Vitamin K2 and D in Patients With Aortic Valve Calcification: A Randomized Double-Blinded Clinical Trial (AVADEC trial)

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On behalf of:

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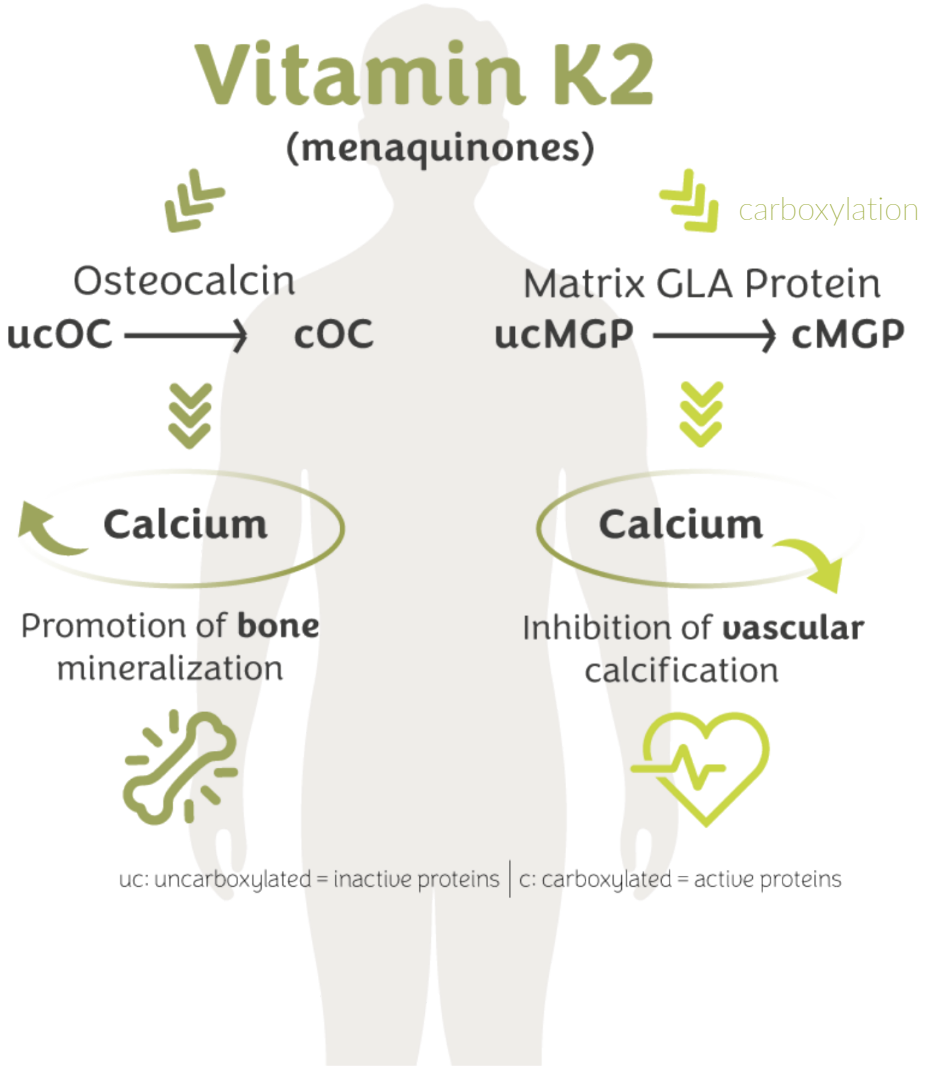
Disclosures

- None

Background



Natural vitamin K2 as MK-7 is the essential cofactor for carboxylation of calcium-regulating proteins – called Matrix-GLA-proteins (MGP) making them able to form calcium-binding groups essential for their biological activity.

By controlling these proteins in vascular tissue, vitamin K2 keeps calcium out of the arteries and drive it to bones.

Relative deficiency due to dietary insufficient intake is common, and severe deficiency is seen by long-term warfarin use and explains its association woth osteoporesis, fractures and vascular calcification

A recent open-label RCT including 99 patients with mild aortic stenosis suggested that vitamin K supplementation may reduce the progression rate of aortic valve calcification (AVC) – but clearly lacked power and perhaps an higher dose K2 vitamin. Circulation. 2017;135:2081-2083.

