Berliner DialyseSeminar

Vitamine

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Berliner DialyseSeminar

Darlegung potentieller Interessenskonflikte

Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

Als Referent versichere ich, dass in Bezug auf den Inhalt des folgenden Vortrags **keine Interessenskonflikte** bestehen, die sich aus einem Beschäftigungsverhältnis, einer Beratertätigkeit oder Zuwendungen für Forschungsvorhaben, Vorträge oder andere Tätigkeiten ergeben.

Vitamin-Supplemente bei CKD bzw. Dialyse-Patienten

In adults with CKD 5D who exhibit inadequate dietary intake for sustained periods of time, *it is reasonable to consider* supplementation with multivitamins, including all the water-soluble vitamins …. to prevent or treat micronutrient deficiencies (OPINION).

Wasserlösliche Vitamine: B12 / B-Komplex / C / Folsäure

Erwachsene, CKD 3-5D oder NTX:

- Keine routinemäßige Folsäure (+/- B-Komplex) Gabe bei Hyperhomozysteinämie **(1A)**
- **Folsäure-, B12- und/oder B-Komplex-Gabe** bei **klinischem Mangel (2B)**

Erwachsene, CKD 1-5D oder NTX:

- **Vitamin-C Gabe** (75 mg/d Frauen, 90 mg/d Männer) **bei Patienten mit Risiko for Vit-C Defizienz (Meinung)**

Domröse U et al, Clin Nephrol 2007;67:221-9

Magdeburg 2007: Multivitamin schützt vor Tod von HD-Patienten

102 Patienten, 4 Jahre Nachbeobachtung, 49 Todesfälle

Multivitamin-Patienten vs. non-Multivitamin:

Mortalitätsrisiko 0,29 (95% Konfidenzintervall: 0,15-0,56)

Signifikanz bleibt bestehen nach Adjustierung für Alter, Herz-Kreislauferkrankung, Albumin, Troponin-T

The NEW ENGLAND JOURNAL of MEDICINE

OCCASIONAL NOTES

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.

Dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function. Specifically, a reduction in the risk of dementia, enhanced performance on some cognitive tests, and improved cognitive function in elderly patients with mild impairment have been associated with a regular intake of flavonoids.[1,2] A subclass of flavonoids called flavanols, which are widely present in cocoa, green tea, red wine, and some fruits, seems to be effective in slowing down or even reversing the reductions in cognitive performance that occur with aging. Dietary flavanols have also been shown to improve endothelial function and to lower blood pressure by causing vasodilation in the peripheral vasculature and in the brain.[3,4] Improved cognitive performance with the administration of a cocoa polyphenolic extract has even been reported in aged Wistar–Unilever rats.[5]

Since chocolate consumption could hypothetically improve cognitive function not only in individuals but also in whole populations, I wondered whether there would be a correlation between a country's level of chocolate consumption and its population's cognitive function. To my knowledge, no data on overall national cognitive function are publicly available. Conceivably, however, the total number of Nobel laureates per capita could serve as a surrogate end point reflecting the proportion with superior cognitive function and thereby give us some measure of the overall cognitive function of a given country.

METHODS

A list of countries ranked in terms of Nobel laureates per capita was downloaded from Wikipedia (http://en.wikipedia.org/wiki/List_of_countries_by_Nobel_laureates_per_capita). Because the population of a country is substantially higher than its number of Nobel laureates, the numbers had to be multiplied by 10 million. Thus, the numbers must be read as the number of Nobel laureates for every 10 million persons in a given country.

All Nobel Prizes that were awarded through October 10, 2011, were included. Data on per capita yearly chocolate consumption in 22 countries was obtained from Chocosuisse (www.chocosuisse.ch/web/chocosuisse/en/home), Theobroma-cacao (www.theobroma-cacao.de/wissen/wirtschaft/international/konsum), and Caobisco (www.caobisco.com/page.asp?p=213). Data were available from 2011 for 1 country (Switzerland), from 2010 for 15 countries, from 2004 for 5 countries, and from 2002 for 1 country (China).

RESULTS

There was a close, significant linear correlation ($r=0.791$, $P<0.0001$) between chocolate consumption per capita and the number of Nobel laureates per 10 million persons in a total of 23 countries (Fig. 1). When recalculated with the exclusion of Sweden, the correlation coefficient increased to 0.862. Switzerland was the top performer in terms of both the number of Nobel laureates and chocolate consumption. The slope of the regression line allows us to estimate that it would take about 0.4 kg of chocolate per capita per year to increase the number of Nobel laureates in a given country by 1. For the United States, that would amount to 125 million kg per year. The minimally effective chocolate dose seems to hover around 2 kg per year, and the dose–response curve reveals no apparent ceiling on the number of Nobel laureates at the highest chocolate-dose level of 11 kg per year.

10.10.2012

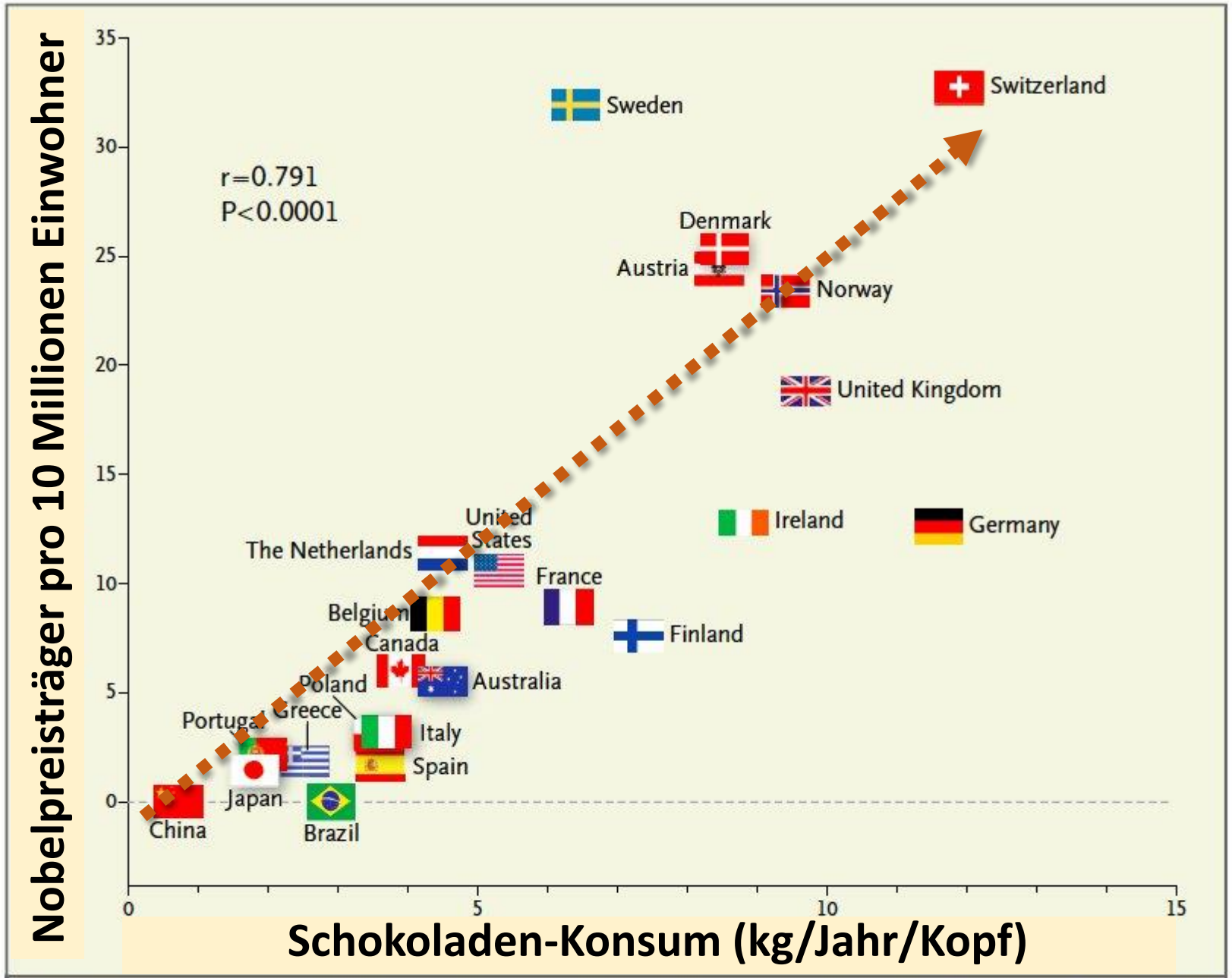


Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Vitamin-Supplemente bei CKD bzw. Dialyse-Patienten

