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Vitamin K …. Another Calcification Nutrient to Consider?

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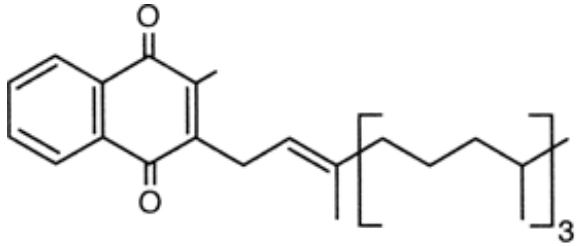
Vitamin K and Calcification

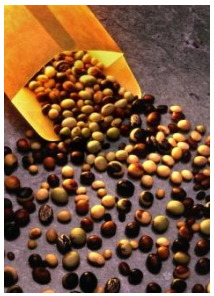
- Forms of vitamin K
- Dietary intakes and requirements
- Role in regulation of calcification
- Evidence for vitamin K interactions with vitamin D
- Implications

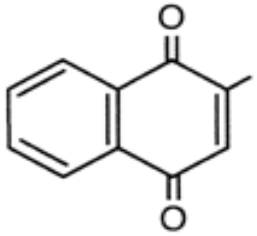
Overview of Vitamin K Forms

Vitamin K Forms



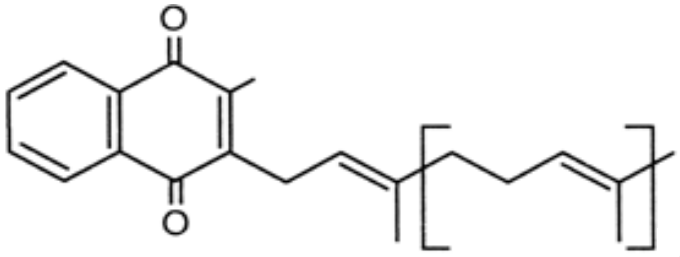
Phylloquinone (PK, VK1)





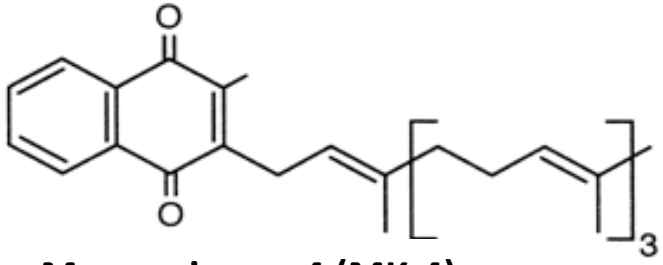
Menadione (MD, VK3)

(2-methyl- 1,4-naphthoquinone)

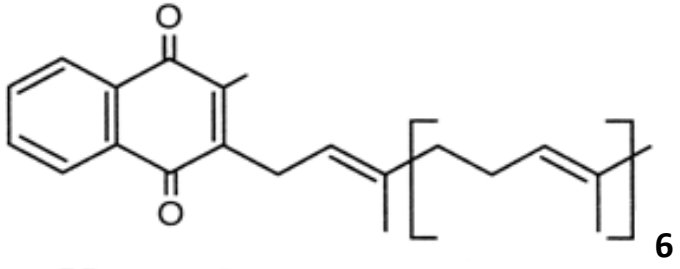


Menaquinone-n (VK2)

(n-1)



Menaquinone-4 (MK-4)



Menaquinone-7 (MK-7)

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Dietary Sources of Menaquinones

(Has not been systematically analyzed in the US food supply)

Food	n	K1	MK-4	MK-5	MK-6	MK-7	MK-8	MK-9
		μg/100 g						
Natto	5	34.7	-	7.5	13.8	998	84.1	-
Buttermilk	6	-	0.2	0.1	0.1	0.1	0.6	1.4
Whole Yoghurt	6	0.4	0.6	0.1	-	-	0.2	-
Hard Cheeses	15	10.4	4.7	1.5	0.8	1.3	16.9	51.1
Soft Cheeses	15	3.6	2.7	0.3	0.5	1.0	11.4	39.6
Curd Cheese	12	0.3	0.4	0.1	0.2	0.3	5.4	18.7
Egg Yolk	8	2.1	31.4	-	0.7	-	-	-

Schurgers L, Vermeer C. Haemostasis 2000; 30:298-307

Dietary Supplements

- **Phylloquinone** is globally available as a dietary supplement
- **MK-7** is globally available as a dietary supplement
- In Japan, **MK-4** is used therapeutically in doses of 45,000 µg/day
- Combinations of **Phylloquinone, MK-4** and **MK-7** are available at doses considerably higher than is available from food
  - No data available on the potential interactions among vitamin K forms when co-administered

Dietary Intakes and Requirements of Vitamin K

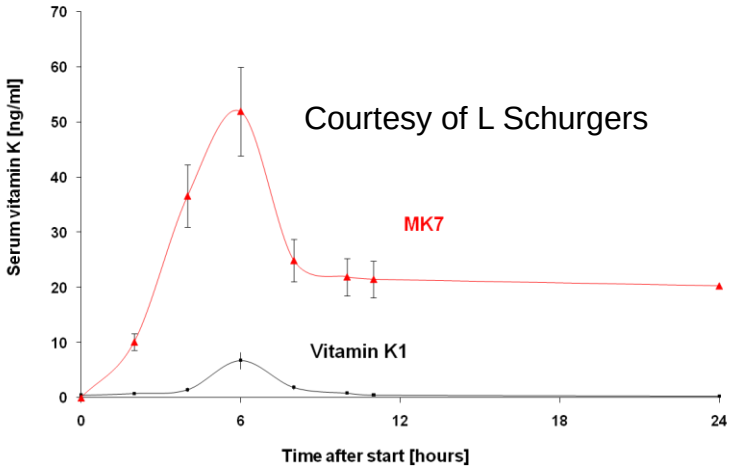
Dietary recommended intakes (DRI) for vitamin K in adults

Country	Sex	DRI (µg/day, unless otherwise indicated)	
		19-50y	>51y
UK	Women	1 µg/(kg d)	1 µg/(kg d)
	Men	1 µg/(kg d)	1 µg/(kg d)
WHO/ Bosnia/ Herzegovina/Poland	Women	55	55
	Men	65	65
New Zealand /Australia	Women	60	60
	Men	70	70
Japan	Women	60, 65[b]	65
	Men	70	70
Germany/Switzerland/ Austria	Women	60	65
	Men	70	80
USA/Canada/ Montenegro/ Albania	**Women**	**90**	**90**
	Men	**120**	**120**

