

VitaK BV

**The triage principle exemplified by vitamin K:
how long-term micronutrient deficiencies
lead to age-related diseases**

Cees Vermeer

Associate Professor of Biochemistry
Cardiovascular Research Institute CARIM
Maastricht University
The Netherlands

CEO
VitaK BV
BioPartner Center Maastricht
The Netherlands

www.vitak.com
c.vermeer@vitak.com

VitaK BV

Function of K vitamins

uncarboxylated (uc) protein
ucOC, ucMGP
no functional activity

Vitamin K
carboxylase

carboxylated (c) protein
cOC, cMGP
biologically active form
proteins are called: **Gla-proteins**

VitaK BV

Classification of vitamin K-dependent proteins

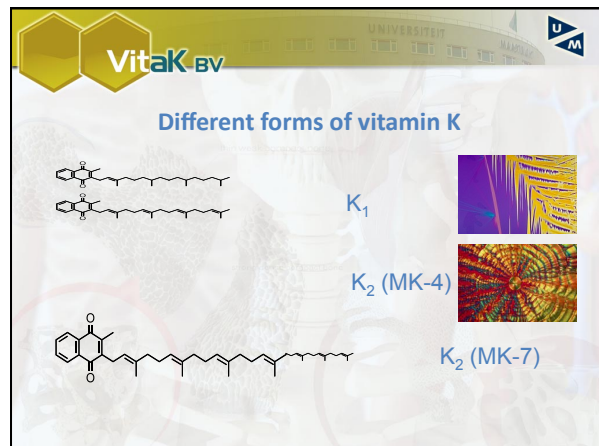
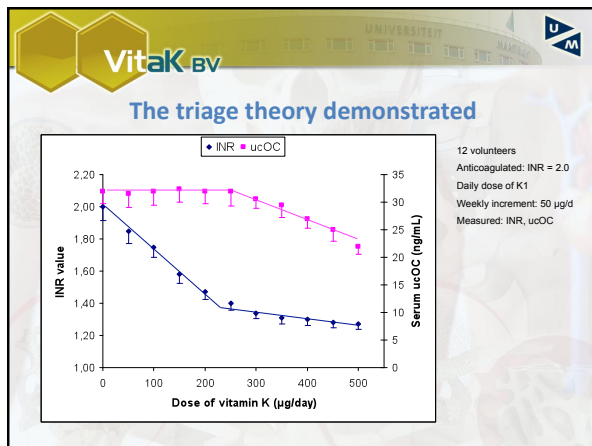
Hepatic:	Extra-hepatic:
<ul style="list-style-type: none"> Blood clotting – <i>Factors II, VII, IX, X</i> Clotting inhibitors – <i>Proteins C, S, Z</i> 	<ul style="list-style-type: none"> Artery calcification inhibition – <i>Matrix Gla-Protein (MGP)</i> Bone growth regulation – <i>Osteocalcin (OC)</i> Cell growth regulation – <i>Gas6</i> Unknown functions – <i>Gla-Rich Protein (GRP)</i> – <i>4 transmembrane Gla-proteins</i> – <i>Periostin & Periostin-Like Factor</i>

VitaK BV

**The triage theory:
during sub-optimal supply, vitamins are primarily
utilized for functions important for immediate survival**

McCann and Ames: Am. J. Clin. Nutr. 2009

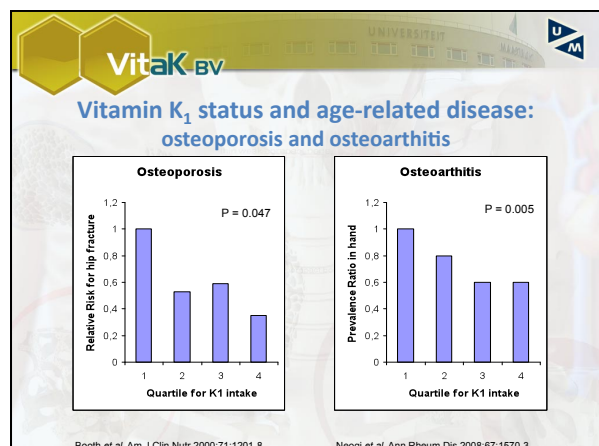
- If blood clotting is disturbed there is an immediate risk for bleeding: life threatening
- If calcification inhibition is sub-optimal there is increased risk for vascular calcification: development of age-related disease in 10-20 years
- So: 'evolution' decided: blood clotting has 1st priority