Vitamin D

Erwachsene, CKD 1-5D: **Cholecalciferol** (D3) **oder Ergocalciferol** (D2) Gabe um einen **25OH-Vit D Mangel oder eine Insuffizienz zu korrigieren (2C)**

Erwachsene, NTX: **Dito (Meinung)**

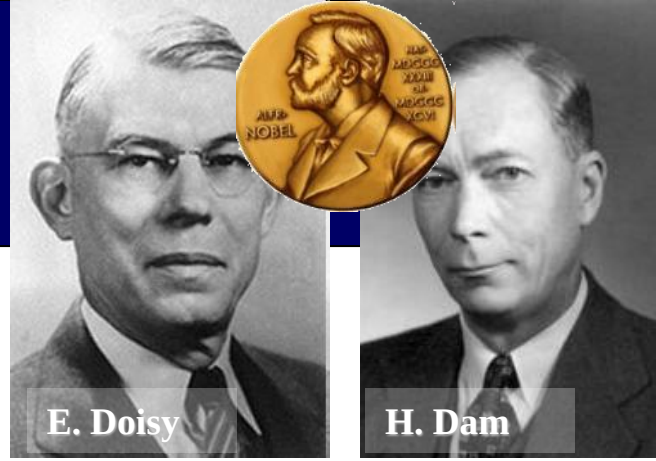
Vitamin A + E

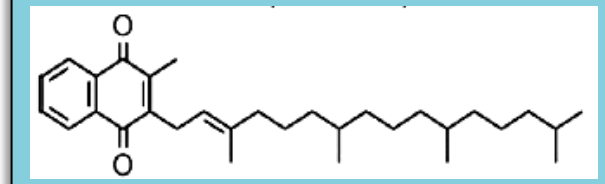
Erwachsene, CKD 5D: **keine Routine-Gabe** wegen Toxizitäts-Gefahr **(Meinung)**

Vitamin K

Nicht geben bei Therapie mit Vitamin-K Antagonisten **(Meinung)**

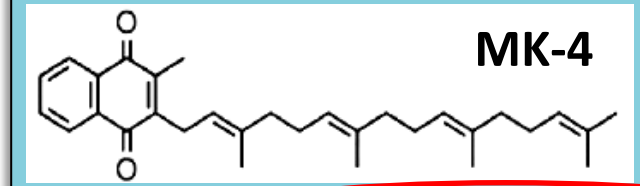
Vitamin K (“K” = Koagulation)

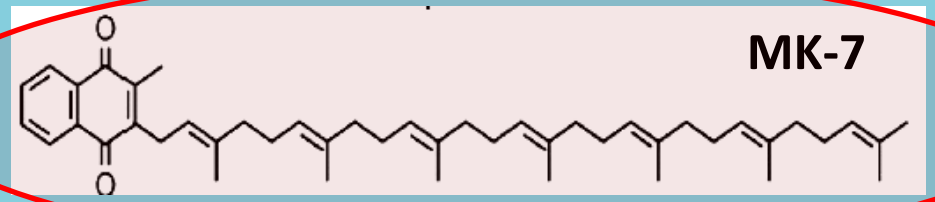




Phylloquinone (“Vitamin K1”)

Menaquinones (“Vitamin K2”)





Menadion (“Vitamin K3”)

- **Fettlöslich**
- **Kofaktor für Vit-K-abhängige Karboxylierung und Aktivierung** (Gerinnungsfaktoren, MGP, Osteocalcin, Calbindin, GAS-6)

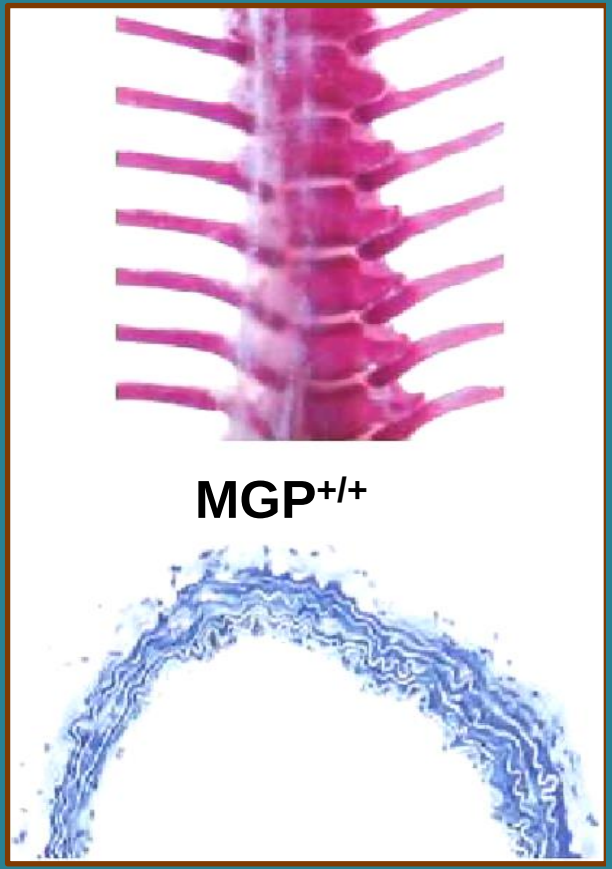
- **Phylloquinone: grüne Blattgemüse**
  Aktivität in der Leber

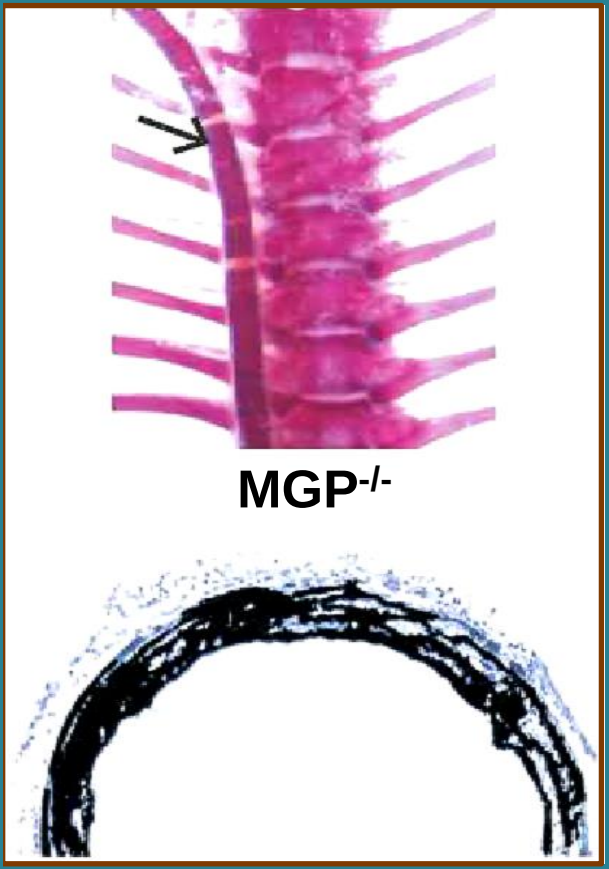
- **Menaquinone: Bakterien + Konversion Phylloquinone → MK-4**
  Aktivität ausserhalb der Leber