Adapted from Shearer *et al* Adv Nutr 2012

Evidence of Adverse Events

- No recorded evidence with phylloquinone or MK-4 among individuals with normal clotting function
- Any vitamin K form will interfere with efficacy of coumarin-based oral anticoagulants (eg. warfarin)
- Some indication that MK-7 may interfere with oral anticoagulants at a much lower dose compared to phylloquinone and MK-4



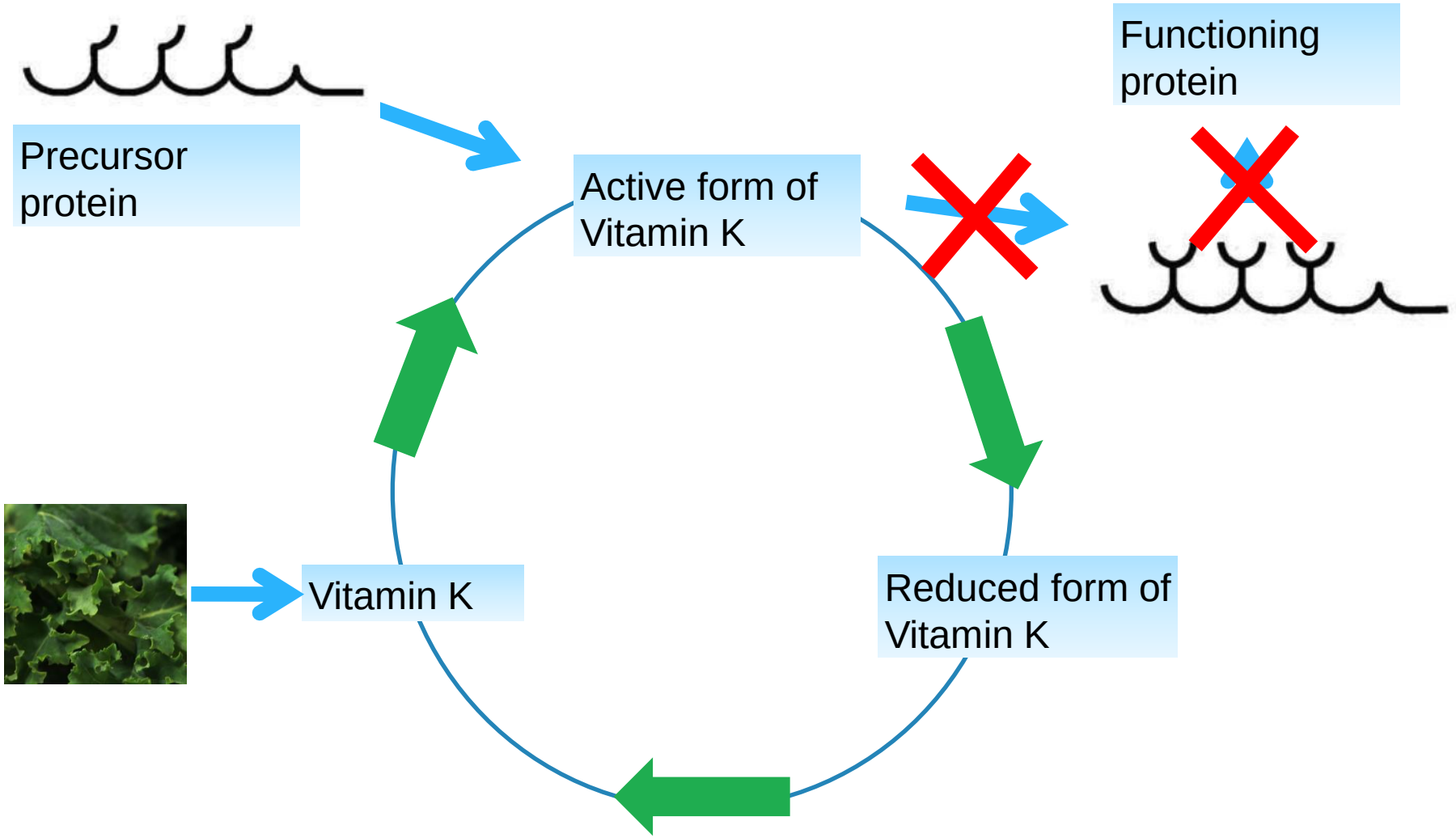
What does this mean?