Hypotheses and design

- A robust investigator-initiated multicenter, randomized, double-blinded, placebo-controlled trial conducted at 4 Danish hospitals
- A dietary supplement of **high dose (720 µg K2) vitamin K2** + 25 µg vitamin D will reduce AVC compared to placebo, if given in 24 months.

- The trial was designed and overseen by a steering committee.
- The trial protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20170059) and the Data Protection Agency (17/19010), and was performed in accordance with the principles of the Declaration of Helsinki. Written and oral informed consent was obtained from each participant.
- The study protocol is available (URL:https://www.clinicaltrials.gov; Unique identifier: NCT03243890).

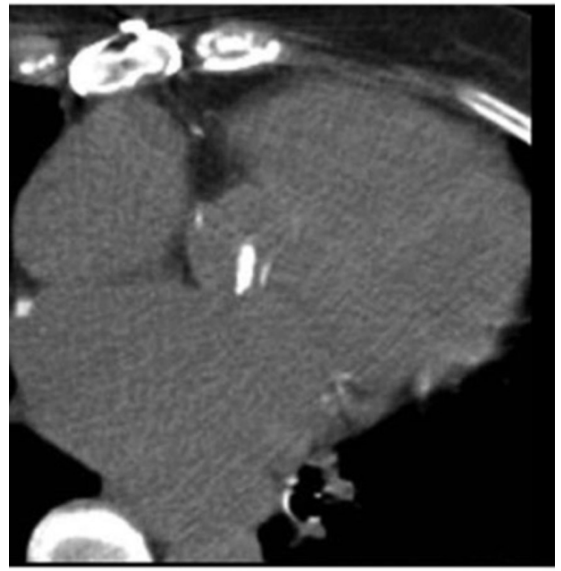
Patients

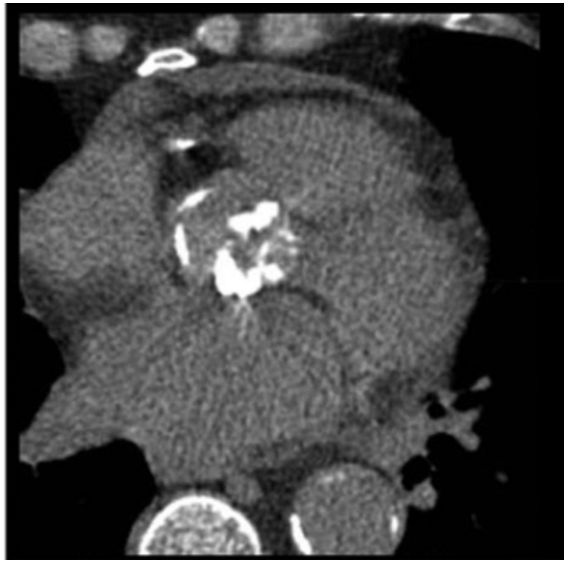
Patients were identified from the DANCAVAS trial, an ongoing trial in which more than 10,000 Danish men from the community aged 65 to 74 years were screened for subclinical atherosclerosis by noncontrast computer tomography (CT) scan.

Eligible patients were men between the ages of 65 and 74 years, with AVC score >=300 arbitrary units (AU; >90th percentile).

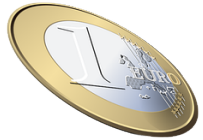
The study was designed to obtain 80% power at 5% significance level to detect a 20% difference in progression of AVC score between the treatment groups after 2 year

At least **354 patients were required** for the study to be conclusive at this power level, and we planned to include 400 patients.