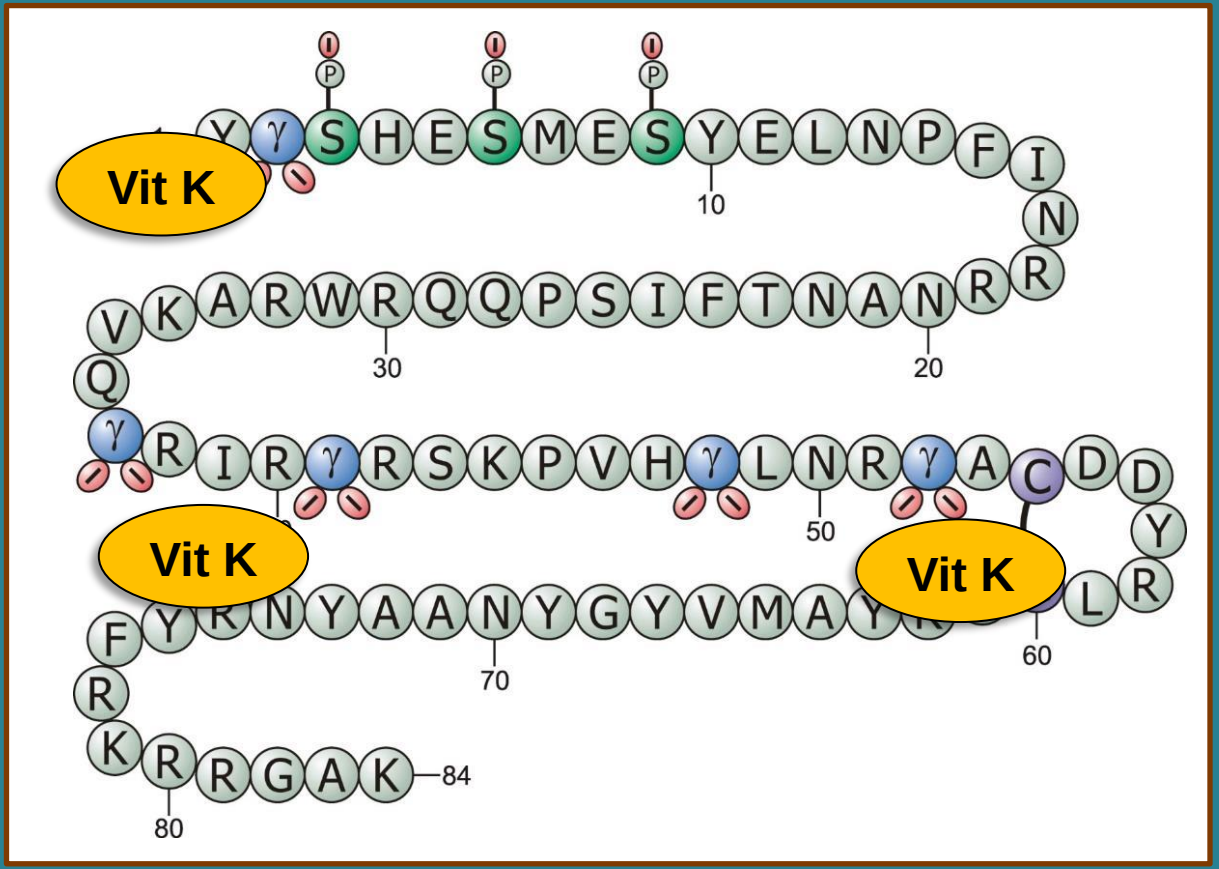
- K3: synthetisch

Adapted from Schurgers LJ, et al. Thromb Haemost 2008;100:593–603.
Murshed M, et al. Genes Dev 2005;19:1093–104.

Matrix Gla Protein (MGP)

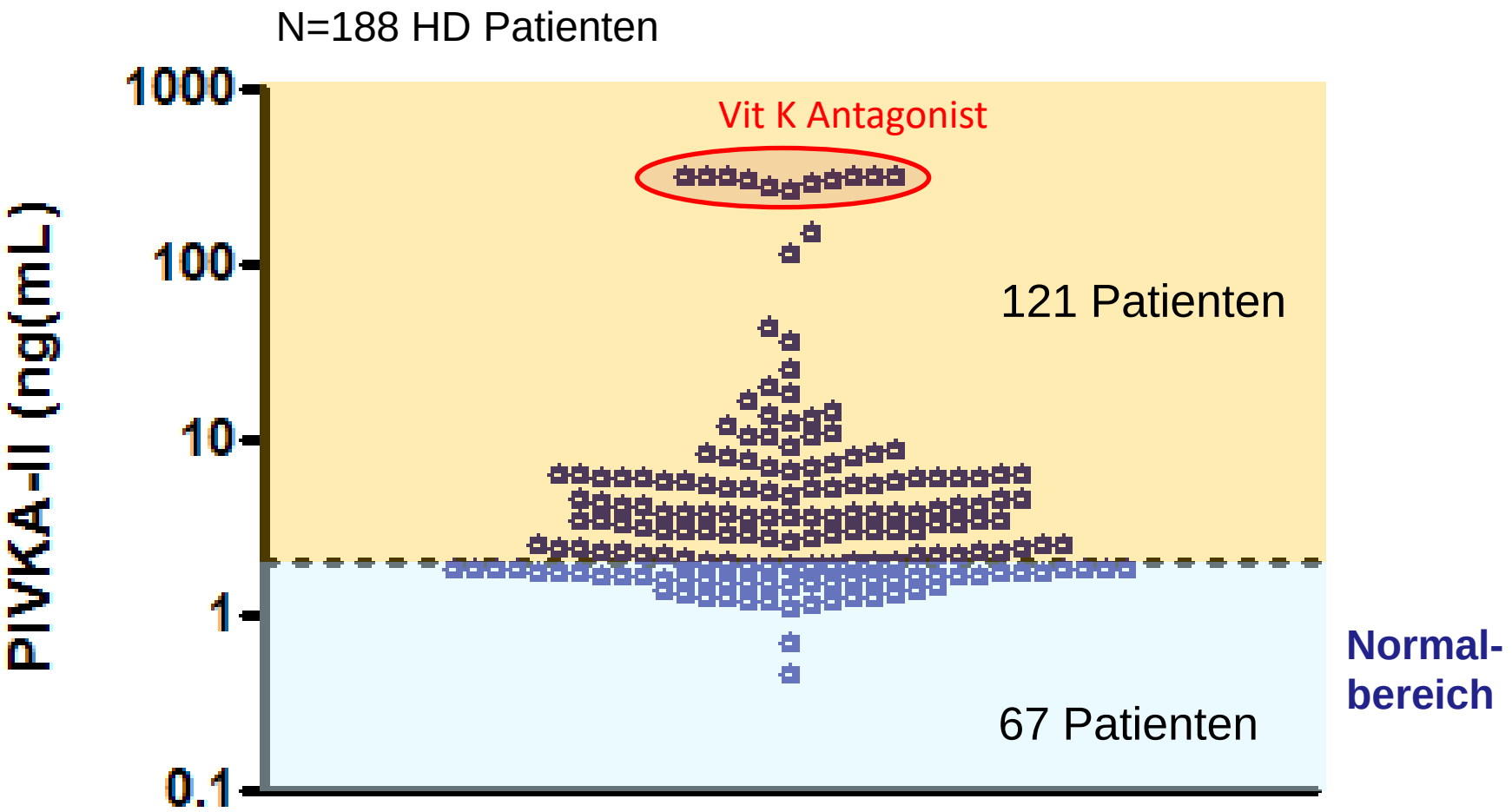






Schlieper G, et al. J Am Soc Nephrol 2011;22:387–95.