- We do not know how much vitamin K is required for optimal health

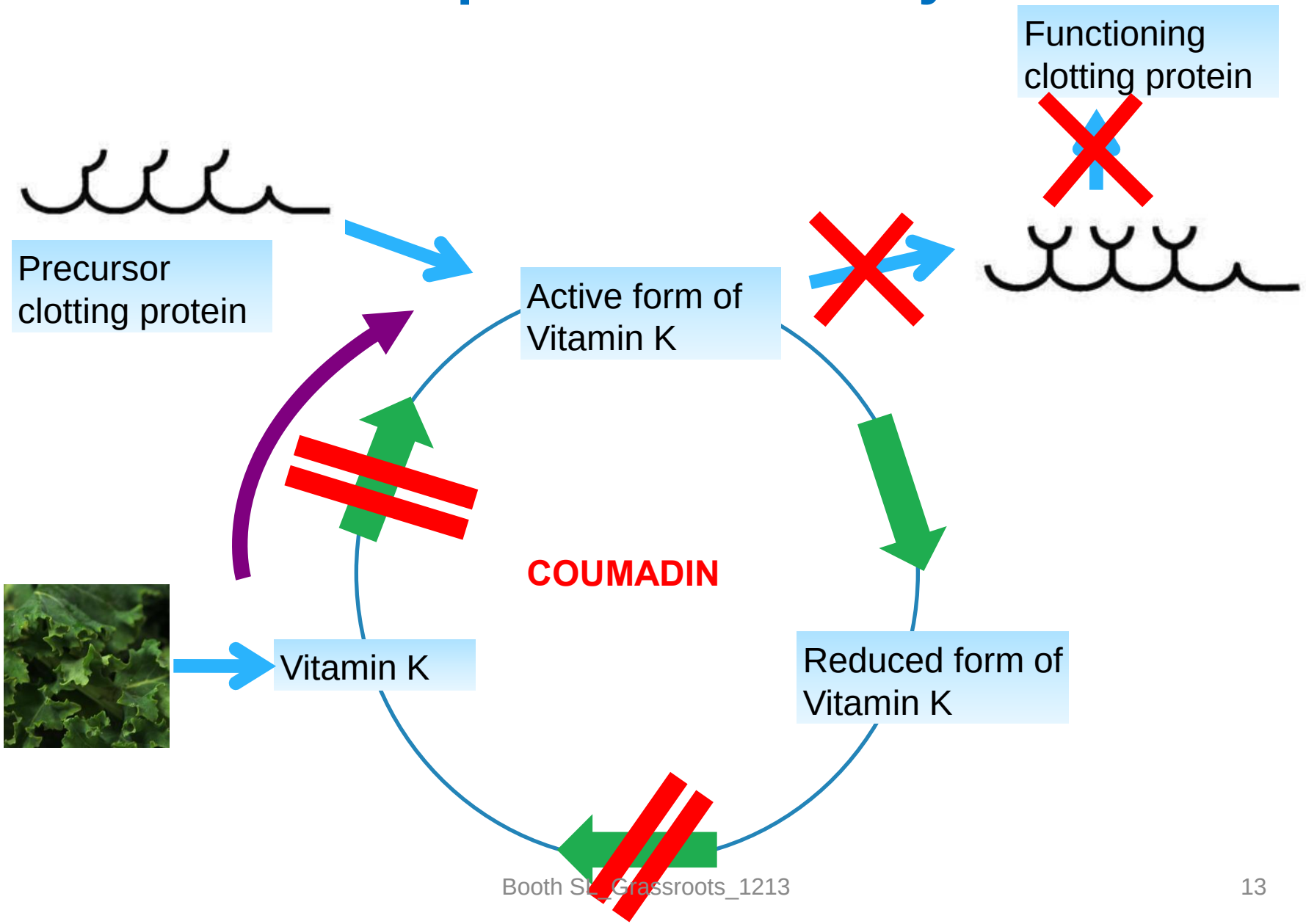
- Current guidance: Eat a diet rich in vegetables and plant oils (DOES NOT APPLY TO PATIENTS ON WARFARIN)

Vitamin K Function

VK is critical for some proteins to function



Warfarin Interrupts Vitamin K Cycle



VK and bone:
Disentangling the myths from facts

Why Consider Vitamin K in Bone Health?

- VK is in bone
- Important bone protein requires VK for function
- VK status rapidly responds to depletion and repletion
- VK intakes are low in certain subpopulations – eg. UK children and elderly

Phylloquinone Intake & Bone: Observational Studies*

Hypothesis	# of Studies In Support of Hypothesis	
	Yes	**No**
↑ K1 intake → ↓ Hip fx	3 (adults)	2 (adults)
↑K1 intake /plasma → ↑ BMD	3 (adults)	2 (children) 2 (adults)

* Cross-sectional and Longitudinal Designs

MK-7 Intake & Bone: Observational Studies*

Hypothesis	# of Studies In Support of Hypothesis	
	Yes	**No**
↑ MK-7 intake/plasma → ↓ Hip fx	2 (adults)	1 (adults)
↑ MK-7 intake/plasma→ ↑ BMD	2 (adults)	-
↑ MK-7 intake → ↓ bone turnover		1 (children)

* Cross-sectional and Longitudinal Designs

Phylloquinone Supplementation Studies

Study	Control (C) vs Treatment (T)	Duration (M)	Difference in Hip BMD	Ref
Tufts (M+F; 60-80y)	C: vit D + Ca T: vit D + Ca + 500 µg K1	36	No difference	Booth JCEM 2008
Maastricht (F; 50-60y)	C: placebo T1: vit D + Ca T2: vit D + Ca + 1,000 µg K1	36	T < C; p <0.05	Braam Calc Tiss Intl 2003
Maastricht (F; endurance athletes)	C: placebo T1: 10,000 µg K1	24	No difference	Braam Am J Sports Med 2003
Wisconsin (F; >55y)	C: vit D + Ca T: vit D + Ca + 1,000 µg K1	12	No difference	Binkley JBMR 2009
UK Bones & Vitamins (F;>60y)	C: placebo T1: vit D + Ca + 200 µg K1 T2: 200 µg K1	24	No difference	Bolton-Smith JBMR 2007
ECKO (F;40-82y)	C: vit D + Ca T: vit D + Ca + 5,000 µg K1	24	No difference	Cheung PLoS Medicine 2008

MK-4 Supplementation Studies

Study	Control (C) vs Treatment (T)	Duration (M)	Difference in Hip BMD	Ref
Maastricht (F; 55--75y)	C: placebo T: 45 mg MK-4	36	No difference (but there was improved femoral neck geometry)	Knapen Osteo Intl 2007
Wisconsin (F; >55y)	C: vit D + Ca T: vit D + Ca + 45 mg MK-4	12	No difference	Binkley JBMR 2009

MK-4 + Calcium Does Not Reduce Fracture Risk Above That Of Calcium Alone

(Four-year trial of 4378 post-menopausal women)

