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

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Introduction
Cardiovascular disease is a major cause of graft loss and premature mortality amongst kidney transplant recipients (KTR). Vascular stiffness (VS) and calcification (VC) are markers of cardiovascular disease which are prevalent in KTR and associated with subclinical vitamin K deficiency. We tested the hypothesis that vitamin K supplementation would reduce VS and VC in prevalent KTR in the Vitamin K for kidney Transplant Organ Recipients: Investigating vEssel Stiffness (ViKTORIES) trial.

Methods
In a single-centre, phase II, parallel-group, randomised, double-blind, placebo-controlled trial (ISRCTN22012044), KTR were randomised 1:1 to vitamin K (menadiol diphosphate 5mg) or placebo thrice weekly for one year. The primary outcome was between-group difference in VS (ascending aortic distensibility by cardiac magnetic resonance imaging) at 1 year by ANCOVA adjusted for the baseline value, age and duration of end-stage kidney disease. Secondary outcomes included VC (coronary artery calcium score on non-contrast computed tomography), cardiac structure and function (on cardiac magnetic resonance imaging), blood pressure, eGFR, proteinuria and quality of life. All outcomes were assessed by intention-to-treat with secondary per-protocol analyses. Missing data were multiply imputed as a sensitivity analysis for the main outcomes. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the West of Scotland Research Ethics Committee 4 (Ref: 17/WS/0101). The results were combined in a meta-analysis with other published data.

Results
Ninety participants were randomised to vitamin K (n=45) or placebo (n=45) and included in the analysis. Baseline demographics, clinical history and immunosuppression regimens were similar between groups: mean age 57.6 ± 9.6 years, 70% male, with median time after transplantation 7.8 (IQR 3.5 - 13.9) years. There was no impact of vitamin K versus placebo on VS after 12 months (-0.2 (-0.5 - 0.2) vs. -0.3 (-0.6 - 0.1) x10-3 mmHg-1; p=0.60), nor on VC (184 (52 - 315) vs 44 (-89 - 177) units; p=0.11), nor on any other outcome measure. Medication adherence was good in both groups (90 vs. 95%; p=0.58). Achieved power was 85%. Serious adverse events were common (vitamin K: 26.7 vs. placebo: 60.0%), though all serious adverse events were classified as expected. Multiple imputation of missing data had no impact on results of VS or VC outcomes. Combining these with other published results, vitamin K supplementation has no significant observed effect on VS or VC, though with few available studies for analysis.

Discussion
In this heterogeneous cohort of prevalent KTR, vitamin K supplementation did not reduce VS or VC over 1 year. Improving vascular health in patients with established kidney disease is likely to require a multifaceted approach.