Dialyse Patienten sind Vitamin-K defizient



PIVKA, undercarboxylated prothrombin.

Cranenburg EC, et al Kidney Int 2012;82:605–10.

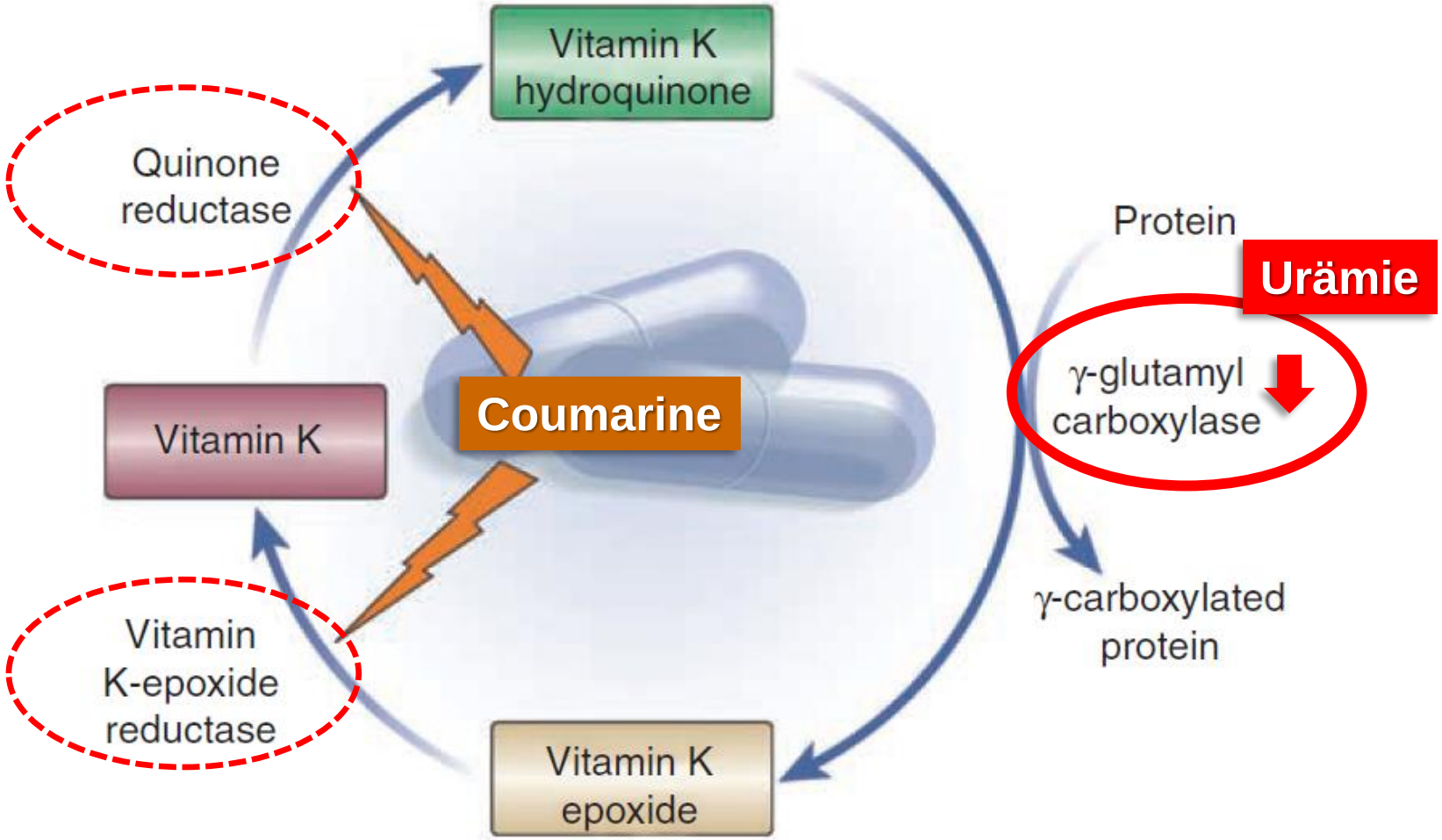
Vitamin K Aufnahme in HD-Patienten ist reduziert

	Vitamin K1	Vitamin K2
Normal	**200** (0–400)	**31** (17–55)
HD Patienten* (N=40)	**118** (18–494)	**21** (2–68)

*Besonders niedrig an HD-Tagen und Wochenenden

Kaesler N, et al. Kidney Int 2014;86:286–93; Krueger N, et al. Kidney Int 2009;76:18–22.

Vitamin K Zyklus & Urämie



J Am Soc Nephrol 2020;31:186-196

CLINICAL RESEARCH www.jasn.org

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

An S. De Vriese,[1,2] Rogier Caluwé,[3] Lotte Pyfferoen,[4] Dirk De Bacquer,[5] Koen De Boeck,[6] Joost Delanote,[4] Didier De Surgeloose,[7] Piet Van Hoenacker,[8] Bruno Van Vlem,[3] and Francis Verbeke[9]

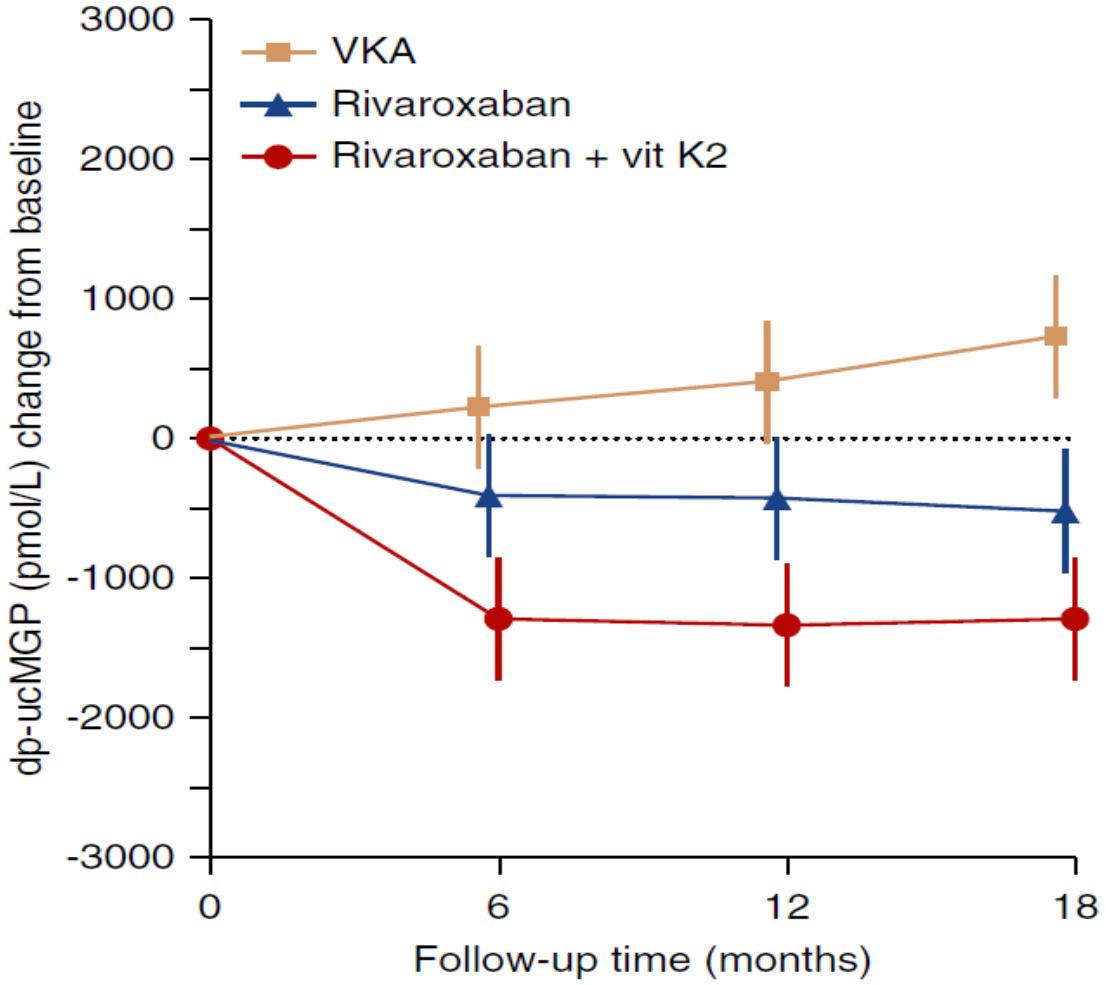
[1]Division of Nephrology and Infectious Diseases and [4]Department of Medical Imaging, AZ Sint-Jan Brugge, Brugge, Belgium; Departments of [2]Internal Medicine and [5]Public Health, Ghent University, Ghent, Belgium; [3]Division of Nephrology and [8]Department of Medical Imaging, Onze Lieve Vrouw Hospital, Aalst, Belgium; [6]Division of Nephrology and [7]Department of Medical Imaging, ZNA Middelheim, Antwerp, Belgium; and [9]Division of Nephrology, University Hospital, Ghent, Belgium