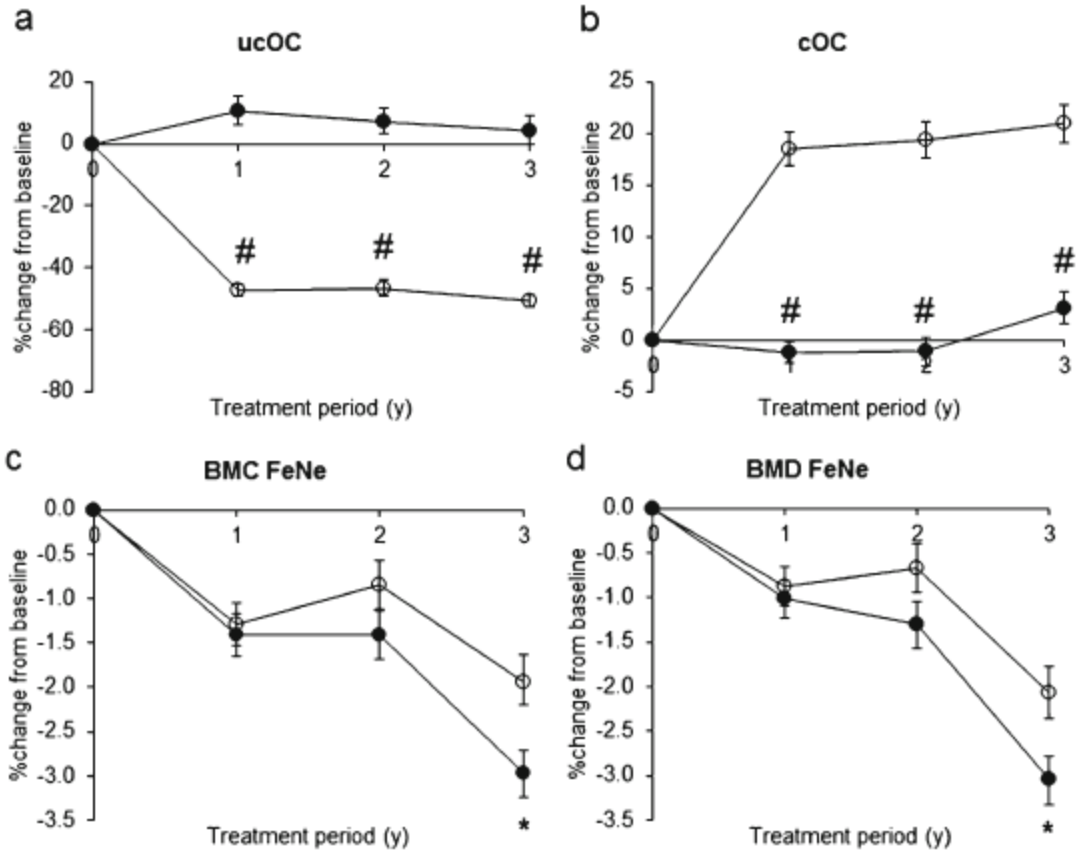
Inoue et al *J Bone Miner Metab* 2009

MK-7 supplementation for three years does protect against bone loss

180 µg/d MK-7 (n=112) vs placebo (n= 111) – no calcium or VD in either group

F; 55-65y (postmenopausal)

* P<0.05; # P<0.001



Knapen et al Osteopor Intl 2013

What does this mean?

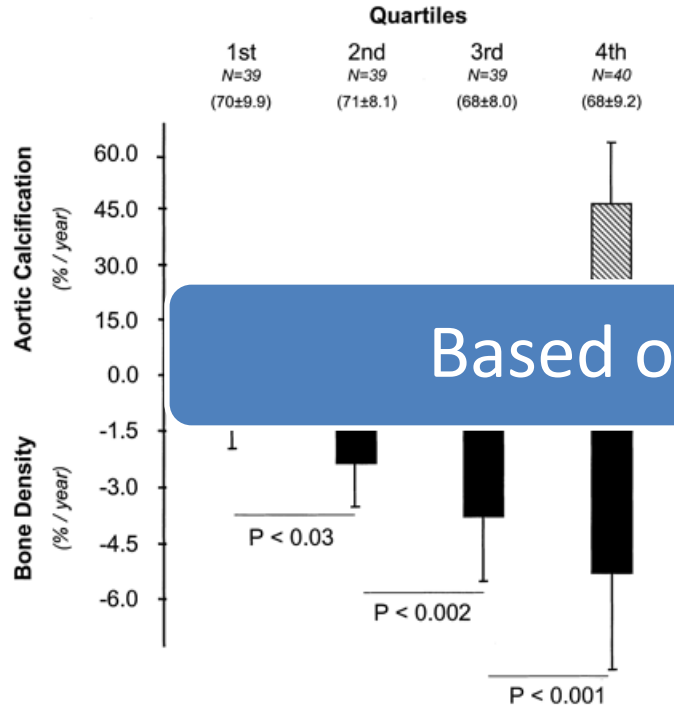
- Phylloquinone and MK-4 supplementation does not appear to reduce bone loss among adults who are calcium- and vitamin D-replete.

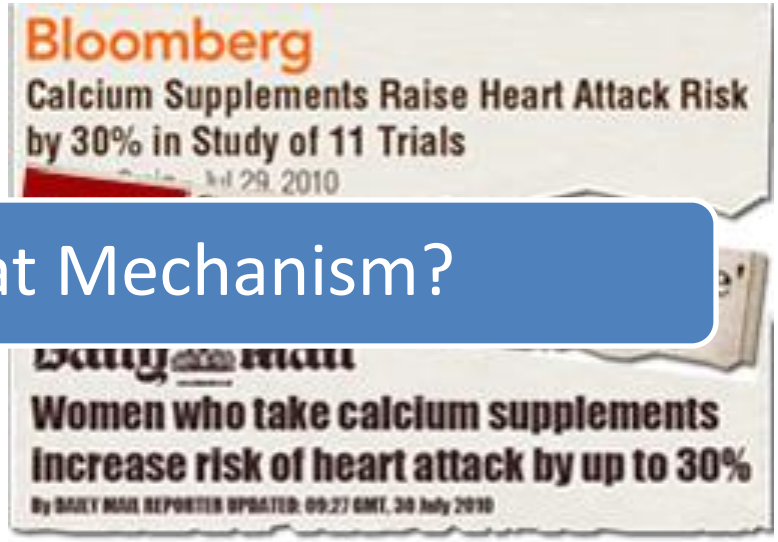
- MK-7 supplementation may modestly reduce bone loss among postmenopausal women who are not receiving calcium and vitamin D supplements.

- Need randomized clinical trials using MK-7 in calcium and vitamin D-replete populations.

The Role of Vitamin K in Pathological Calcification

Osteoporosis & Vascular Calcification:
A Calcium Imbalance?

