Supplementary Table 1:

Reproducibility of magnetic resonance imaging outcome measures

Imaging measure	**Inter-observer consistency**	**Intra-observer consistency**
Aortic distensibility (ascending)	0.88 (0.79 – 0.94)	0.95 (0.91 – 0.97)
Aortic distensibility (descending)	0.78 (0.60 – 0.88)	0.91 (0.83 – 0.95)
LV mass index	0.83 (0.69 – 0.91)	0.96 (0.92 – 0.98)
LV ejection fraction	0.83 (0.69 – 0.91)	0.96 (0.93 – 0.98)
LV Global longitudinal strain	0.86 (0.73 – 0.93)	0.96 (0.92 – 0.98)
RV Global longitudinal strain	0.42 (0.11 – 0.66)	0.63 (0.39 – 0.79)
Left atrial max area	0.96 (0.92 – 0.98)	0.99 (0.98 – 0.99)
Right atrial max area	0.80 (0.64 – 0.89)	0.94 (0.88 – 0.97)
Global myocardial T1 time	0.96 (0.92 – 0.98)	1.00 (0.99 – 1.00)
Global myocardial T2 time	0.75 (0.56 – 0.87)	0.93 (0.86 – 0.96)

Results are displayed as mean (95% confidence interval). LV = left ventricular; RV = right ventricular.

Supplementary Table 2:

Table of studies in an updated meta-analysis of the effect of vitamin K supplementation on vascular health[1]

Author	Year	Country	N	Population	Vitamin K form	Dose (micrograms/day)	Duration (months)	Control
Vascular stiffness								
Braam[1]	2004	Netherlands	121	Healthy	K1	1000	36	Co-intervention with multivitamin
Knapen[2]	2015	Netherlands	244	Postmenopausal women	K2-MK7	180	36	Placebo
Fulton[3]	2016	Scotland	80	Older adults, vascular disease	K2-MK7	100	6	Placebo
Witham[4]	2020	Scotland		Chronic kidney disease	K2-MK7	400	12	Placebo
Vascular calcification								
Shea[4]	2009	USA	295	Older adults	K1	500	36	Co-intervention with multivitamin
Kurnatowska[5]	2015	Poland	40	Chronic kidney disease	K2-MK7	90	9	Co-intervention with vitamin D
Brandenburg[6]	2017	Germany	72	Aortic stenosis or sclerosis	K1	2000	12	Placebo
Oikonomaki[7]	2019	Greece	102	Haemodialysis	K2-MK7	200	12	No treatment
Zwakenberg[7]	2019	Netherlands	68	Type 2 diabetes and cardiovascular disease	K2-MK7	360	6	Placebo
De Vriese[9]	2020	Belgium	132	Haemodialysis and atrial fibrillation	K2-MK7	2000	18	Co-intervention with rivaroxaban
Witham[4]	2020	Scotland		Chronic kidney disease	K2-MK7	400	12	Placebo

1. Lees JS, Chapman FA, Witham MD, Jardine AG, Mark PB. Vitamin K status, supplementation and vascular disease: A systematic review and meta-analysis. *Heart*. 2018;105:935-945.
2. Braam L, Hoeks A, Brouns F, Hamulyak K, Gerichhausen M, 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(2):373-380.
3. Knapen M, Braam L, Drummen N, Bekers O, Hoeks A, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women: A double-blind randomised clinical trial. *Thromb Haemost*. 2015;113(5):1135-1144.
4. Fulton RL, McMurdo MET, Hill A, … Witham MD. Effect of Vitamin K on Vascular Health and Physical Function in Older People with Vascular Disease--A Randomised Controlled Trial. *J Nutr Health Aging*. 2016;20(3):325-333.
5. Witham MD, Lees JS, White M, … Mark PB. Vitamin K supplementation to improve vascular stiffness in CKD: The K4Kidneys randomized controlled trial. *J Am Soc Nephrol*. 2020;31(10):2434-2445.
6. Shea MK, Donnell CJO, Hoffmann U, … Booth SL. Vitamin K supplementation and progression of coronary artery calcium in older men and women. *Am J Clin Nutr*. 2009;89(6):1799-1807.
7. Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, … Nowicki M. 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(9):631-640.
8. Brandenburg VM, Reinartz S, Kaesler N, … Koos R. Slower progress of aortic valve calcification with Vitamin K supplementation: Results from a prospective interventional proof-of-concept study. *Circulation*. 2017;135(21):2081-2083.
9. Oikonomaki T, Papasotiriou M, Ntrinias T, … Papachristou E. The effect of vitamin K2 supplementation on vascular calcification in haemodialysis patients: a 1-year follow-up randomized trial. *Int Urol Nephrol*. 2019;51(11):2037-2044.
10. Zwakenberg SR, De Jong PA, Bartstra JW, … Beulens JWJ. The effect of menaquinone-7 supplementation on vascular calcification in patients with diabetes: A randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2019;110(4):883-890.
11. De Vriese AS, Caluwé R, Pyfferoen L, … Verbeke F. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study. *J Am Soc Nephrol*. Published online 2019:ASN.2019060579.

VIKTORIES Statistical Analysis Plan – FINAL v1.1

SAP Objectives

The objective of this SAP is to describe the statistical analyses to be carried out for the final analysis of the ViKTORIES study.