- Einfluß von Vitamin K2 (2 mg MK-7 an HD) auf den Progress vaskulärer Verkalkungen
- 132 alte HD Patienten mit Vorhofflimmern
- Randomisierung:
  - Vitamin K Antagonist
  - Rivaroxaban 10 mg/d
  - Rivaroxaban 10 mg/d + MK-7
- 18 Monate

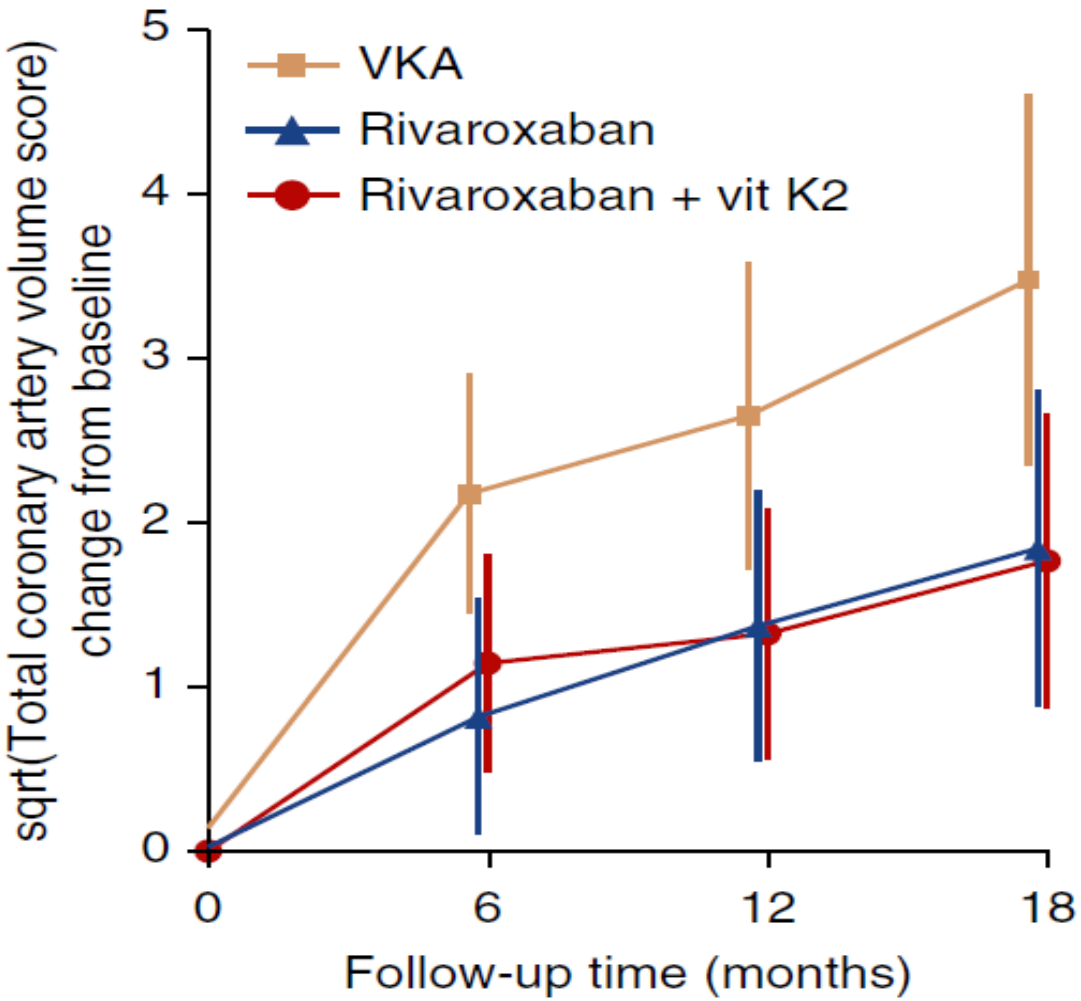
Valkyrie Studie:
Vit K Antagonist vs Rivaroxaban ± Vit K2 in HD Patienten mit Vorhofflimmern

De Vriese AS, et al. J Am Soc Nephrol 2020; *in press*
De Vriese AS, et al. ASN 2019; Poster TH-PO1193

Unterkarboxyliertes Matrix Gla Protein



Koronararterieren-Verkalkung



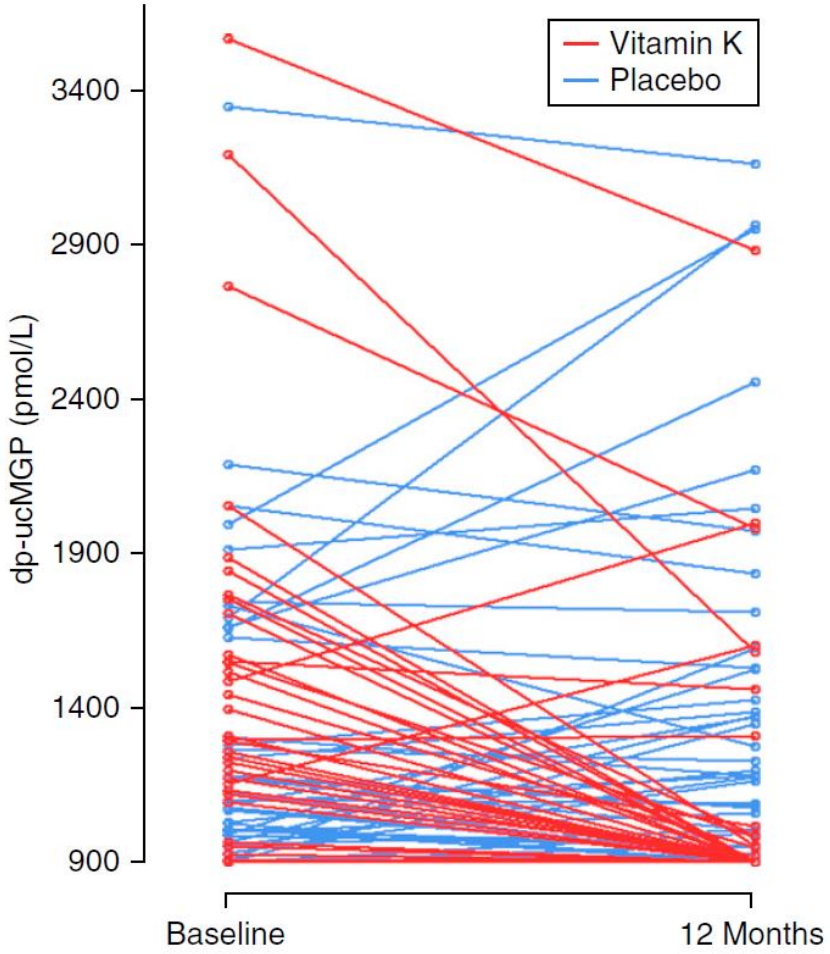
Oikonomaki T et al, Int Urol Nephrol. 2019;51:2037-2044.