VitaK_{BV}

Misconception about vitamin K: Healthy subjects are adequate in vitamin K

False: only the blood clotting factors (synthesized in the liver) are fully carboxylated in non-supplemented subjects; all extrahepatic Gla-proteins examined thus far were undercarboxylated for 20-30%. This is suggestive for extrahepatic vitamin K-insufficiency



VitaK_{BV}

Vitamin K₂ and prostate cancer: the EPIC study

- > 23,000 subjects
- Healthy, 35-65 yrs
- 14 years follow-up

- reduction of cancer incidence
- reduction of fatal cancers
- strong reduction of total cancer mortality
- Also for most other forms of cancer

Quartile	K1 (RR)	K2 (RR)
Q1	1.0	1.0
Q2	~1.2	~0.8
Q3	~1.1	~0.6
Q4	~1.1	~0.4

RR per 10 µg K₂: 0.76

Only for K₂

K. Nimptsch et al., Am. J. Clin. Nutr. 87 (2008) 985-992

VitaK_{BV}

K₂ and cardiovascular health: the Rotterdam study

- Over 4,800 subjects
- Healthy elderly, 55 years and older
- 10 years follow-up

- 50% reduction of arterial calcification
- 50% reduction of cardiovascular death
- 25% reduction of all cause mortality

Intake (µg/day)	Aorta calcification	Cardiovascular mortality	All cause mortality
<21	100	100	100
21-32	~70	~70	~90
>32	~50	~45	~75

Only for K₂

Geleijnse et al., J. Nutr. 2004

VitaK_{BV}

Hazard ratio for coronary heart disease risk per 10 µg increase of K intake

- PROSPECT Study cohort
- Included: 16,057 women 50-70 years old
- Longitudinal survey, follow-up period > 10 years

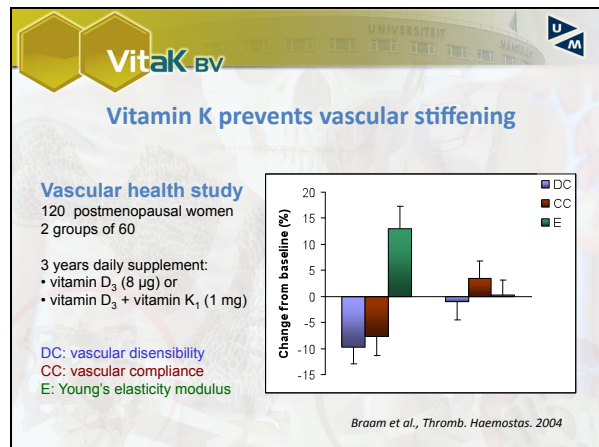
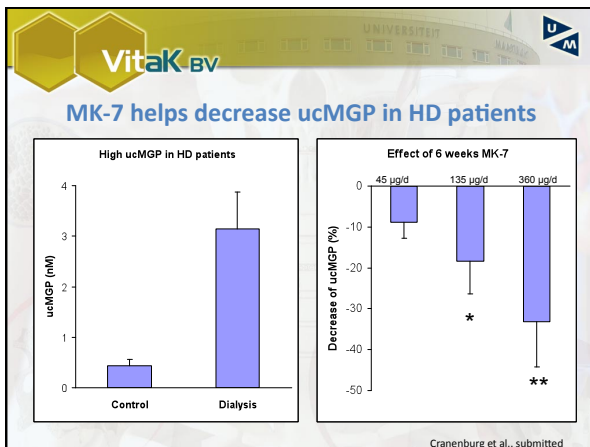
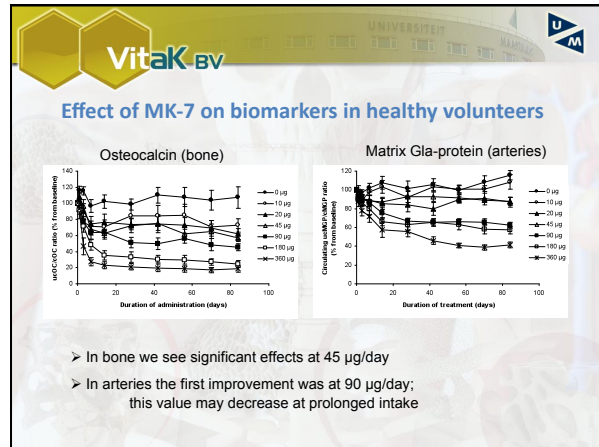
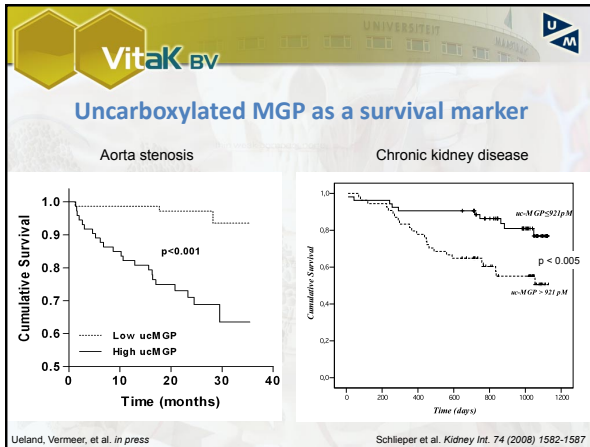
Type of K	HR	95% CI	P-value
K ₁	1.00	1.00-1.02	0.51
K ₂	0.91	0.85-0.99	0.04