GENERAL PRINCIPLES

Data will be summarised overall and by treatment group. Continuous variables will be summarised as number of observed values, number of missing values, mean and standard deviation, median and interquartile range and minimum and maximum. Categorical data will be summarised as number of observed values, number of missing values, number and percentage in each category.

All analyses will be conducted by modified intention to treat (ITT) and per-protocol methods.

CURRENT PROTOCOL

The current version of the protocol is version 5 (05/01/2018). Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary.

ADDITIONAL ANALYSES TO THOSE SPECIFIED IN STUDY PROTOCOL

All analyses that will be carried out will be those specified in the current study protocol and no additional analyses will be done.

SOFTWARE

The statistical software packages used will be R statistical software (version 3.5.3 or higher) using RStudio version 1.1.447 or higher.

ANALYSIS

STUDY POPULATIONS

The Randomised population will consist of all randomised participants.

For efficacy analyses, the Full Analysis Set (FAS) will consist of all randomised subjects who received at least one dose of randomised study treatment. FAS data will be analysed according to the ITT principle, that is, in relation to randomised group, regardless of whether study medication was continued for the whole study.

For safety analyses, the Safety population will consist of all randomised participants who received at least one dose of study medication.

SUBJECT DISPOSITION

To enable the creation of a CONSORT diagram, the following will be presented:

- Number of subjects who consented
- Number of subjects that were randomised

- Number of subjects in the FAS and Safety populations

- Number of subjects that have attended each visit

- Number of subjects that have withdrawn (from study or treatment) and the reasons for withdrawal where available

BASELINE CHARACTERISTICS

The following baseline characteristics and measures will be summarised as a whole and by each study arm:

- Demographics: age, gender and ethnicity

- Renal/medical history: transplant age, duration of ESKD, primary renal disease, other medical history including cardiovascular diseases.

- Anthropometric data: blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure and pulse pressure), body mass index

- Social history: smoking, alcohol, home circumstances

- Biochemical data: transplant function (eGFR by CKD-EPI equation), full blood count, urea and electrolytes, bone profile, lipids, vitamin D status

- Medication data: immunosuppression regimen, use of vitamin D or its analogues, antihypertensives

- Vascular function: aortic distensilblity (ascending and descending), carotid-femoral pulse wave velocity, augmentation index corrected to pulse 75bpm (Aix75)

- Vascular calcification: coronary artery calcification (Agatston) score

In addition to the above, all measures that are included as primary and secondary outcomes will also be summarised at baseline as a whole and by study arm.

Summaries of the baseline data recorded for the subjects excluded from the FAS population will be produced. This will allow comparisons to be carried out, determining if there are any differences between the FAS population and the excluded subjects.

EFFICACY ANALYSIS

PRIMARY OUTCOME

Analysis of covariance (ANCOVA) will be used to determine difference in aortic distensibility (ascending) at 12 months, adjusted for age, duration of end-stage kidney disease and the baseline value. The treatment effect estimate, 95% confidence interval (CI) and p-value will be presented.

SECONDARY OUTCOMES

Using ANCOVA adjusted for age, duration of end-stage kidney disease and the baseline value, the between-group difference at 12 months will be calculated for each of the secondary

outcomes, reporting the treatment effect estimates, 95% CIs and p-values. As a number of the secondary outcomes are biomarkers, we will assess the residual distribution and if required, the outcome data will be transformed.

SECONDARY ANALYSES

Subgroup analyses will be performed in older versus younger participants (age >65 years vs <65 years).

SENSITIVITY ANALYSIS

The impact of missing data will be evaluated using multiple imputation, assuming that the criterion of data Missing at Random is fulfilled. This analysis will be carried out for the primary outcome analysis, using imputation of missing aortic distensibility readings that are missing for reasons other than because the patient had died or withdrawn consent from the study. For a number of the secondary outcomes, including cfPWV, augmentation index and Agatston score, multiple imputation will be used to assess the robustness of the analysis.

SAFETY OUTCOMES

SERIOUS ADVERSE EVENTS

The safety tables will analyse the safety data according to treatment received.

The number and characteristics of serious adverse events (SAE) will be summarised as a whole and by study arm, where treatment received is known. The number and percentage of subjects experiencing at least one SAE will be summarised overall and by MedDRA System Organ Class. The table will be sorted by the MedDRA SOC term order and by preferred term order within SOCs.

These tabulations will be repeated for all possible related SAEs, fatal SAEs and all Suspected Unexpected Serious Adverse Reactions (SUSARs).

ADVERSE EVENTS

The same tabulations produced for the SAEs will be produced for the Adverse Events (AE).

DOCUMENT HISTORY

This is version 1.1 of the SAP for the ViKTORIES study, dated 19/07/2019 and this is the final version of this document.

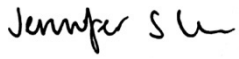
TABLES

Dummy tables will be produced during the development of the statistical analysis programs for review and feedback. Approval of the content of the final statistical outputs will be a requirement for database lock.

FIGURES

Dummy figures will be produced during the development of the statistical analysis programs for review and feedback. Approval of the content of the final statistical outputs will be a requirement for database lock

ViKTORIES statistical analysis plan v1.1 19/07/2019

Signed by: 

Print: **Jennifer S Lees**

Designation: **Principal investigator**

Date: **19/07/2019**