Vitamin K2 (MK-7) Gabe und Progress von Gefäßkalk in Dialysepatienten

- Prospektive randomisierte Studie in **102 HD Patienten**
- **200 µg MK-7 täglich vs kein MK-7 für 1 Jahr**
- Nach 1 Jahr: 22 Patienten Vitamin K2 vs 30 Kontroll-Patienten

Witham MD et al, JASN 31: 2434–2445, 2020

Vitamin K2 (MK-7) Gabe und Gefäß-Steifigkeit in CKD Stadien 3-4



- **400 µg orales MK-7** oder Plazebo täglich für 1 Jahr
- 159 Patienten **CKD 3-4**
- **Keine Unterschiede** nach 1 Jahr für:
  - Pulswellengeschwindigkeit
  - Augmentations-Index
  - Blutdruck
  - BNP i.S.
  - Leistungsfähigkeit

Brandenburg V, et al. Circulation 2017;135:2081–83.

Vitamin K & Progression von Aortenklappen-Kalk (CKD Stadium 0-3)

2 mg Vitamin K1 pro Tag für 1 Jahr (n=38) vs Plazebo (n=34)

	Vitamin K1	Plazebo
Δ-ucMGP [pmol/l]	**-199** (±233)	**+37** (±112)***
Δ-Kalkvolumen [ml]	**+78** (±165)	**+181** (±234)*
Δ-Peak-Fluss [m/s]	**-0.05** (±0.38)	**+0.09** (±0.40)
Δ-Klappengradient [mmHg]	**0** (±1)	**3** (±3)***

*P<0.05; ***P<0.001

Vitamin K abhängige Mechanismen kardiovaskulärer Verkalkungen bei CKD

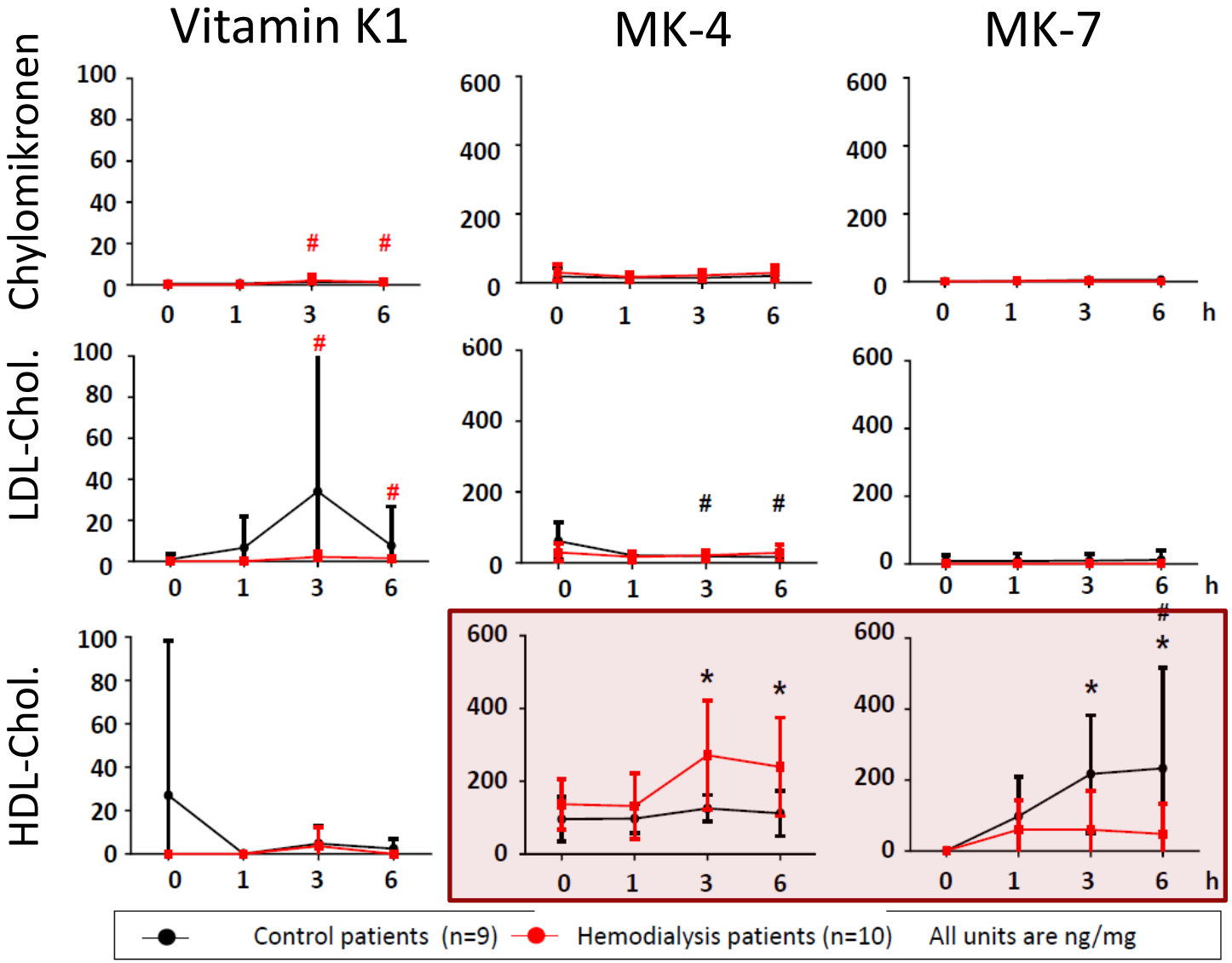
+

Gesunde Kontrollen N=10

Hämodialyse N=10

N Kaesler et al, Kidney Int in press

Vitamin K abhängige Mechanismen kardiovaskulärer Verkalkungen bei CKD



- HDL Partikel von HD Patienten können in vitro nicht mit MK-7 beladen werden
- Urämische HDL-Partikel + MK-7 induzieren in glatten Muskelzellen nur geringe Karboxylierung (d.h. geringe Vit K Aktivität)

Krueger T, et al. Nephrol Dial Transplant 2014;29:1633–8
Saritas T et al, ASN-Kongress 2021

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Registered Charity n° 1060134

VitaVasK-Studie: Design

Population

- HD-Patienten
- Keine Coumarine
- CAC Score >30

Randomisierung (1:1)

Standard Therapie

Vitamin K1 5mg/HD + Standard Therapie

Baseline

12 Monate

18 Monate

- **Endpunkte**: Primärer = Progress von Verkalkung der Aorta thorakalis + Koronarien
  Sekundär = Progress von Klappen-Verkalkungen