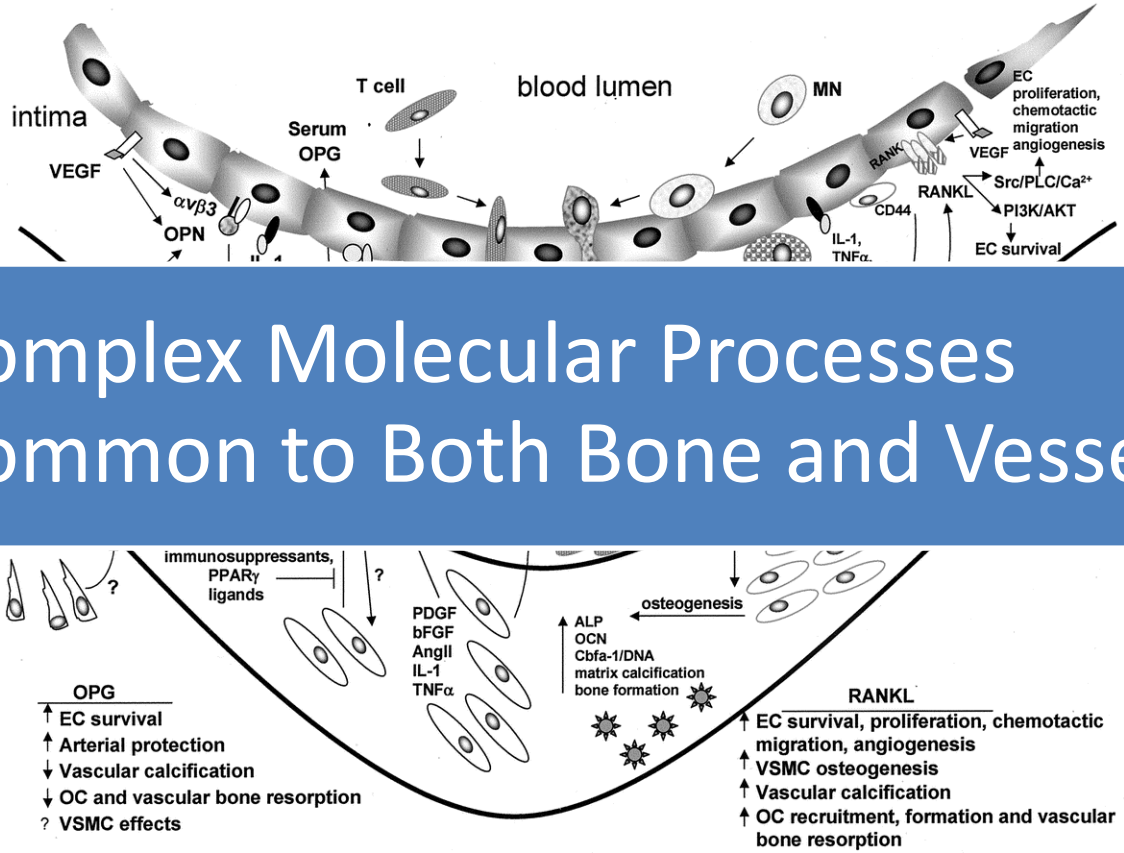




Based on What Mechanism?

Schulz, E. et al *J Clin Endo & Metab*. 2004

Osteoporosis & Vascular Calcification:



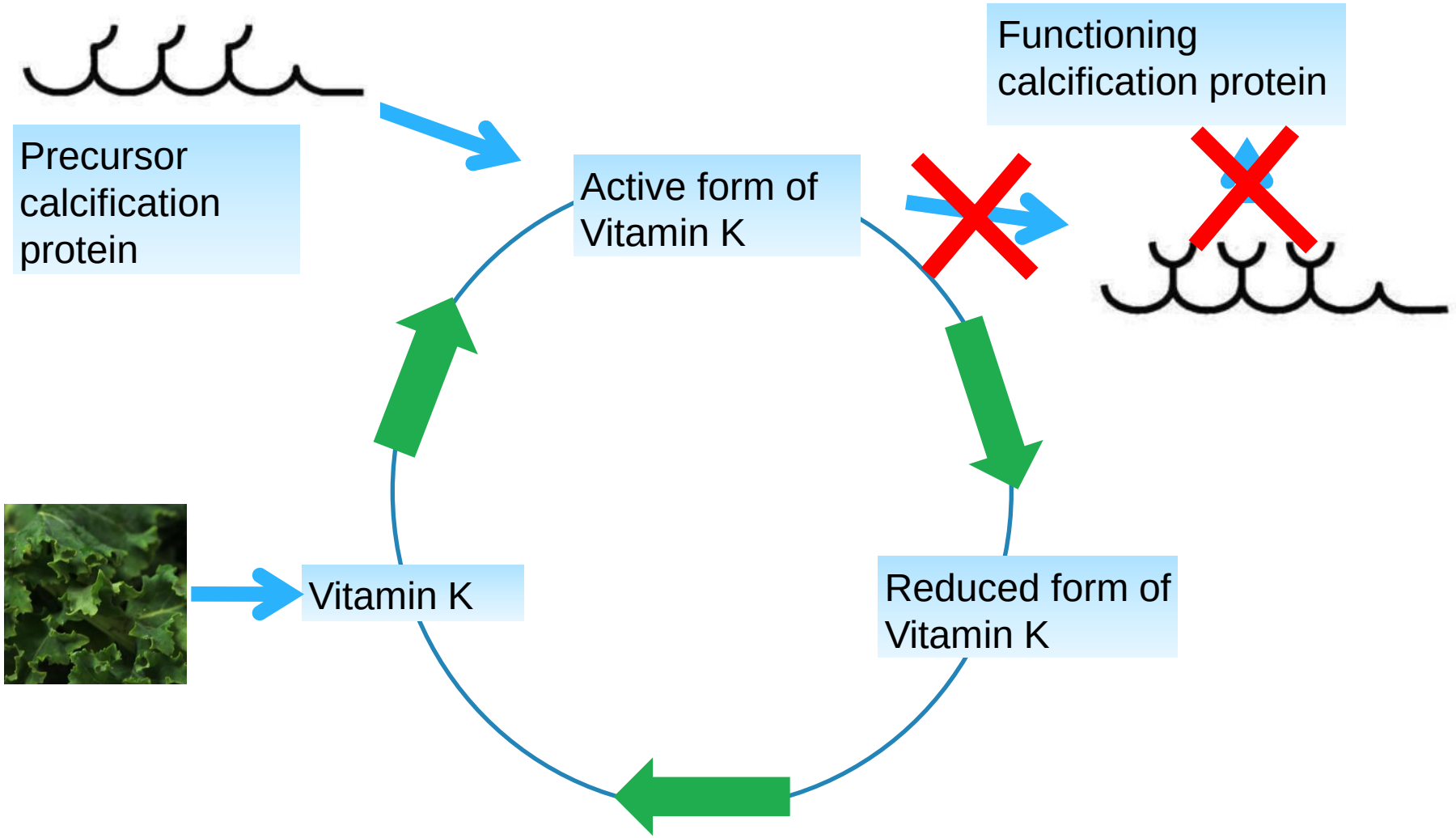
Complex Molecular Processes Common to Both Bone and Vessels!

