Role of Vitamin K in arterial calcifications and cardiovascular diseases

Leon J Schurgers, PhD
Department of Biochemistry
Maastricht University
The Netherlands
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Conclusions

- VSMC phenotype switching
- Arterial Remodeling
  - Elastin degradation
  - Collagen deposition
- Calcification
- MGP
- Proteolysis, MMP
- Mechanical stretch
- Shear stress
- Endothelial dysfunction
- Chemokine release

Coagulation
- Pro-inflammatory macrophages

Clinical
- Arterial Stiffness
- Aberrant hemodynamics
- Cardiovascular disease

Warfarin
DOAC
Coronary artery calcium is a better predictor of cardiovascular events than the Framingham risk score and can help to reclassify asymptomatic individuals into high-risk or low-risk categories.
Calcification is passive process

Coronary Arterial Calcification as an Active Process: A New Perspective on an Old Problem

T. M. Doherty, R. C. Detrano

Division of Cardiology, Harbor-UCLA Medical Center, and Saint John’s Cardiovascular Research Center, Torrance, California, USA

Received: 20 July 1993 / Accepted: 15 September 1993

Matrix Gla-protein (MGP)

- Vitamin K-dependent protein
- 84 amino acids (Mw ~11 kD)
- Gla-residues (required for activity)

Abstract. The mechanism and purpose of coronary atherosclerotic calcification remain unknown. However, evidence reviewed here suggests that calcification is not passive precipitation or adsorption, but instead is organized and regulated. Gla containing proteins and other proteins normally associated with bone metabolism appear to play an important role in this process. A variety of studies are currently in progress in our laboratory which we hope will provide a more comprehensive understanding of processes leading to coronary calcification as well as prognostic data useful in clinical cardiologic practice. A clearer understanding of the nature and significance of coronary calcification may well pave the way toward new interventions to protect myocardium and minimize the morbidity and mortality associated with coronary artery disease.

Key words: Coronary calcification — Bone proteins
# Vitamin K

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<th>Menadione</th>
<th>Phylloquinone</th>
<th>Menaquinone</th>
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<td><img src="image" alt="Phylloquinone" /></td>
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Vitamin K1

Vitamin K2
Vitamin K-metabolism

[Diagram showing the metabolism process with molecular structures and labels such as KH₂, KO, and COO⁻]
Vascular calcification is mediated by VSMC phenotypic switching

Medial vs intimal calcification

- **MEDIAL**
  - Stiffness
  - Increased risk of myocardial infarction
  - Surgical complications
  - Valve calcification
  - Linear crystal deposits along elastin

- **INTIMAL**
  - Measure of atherosclerotic load
  - Punctate, speckled nano/microcrystalline deposits
  - Unstable plaques

London G et al NDT 2003
Budoff et al JACC 2007
Influence of VKA on medial calcification

\[ \text{Calcium content [mg/g dry weight]} \]

**A. Aorta**

<table>
<thead>
<tr>
<th>Control</th>
<th>7 days</th>
<th>28 days</th>
<th>49 days</th>
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**B. Myocard**

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*250μm*

[Image E-H: Representative images of aorta sections.]  
[Image I-L: Representative images of myocardial sections.]

Influence of VKA on medial calcification

Oral anticoagulation results in medial vascular calcification, associated with vascular smooth muscle cell loss and parameters of vascular stiffening.
Influence of VKA on atherosclerosis

C57BL/6 ApoE^{-/-}

WTD

WTD + DE

WTD + Warfarin

Sacrifice

Arch

Calcification (Total Hounsfield Units X1000)

Plaque progression (6 weeks - 20 weeks (fold change))
**VKA - Rivaroxaban**  
- **Design** -

**Population**

- CAC-patients (n = 200)
- CAC score >100; < 400

**VKA therapy**  
(n = 100)

randomised (1:1)  
follow-up = 2.0 years

**Rivaroxaban therapy**  
(n = 100)

- Week 0
- Week 52
- Week 104

**End points:**

primary = progress of coronary calcification
secondary = vascular stiffness and biomarkers
Vitamin K status in patients having AS

149 aortic stenosis patients
Age 74 years, 55% male
Cardiac index / HF, outcome (death)

Ueland, T et al, JIM 2011
Less progression of AVC by vitamin K

**VitaK-CAC Study**
- Design -

Placebo (n=100) vs Vitamin K2 (n=100)
2 year treatment
Primary readout: **progression calcification**
Measured with CT

**BASIK2**
- Design -

Placebo (n=20) vs Vitamin K2 (n=20)
1 year treatment
Primary readout: **progression valve calcification**
Measured with PET/MRI en CT

Brandenburg et al. Circulation 2017
What did Leon say…?
- Chris Reutelingsperger
- Gosia Furmanik
- Martijn Chatrou
- Brecht Willems
- Dennis Kusters
- Armand Jaminon
- Rick van Gorp
- Henri Spronk
- Tilman Hacker
- Erik Biessen

- Bram Kroon
- Roger Rennenberg
- Harry Crijns
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- Harald Schmidt

- Catherine Shanahan
- Alexander Kapustin
- Rukshana Shroff

- Martin Bennett
- Murray Clark
- Diane Proudfoot

- Juergen Floege
- Willi Jahnen-Dechent
- Nikolaus Marx
- Vincent Brandenburg
- Thilo Krueger
- Georg Schlieper
- Robert Stohr
- Mathias Burgmaier

- Ralf Westenfeld
- Malte Kelm

- Marie-Luce Bochaton-Piallat