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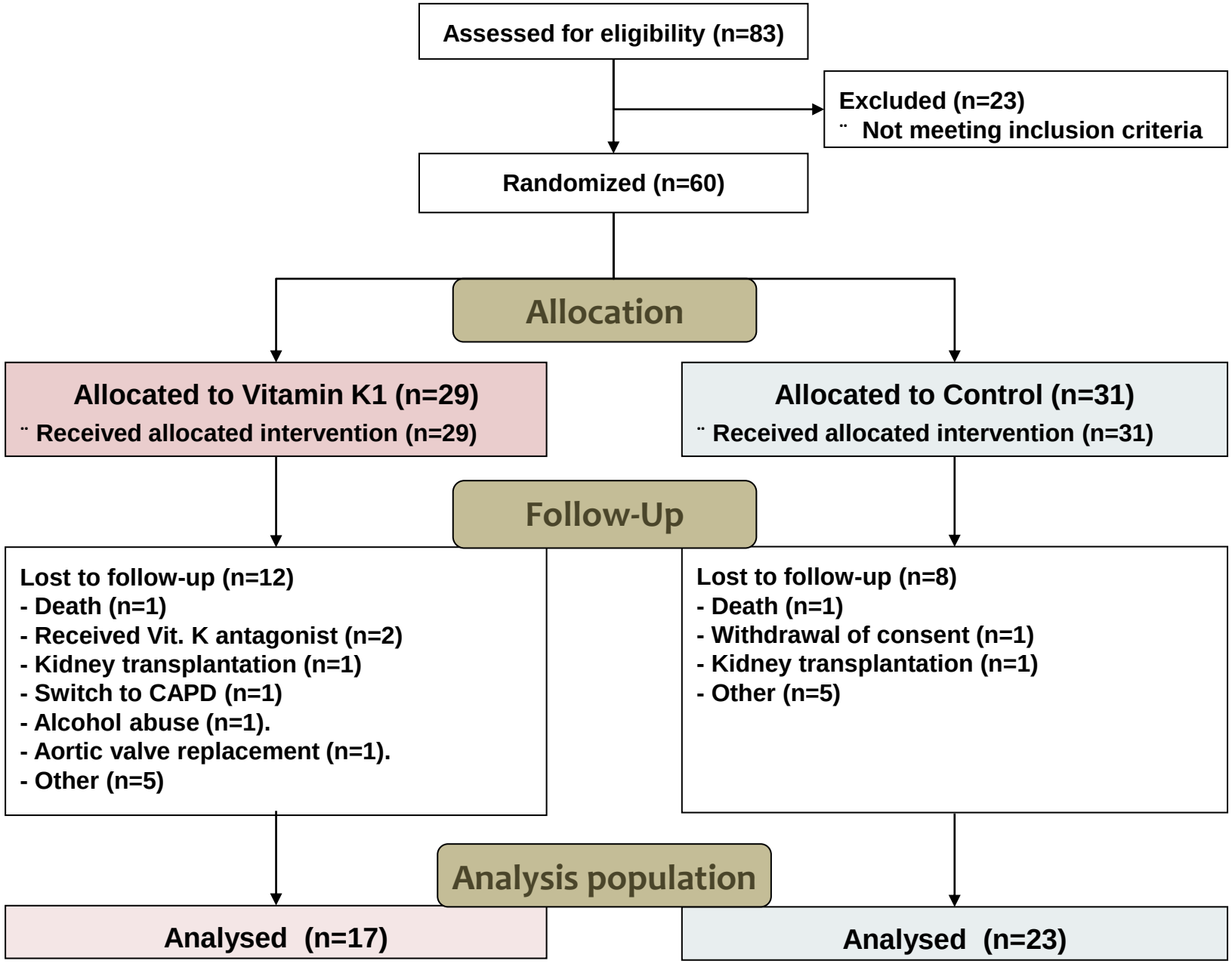
VitaVasK Studie:

Patienten-Randomisierung



Saritas T et al, ASN-Kongress 2021

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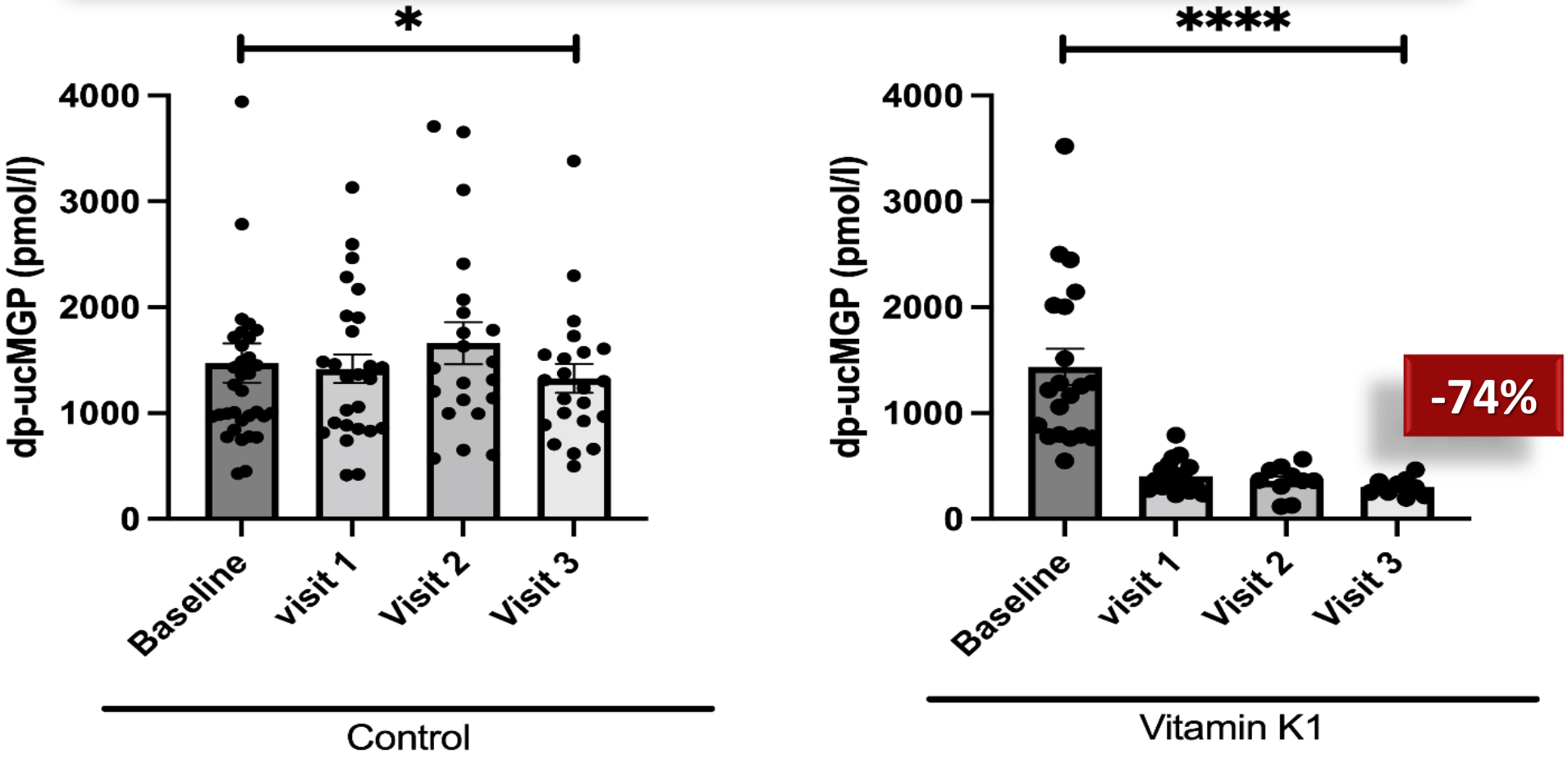
VitaVasK-Studie: Biochemische Endpunkte

