Slower Progress of Aortic Valve Calcification With Vitamin K Supplementation Results From a Prospective Interventional Proof-of-Concept Study

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Results From a Prospective Interventional Proof-of-Concept Study

Vincent M. Brandenburg, MD
Sebastian Reinartz, MD
Nadine Kaesler, PhD
Thilo Krüger, MD
Tim Dirrichs, MD
Rafael Kramann, MD, PhD
Frederique Peeters, MD
Jürgen Floege, MD
Andras Keszei, PhD
Nikolaus Marx, MD
Leon J. Schurgers, PhD*
Ralf Koos, MD*

Calcific aortic stenosis is a common degenerative disease characterized by progressive aortic valve calcification (AVC).[1] Effective medical treatment options to retard the progression of AVC are sparse.[1] Epidemiological data point to vitamin K as a potential protective factor for cardiovascular health, particularly for protection against vascular calcification.[2,3] Matrix Gla-protein (MGP), a potent inhibitor of cardiovascular calcification, requires vitamin K for posttranslational carboxylation and hence full bioactivity.[4] Thus, vitamin K supplementation might retard the progression of AVC.[1,2] Dephosphorylated undercarboxylated MGP (dp-ucMGP) serves as a circulating marker for vitamin K deficiency.[2,3]

We performed a 12-month prospective, single-center, open-label, randomized interventional trial in patients with asymptomatic or mildly symptomatic AVC. Written informed consent was obtained before inclusion in the trial (URL: http://www.clinicaltrials.gov. Unique identifier: NCT00785109; RWTH Aachen Institutional Review Board No. 165/08). Inclusion criterion was a peak flow velocity exceeding 2 m/s. The main exclusion criteria were chronic kidney disease (estimated glomerular filtration rate <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), expected valve replacement within the next year, and anticoagulation with vitamin K antagonists. Patients were randomized 1:1 to receive 2 mg phytomenadione (vitamin K_1, Ka-vit, INFECTOPHARM Arzneimittel CONSILIUM GmbH, Heppenheim, Germany) or matching placebo once daily orally. Patients underwent a baseline and end-of-study cardiac computed tomography (CT) scan for AVC quantification (volume calcification score). All CT examinations were performed on a 128-slice dual-source CT scanner (SOMATOM Definition Flash, Siemens, Germany) and were reanalyzed in a blinded fashion by 2 radiologists experienced in cardiac CT. The primary end point was the difference in progression of AVC volume score between vitamin K and placebo. We also assessed changes of dp-ucMGP plasma levels (IDS, Boldon, UK) as a secondary end point. Linear regression models for AVC change with treatment effect and baseline measures were used as independent variables, and 95% confidence intervals for treatment effects were calculated.

The trial cohort included 99 patients (82% male; 35% with aortic sclerosis [≤2.5 m/s], 38% with mild aortic stenosis [2.6–2.9 m/s], and 27% with moderate aortic stenosis [3.0–4.0 m/s]; 71% of each group received statins). Seventy-two participants also underwent an end-of-study cardiac CT scan (representing the per-protocol analysis cohort: n=38 vitamin K, n=34 placebo). Twenty-seven patients (12 vitamin K, 15 placebo) dropped out of the study. Reasons for discontinuation were initiation of oral anticoagulant treatment (n=3 placebo, n=4 vitamin K), loss to follow-up, withdrawal of consent (n=6 placebo, n=3 vitamin K), cardiac surgery (n=2 each), death (n=1 each), or other reasons (n=3 placebo, n=2 vitamin K).

Over the 12-month period, the AVC volume score progressed by 10.0% in patients in the vitamin K group compared with 22.0% in the placebo group (Table), representing a significant attenuation of AVC progression by vitamin K compared with placebo. Linear

*Drs Schurgers and Koos contributed equally.