Gast et al.: Nutr. Metab. Cardiovasc. Dis. (2009)

VitaK_{BV}

Structure of Matrix Gla-Protein (MGP)


- Both domains strongly bind calcium
- Gla-domain is required for function
- No function known for Phosphoserine domain






Conclusions for cardiovascular disease

- Vitamin K insufficiency of the vessel wall is widespread in the adult healthy population
- This results in sub-optimal MGP carboxylation and thus in poor calcification-inhibitory activity
- Poor MGP carboxylation is a strong and independent risk factor for vascular calcification and mortality



General conclusions

- Besides clotting factors, osteocalcin and MGP there are 8 vitamin K dependent proteins the function of which is not or only partially known
- Hence more physiological processes may turn out to be controlled by vitamin K
- In this respect it is of great concern that vitamin K intake has been going down all the time during the last 2000 years
- Recommendations for vitamin K intake should be shifted upwards and separate recommendations should be given for vitamins K1 and K2



Business strategy for VitaK (1)

1. Find new diseases related with vitamin K insufficiency and file user-patent for the use of vitamin K supplements and fortified foods



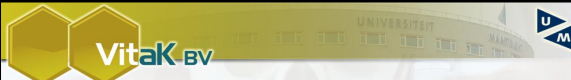
Business strategy for VitaK (2)

1. Find new diseases related with vitamin K insufficiency and file user-patent for the use of vitamin K supplements and fortified foods
2. Design and develop simple tests to monitor vitamin K-insufficiency in specific tissues



Business strategy for VitaK (3)

1. Find new diseases related with vitamin K insufficiency and file user-patent for the use of vitamin K supplements and fortified foods
2. Design and develop simple tests to monitor vitamin K-insufficiency in specific tissues
3. License out or sell the patents in exchange for long-lasting R&D contracts



Approach to achieve growing business

1. Yearly "in house" R&D budget > € 300.000,--
2. 15-20 high impact scientific papers yearly
3. Long-lasting (3-10 years) R&D contracts with third parties
4. All K-related technology available
 - Analytical (sensitive detection of all forms of vitamin K)
 - In vitro (cell culture, ELISA-assays, cell-free systems)
 - Animal models (K-deficient, transgenic, calcifying)
 - Clinical trials (up to 1,000 participants according to GCP guidelines)
 - Iso-9001 certification



Personnel employed at VitaK

President:	Cees Vermeer, PhD	
Vice-president:	Leon Schurgers, PhD	
Scientific staff:	Elke Theuwissen, PhD	
	Lavienja Braam, PhD	
AIOs:	Ellen Cranenburg (MD)	
	Marjo Knapen (MSc)	
	vacancy	
Technicians:	Elke Magdeleyns, BSc	Nadja Drummen, BSc
	Kirsten Teunissen, BSc	Marjolein Herfs, BSc
	Stefan Pantus, BSc	Noura Ahmed, BSc
	Peggy Pijpers	vacancy