Dephosphoryliertes, unterkarboxyliertes Matrix Gla Protein



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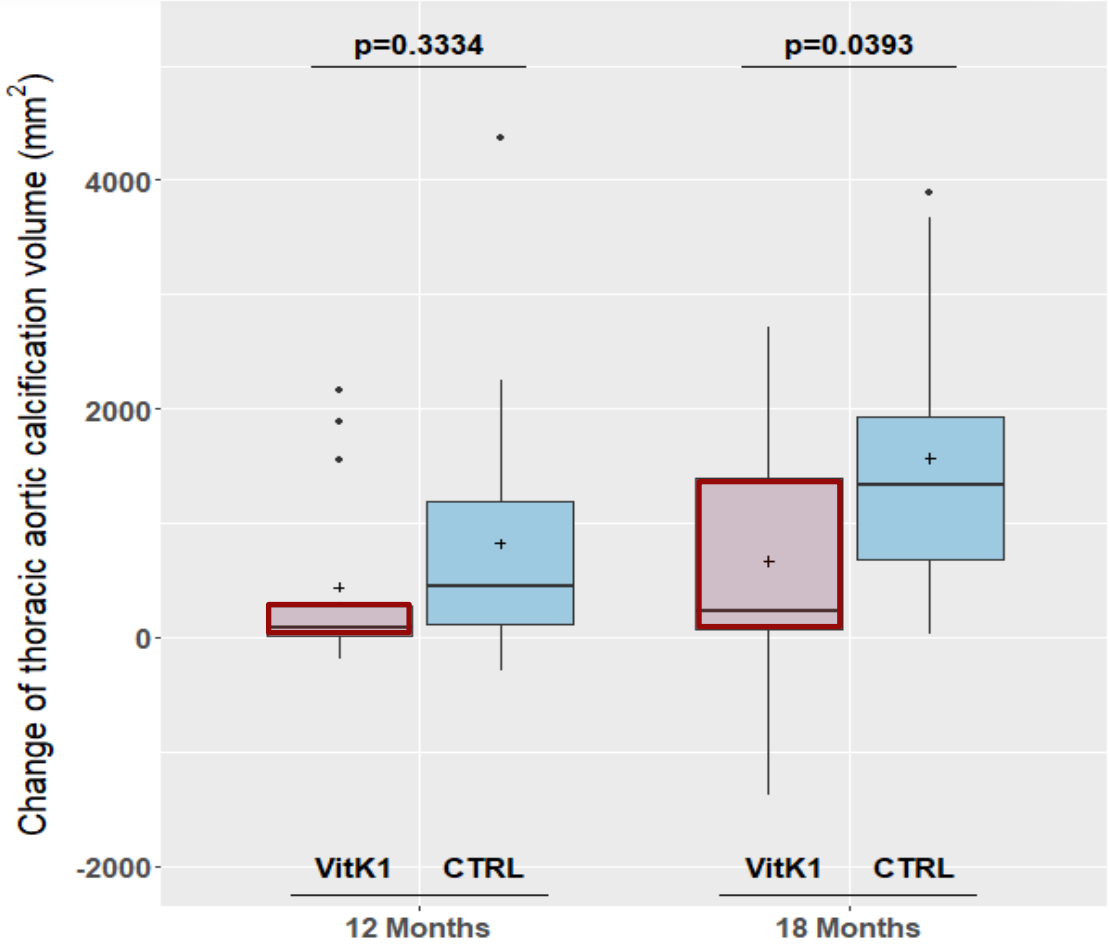
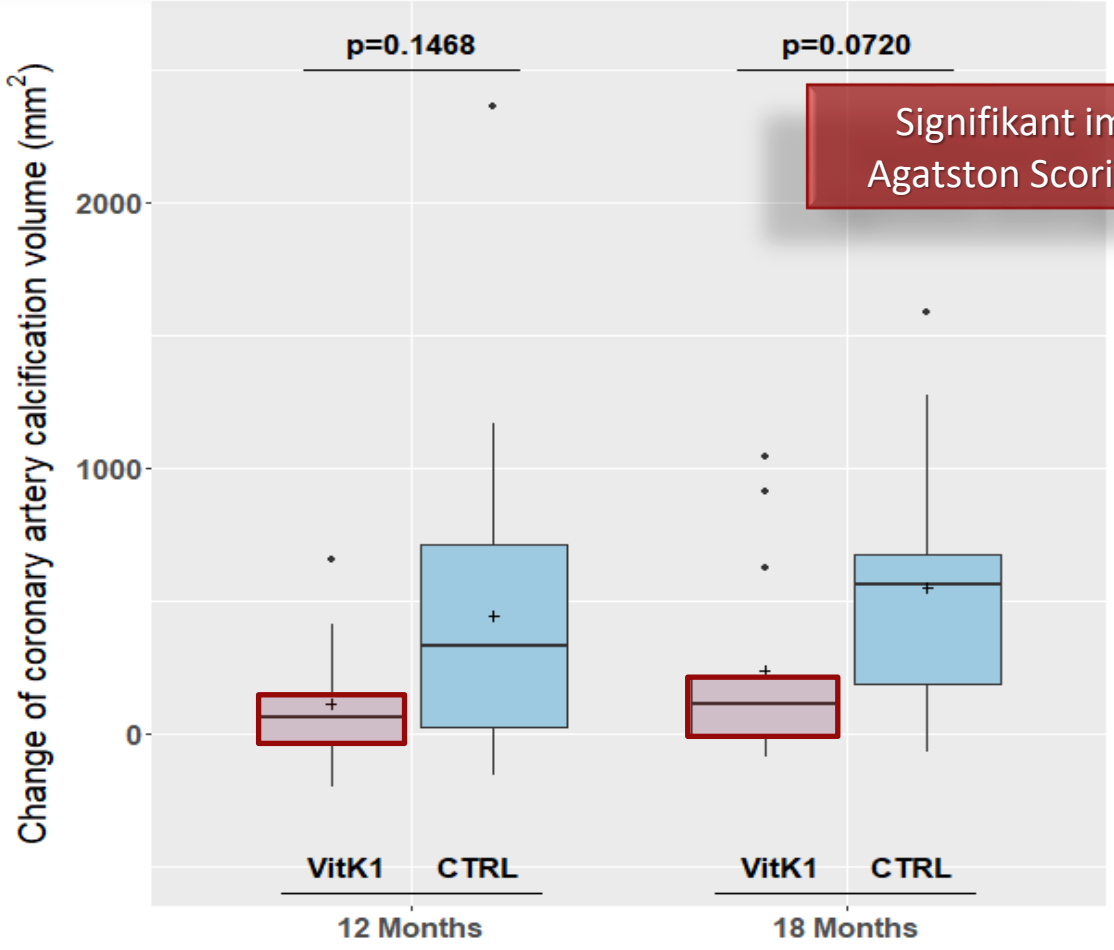
VitaVasK-Studie: Primäre Endpunkte

Thorakale Aortenverkalkung



Koronararterien-Verkalkung



Signifikant im Agatston Scoring

Vitamine bei CKD….?

Vitamine bei CKD: viel Meinung, wenig Daten….

- Wasserlösliche Vitamine zumindest nicht toxisch

- Fettlösliche Vitamine bei Mangel, Cave Toxizität

Vitamin K:

- **Mangel nimmt mit zunehmender CKD zu**
- **Aktivierung von Verkalkungshemmern** (Matrix Gla Protein)
- **Kein Gefäß-Benefit durch MK-7 (K2) in CKD 4-5D**
- **Gestörter MK-7 Transport in urämischem HDL**
- **VitaVasK: Gefäß-Benefit unter 5 mg K1 an der Dialyse**