Collin-Osdoby P. *Circ Research*. 2004.

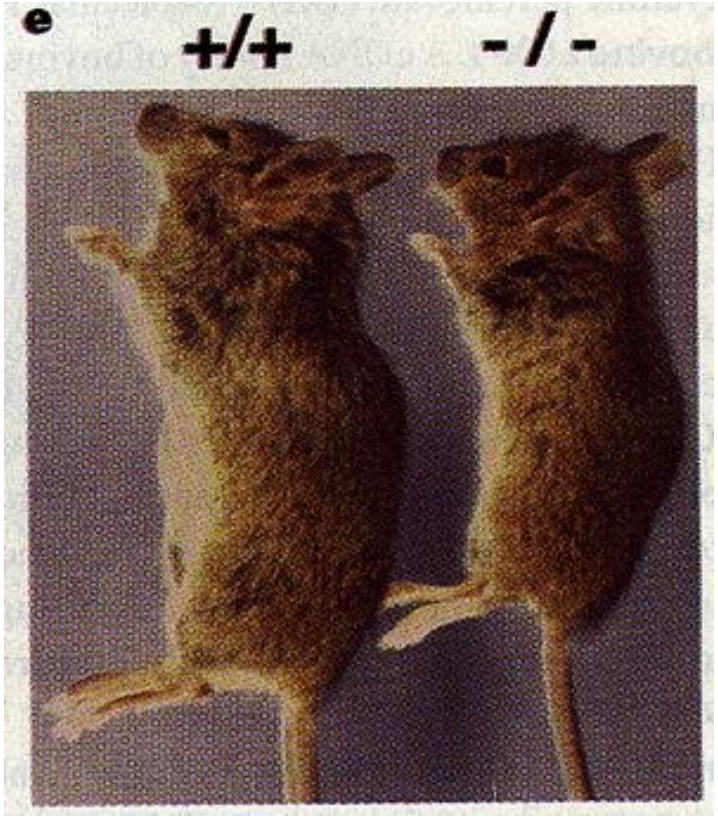
Pathological Calcification Associated with Low VK

Tissue/Location	Disease outcome
Coronary arteries (atherosclerosis)	Coronary heart disease
Vascular (Monckeberg's sclerosis-medial layer)	Chronic kidney disease, Diabetes
Coronary valves	Aortic valve disease
Cartilage (chondrocalcinosis)	Osteoarthritis