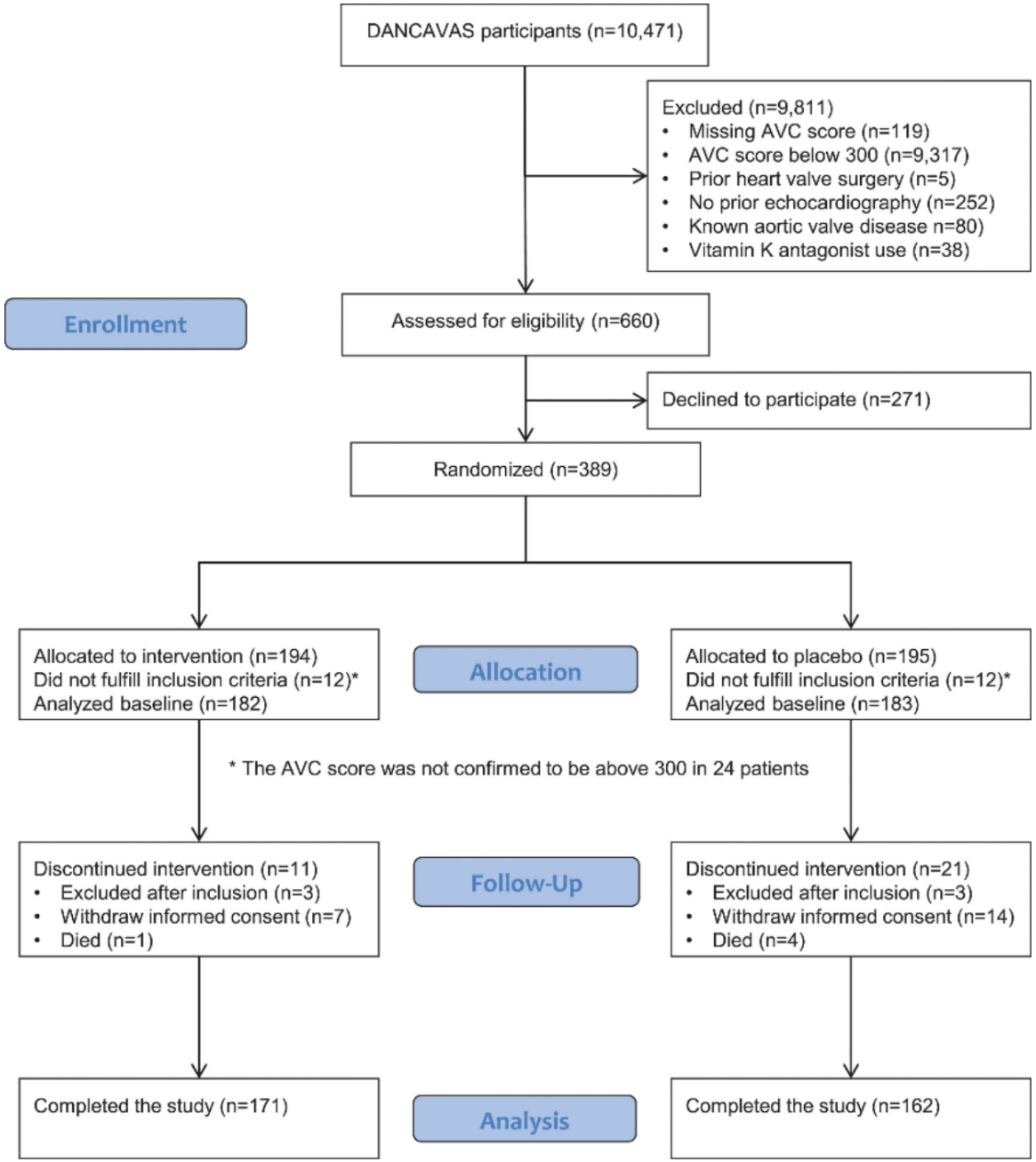
Randomisation and masking



- Computerbased by the pharmacy at Odense University Hospital.
- 1:1 on the basis of a computer-generated assignment scheme
- The randomization was stratified according to center and according to AVC score (300-599 AU or >=600 AU).
- The allocation was concealed in opaque envelopes.
- The tablets had a random number according to the sequential order of the randomization center.
- The placebo tablet had identical appearance to the intervention tablet matched for taste, color, and size.
- The randomization list was available to the data and safety monitoring board, but patients, nurses, physicians, and other data collectors were kept blinded to the allocation until the last patient completed the study and all analyses were finalized.