Correspondence to: Vincent M. Brandenburg, MD, Department of Cardiology, University Hospital Rheinisch-Westfälische Technische Hochschule Aachen, Pauwelsstraße 30, D-52057 Aachen, Germany. E-mail vincent.brandenburg@post.rwth-aachen.de

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Table. Longitudinal Development of Valvular Calcification and Echocardiographic Parameters and Matrix Gla-Protein Levels, by Intervention Group

	Vitamin K Group (n=38)					Placebo Group (n=34)				
	t0		t12			t0		t12		
	Mean	SD	Mean	SD	*P* Value	Mean	SD	Mean	SD	*P* Value
Age, y	69.3	10.1						68.9	7.9	
Calcification volume, mL	793	742	871	791	0.006*	836	856	1017	939	<0.001†
Mean valvular gradient, mm Hg	17	6	17	7	0.63*	18	8	21	11	0.03†
Peak flow velocity, m/s	2.70	0.44	2.63	0.56	0.42*	2.82	0.62	2.95	0.70	0.24†
dp-ucMGP, pmol/L	432	149	243	165	<0.001*	483	215	515	276	0.10†
Delta calcification volume, mL			78	165				181	234	0.04‡
Delta calcification volume index, mL/m^2 BSA			41	84				91	113	0.04‡
Δdp-ucMGP, pmol/L			−199	233				37	112	<0.001‡
Delta peak flow velocity, m/s			−0.05	−0.38				0.09	0.40	0.16‡

BSA indicates body surface area; and dp-ucMGP, dephosphorylated undercarboxylated matrix Gla-protein.

*Nominal *P* values from paired comparison between baseline (t0) and 12 months (t12) in the vitamin K group.

†Nominal *P* values from paired comparison between t0 and t12 in the placebo group.

‡Nominal *P* values from unadjusted, unpaired comparison of delta values between treatment groups.

regression with treatment group and baseline AVC as independent variables revealed an estimated difference in the change in AVC volume score between the vitamin K and placebo groups of −101 mL (95% confidence interval, −194 to −8.3; P=0.03, adjusted R^2=0.08). Adding age to the model did not improve the model or change the estimated difference. Baseline mean gradient and peak flow velocity were highly correlated (r=0.88). After adjustment for mean gradient, the estimated difference in AVC volume progression was −65 (95% confidence interval, −147 to 17; P=0.12; adjusted R^2=0.26). Similar results were obtained after AVC was indexed to body surface area. Plasma dp-ucMGP concentration significantly decreased in the vitamin K group by 45% (P<0.001; Table). Statistically, the change in peak flow velocity was not significantly different between the 2 groups. No thromboembolic events occurred.

The present study is the first randomized controlled trial in men to demonstrate that vitamin K supplementation might decelerate the progression of AVC. Our findings are clinically meaningful because a strong, significant correlation exists between the AVC volume score and functional valvular parameters such as mean gradient or peak flow velocity.[5] Hence, deceleration of AVC progression, a direct precursor of hemodynamic impairment, might finally translate into a stabilization of valvular functionality in calcific aortic stenosis and a slowing of cardiac and clinical deterioration. In parallel, vitamin K treatment induced a marked reduction of plasma dp-ucMGP, indicating increased vitamin K bioactivity.

We consider the present study results to represent the first proof of concept in the evaluation of the potential anticalcification effects of vitamin K treatment in human calcific aortic valvular disease. We acknowledge that our results need to be confirmed and should therefore be interpreted with caution. Limitations of our trial are the relatively small study size and the additional high dropout rate, resulting in missing data for primary end-point interpretation, as well as the short duration of follow-up, the open-label design, and the broad spectrum of severity of valvular disease at baseline. Moreover, the study was not powered to assess valve functionality using echocardiography, an important determinant for clinical end points. Despite these limitations, our data lay the basis for future intervention trials to investigate valvular hemodynamic parameters or patient outcomes in parallel to calcification parameters.

In summary, vitamin K supplementation may represent an effective and safe therapy in cardiovascular disease related to ectopic calcification such as calcific aortic stenosis.

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AFFILIATIONS

From Departments of Cardiology (V.M.B., N.M., R. Koos), Radiology (S.R., T.D.), Nephrology (N.K., T.K., R. Kramann, J.F.), and Medical Informatics (A.K.), University Hospital of Rheinisch-Westfälische Technische Hochschule Aachen, Germany; and Department of Cardiology (F.P.), Maastricht University Medical Centre, and Department of Biochemistry (L.J.S.), Cardiovascular Research Institute Maastricht, Maastricht University,The Netherlands.

FOOTNOTES

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