VK is critical for some proteins to function

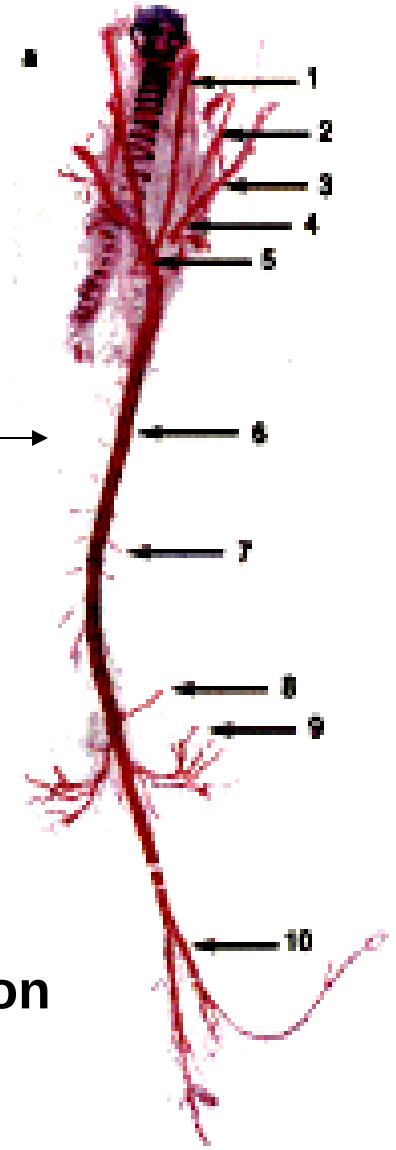


MGP Knockout Mouse Model



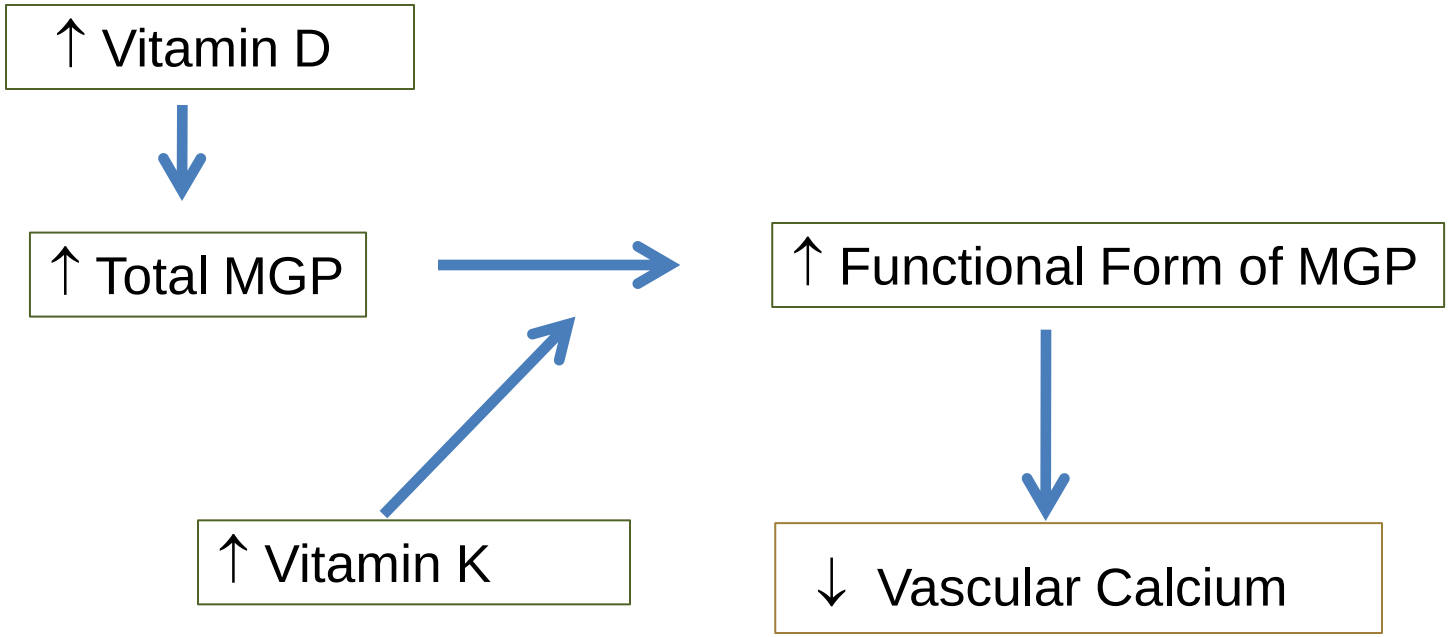
Luo *et al*, Nature 1997

Trachea and aorta is completely calcified



- **Osteopenia**
- **Abnormal calcification of cartilage**

Central Hypothesis



Excessively High Amounts of the Active Form of Vitamin D causes Kidney Calcification

- 1, 25 $(OH)_2D_3$ causes kidney calcification in mice model

	$1,25(OH)_2D_3$ (µg/kg diet)		
	0	2.5	5.0
%calcium deposits	0/14 (0%)	4/14 (28%)	9/11 (82%)

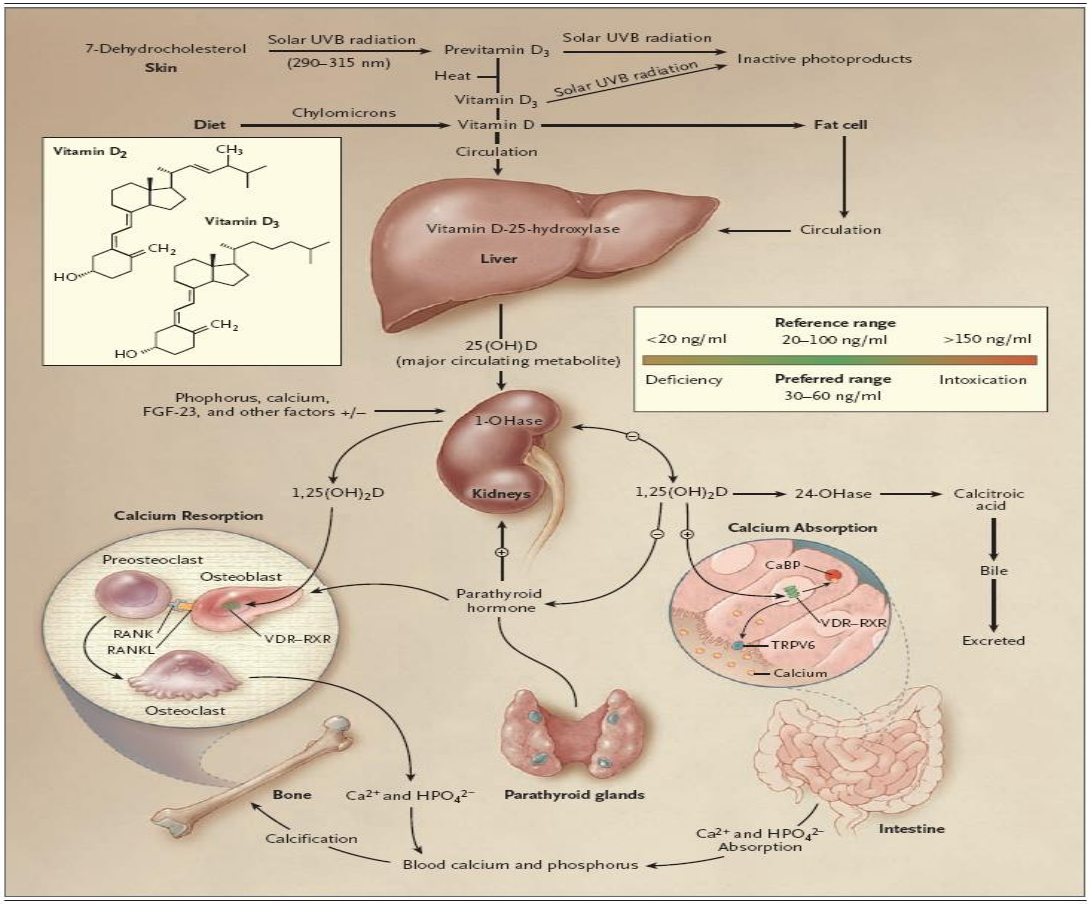
Mernitz *et al*. 2007

- 1, 25 $(OH)_2D_3$ ↑ MGP and in the absence of vitamin K, ↑ non-functional MGP

$1,25(OH)_2D_3$ (µg /kg diet)	Total MGP	Non Functional MGP: Functional MGP
0	12.6	1:1
2.5	23.2	1.6:1
5.0	27.3	1.7:1