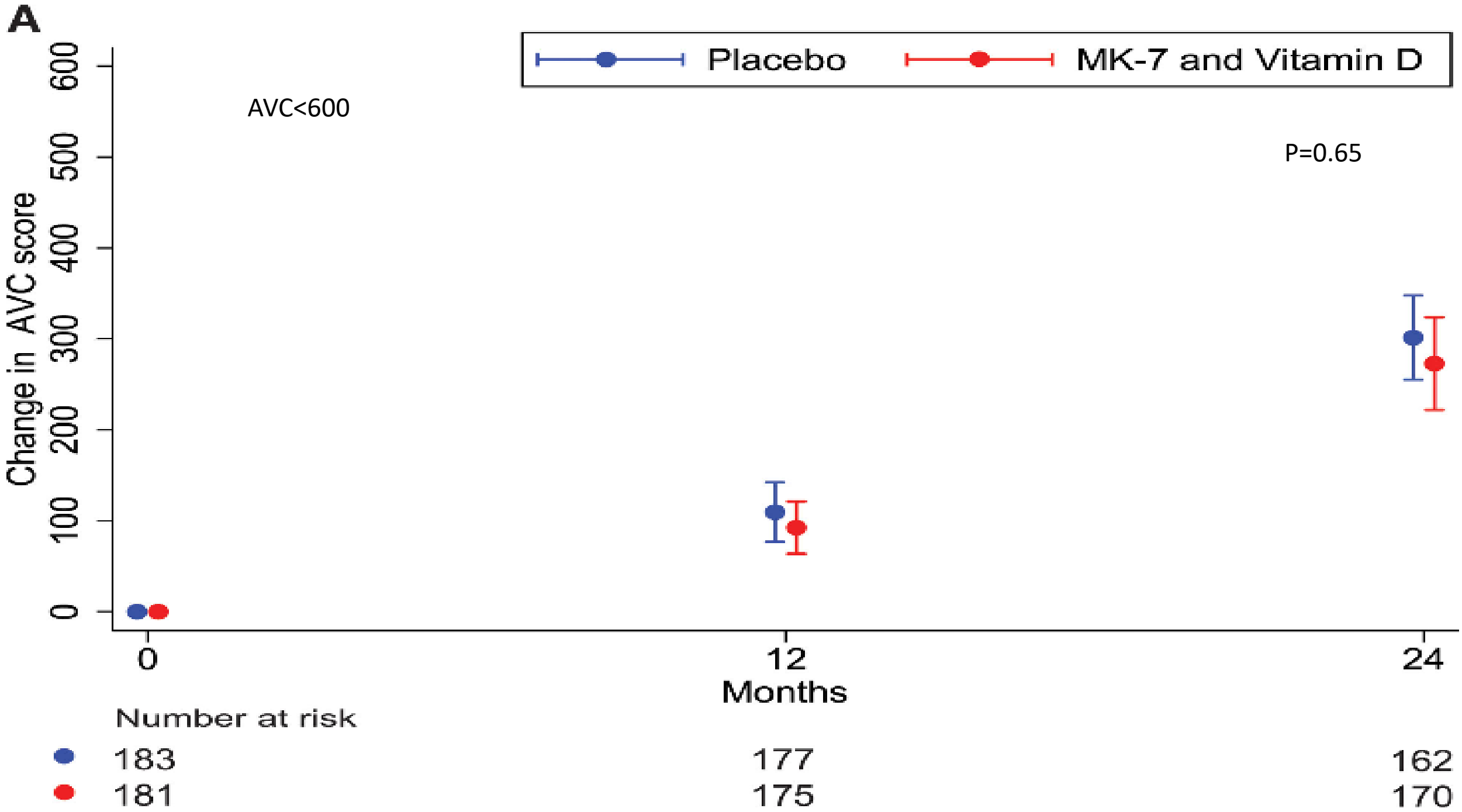
Outcomes

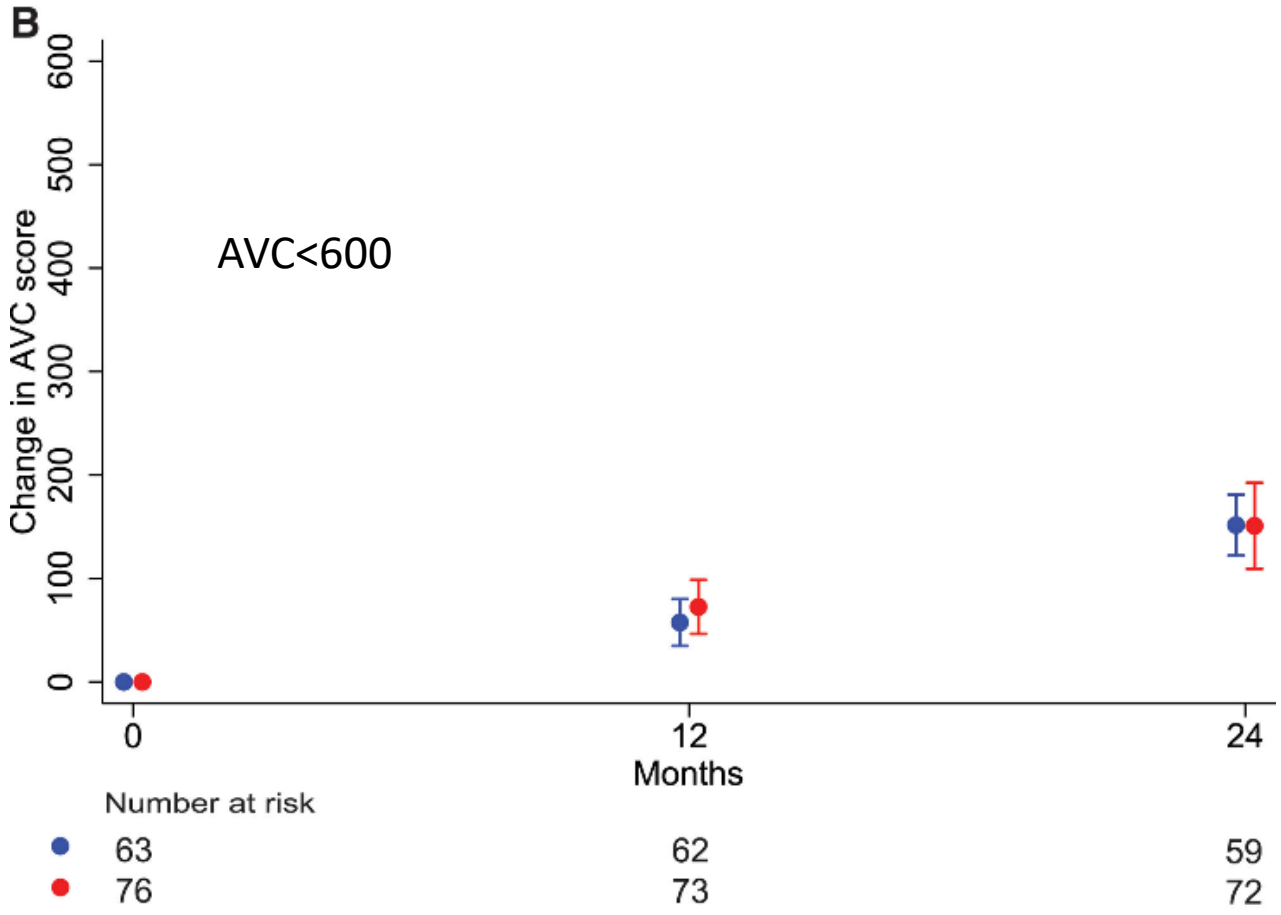
- The primary outcome
  - change in AVC score (including the two subgroups of AVC > 600 <)
- Secondary outcomes (selected)
  - change in aortic valve area and peak aortic jet velocity
  - heart valve surgery,
  - change in aortic and coronary artery calcification
  - Aortic diameter
  - change in dp-ucMGP
- Safety outcomes included
  - all-cause death and cardiovascular events.

