign that vitamin K supplementation regressed or reduced progression of vascular stiffness and calcification in this heterogeneous cohort of prevalent KTRs over 1 year. These results are in keeping with meta-analyses containing data from other published reports. Vascular stiffness and calcification have complex, multifactorial etiology, develop and progress over many years, and are unlikely to be improved substantially by replacement of a single dietary component on a population basis.

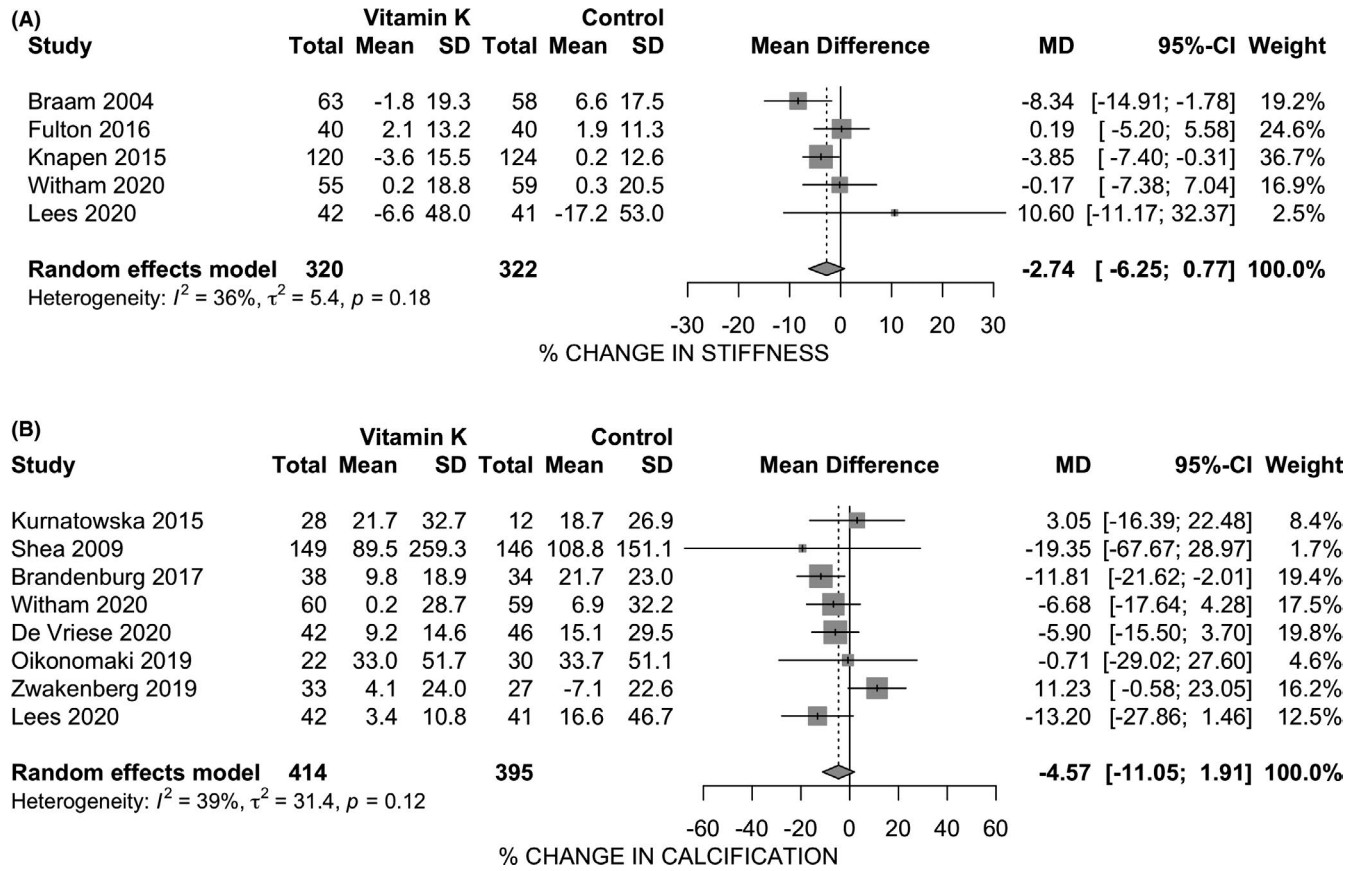

FIGURE 3 Meta-analysis of the effect of vitamin K supplementation on (A) vascular stiffness and (B) vascular calcification

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

ORCID

Jennifer S. Lees https://orcid.org/0000-0001-6331-0178
Patrick B. Mark https://orcid.org/0000-0003-3387-2123

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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