

# Vitamin K supplementation and vascular health after kidney transplantation: Authors' response

## To the Editor:

We thank Drs te Velde-Keyzer and de Borst<sup>1</sup> for their interest in our trial. We agree that in the small, heterogeneous cohort of kidney transplant recipients (KTR) in ViKTORIES, the lack of evidence of benefit of vitamin K supplementation does not rule out a possible role for vitamin K to improve vascular health in specific circumstances or populations. However, we note that Drs te Velde-Keyzer and de Borst do not provide evidence of any clinical trials, where this effect has been demonstrated in patients with kidney failure. Instead, they quote observational data, and a trial which demonstrated that vitamin K2 supplementation decreased desphospho-undecarboxylated Matrix Gla Protein (dp-ucMGP) in patients on dialysis, but did not assess any measure of vascular calcification.<sup>2</sup>

Vascular calcification is more commonly detected in KTR with cardiometabolic comorbidity.<sup>3</sup> ViKTORIES participants had evidence of excess vascular stiffness (higher than the expected normal range and 95% confidence limits for age and sex) and calcification (>75% of that expected for age and sex) in 27.8% and 67.8%, respectively. There was a statistical multiplicative interaction between baseline dp-ucMGP, duration of end-stage kidney disease and vascular calcification ( $p = .017$ ), but not vascular stiffness ( $p = .480$ ). There may be a heavier baseline burden of vascular stiffness and calcification in ViKTORIES participants than in other populations of KTR. In a recent meta-analysis, 32% of KTR had detectable vascular calcification in the abdominal aorta, though calcification severity was not consistently reported across studies.<sup>3</sup>

Vitamin K deficiency, as assessed by dp-ucMGP, was only detectable in our study in 32.2% of participants, though a greater proportion may have had biochemical evidence of vitamin K deficiency if we had been able to measure dp-ucMGP below 900 pmol/L. The threshold of dp-ucMGP > 500 pmol/L for vitamin K deficiency, suggested by Drs te Velde-Keyzer and de Borst,<sup>1</sup> is supported by a study in adults with diabetes, with and without kidney disease.<sup>4</sup>

Detecting vitamin K deficiency in clinical trials and clinical practice requires an available, reliable, and consistently reproducible test. dp-ucMGP is considered to be the most sensitive marker to detect subclinical vitamin K deficiency, the IDS<sup>®</sup>-iSYS InaKtif assay is the only commercially available system to measure this

biomarker and the lowest calibration threshold for the assay is set at 920 pmol/L.<sup>4</sup> We believe that this assay needs to be more robustly calibrated to values below 900 pmol/L, particularly as the threshold for vitamin K deficiency is considered to be substantially lower.

Importantly, in two separate, recent trials of vitamin K supplementation in patients requiring dialysis (therefore similar to participants in ViKTORIES), vitamin K supplementation with vitamin K2 had no effect on coronary arterial and abdominal aortic calcification compared to placebo.<sup>5,6</sup>

Vitamin K supplementation provided earlier in the disease course before vascular stiffness and calcification become established, and/or in populations with clear evidence of vitamin K deficiency, may yet be associated with a clinical benefit. We, and others, have not been able to establish this in clinical trials in patients with kidney failure requiring dialysis, or in KTR.

## KEYWORDS

cardiovascular disease, clinical trial, editorial/personal viewpoint, kidney disease, kidney transplantation/nephrology

## DISCLOSURE

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

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