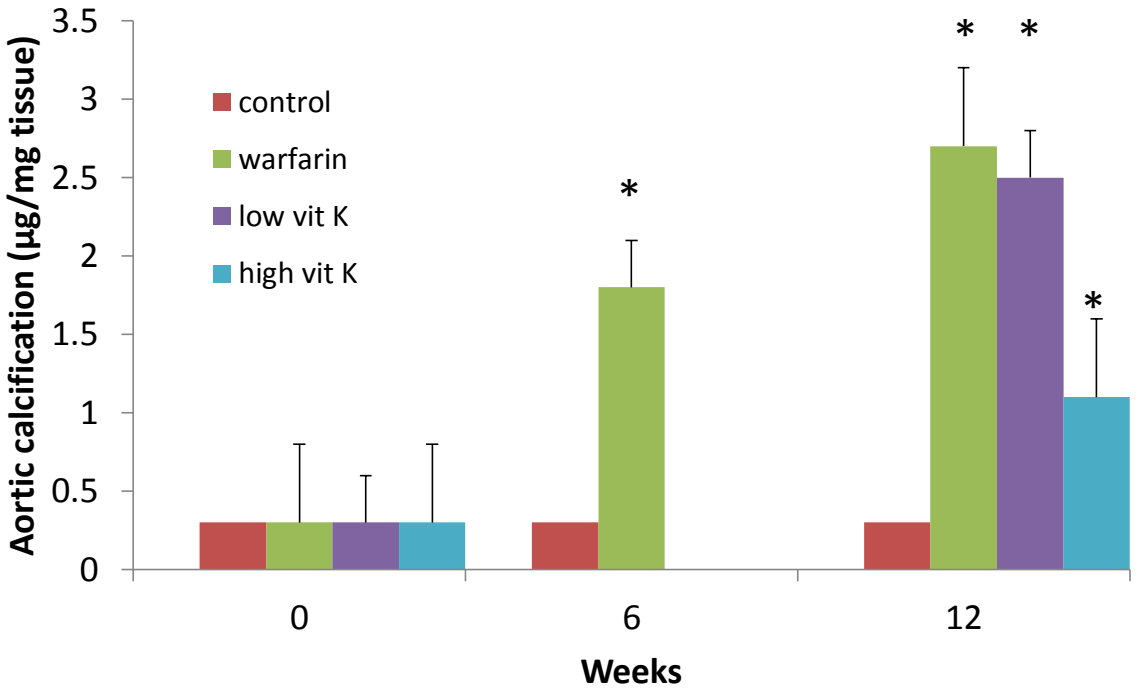
Fu *et al*. 2008

But We Do Not Consume Vitamin D in the Form of Calcitriol !!!!



Holick M NEJM 2007

Can we stop or even *regress* pre-formed arterial calcification with vitamin K?



* = P < 0.001

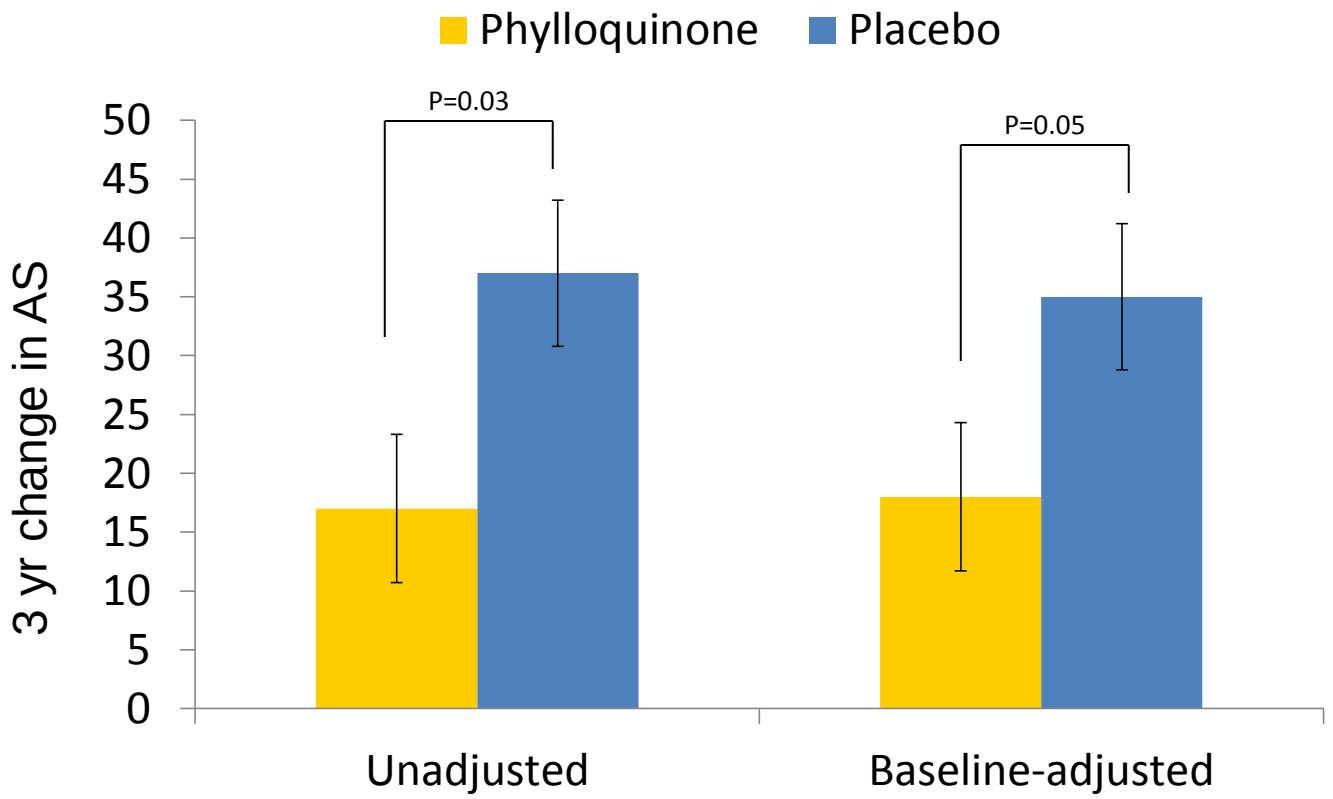
37% reduction

Courtesy of Leon Schurgers

Schurgers et al., Blood 2007

Phylloquinone supplementation reduced coronary artery calcification progression

Mean (SEM) 3-year change in CAC in older men and women (60-80 yrs old); Vitamin D and calcium replete



Shea et al. Am J Clin Nutr., 2009

What does this mean?

- Vitamin K appears to control progression of abnormal calcification
- There is currently no evidence that very high vitamin D intake causes increased calcification in humans
- Current guidance: Eat a diet rich in vegetables and plant oils for vitamin K

Frequently Asked Questions Regarding Vitamin K and Vitamin D

- What is the best form of vitamin K to consume and how much should I consume?
- Is it important to consume vitamin K with vitamin D supplements?
- What is the right balance between calcium, vitamin D and vitamin K?

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Thank you for listening, and feel free to email me at:

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