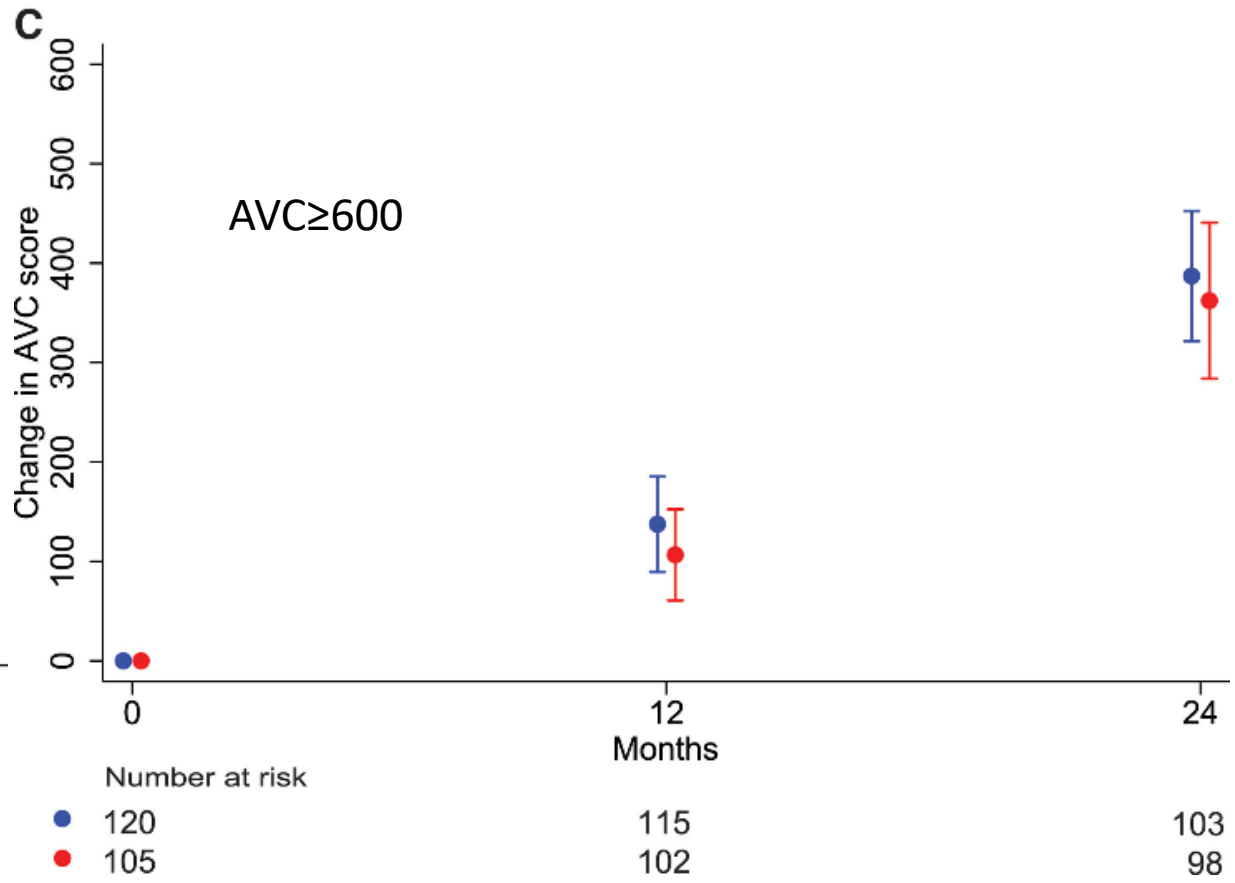


Characteristic	MK-7 + vitamin D group (N=182)	Placebo group (N=183)	*P* value
Age, y	70.8 (5.8)	71.3 (2.2)	0.32
Baseline AVC, AU	675 (486–988)	726 (509–1039)	0.25
Echocardiography			
Bicuspid aortic valve, n (%)	4 (2%)	4 (2%)	0.99
V_{max}, cm/s	186 (153–224)	187 (154–229)	0.79
Aortic valve area, cm^2	1.9 (1.5–2.2)	1.8 (1.5–2.2)	0.42
Left ventricular ejection fraction, %	59 (57–60)	59 (56–60)	0.68
Estimated GFR, ml/min/1.73 m^2	81 (67–89)	79 (68–88)	0.56
dp-ucMGP, pmol/L	728 (633–857)	730 (641–878)	0.83
Body mass index, kg/m^2	28.0 (26.0–32.0)	28.0 (26.0–31.0)	0.99
Systolic blood pressure, mm Hg	144 (133–155)	146 (132–158)	0.17
Smoking, n (%)			
Active smokers	21 (12%)	21 (11%)	0.95
Former smokers	107 (59%)	106 (58%)	
Nonsmokers	52 (29%)	56 (31%)	
Coexisting condition, n (%)			
Hypertension	126 (69%)	116 (63%)	0.27
Diabetes	36 (20%)	28 (15%)	0.27
Ischemic heart disease	35 (19%)	43 (23%)	0.37
Atrial fibrillation	20 (11%)	22 (12%)	0.87
Renal failure (estimated GFR<60)	21 (12%)	21 (12%)	0.99
Medications, n (%)			
ACE inhibitor or ARB	99 (54%)	101 (55%)	0.91
β-Blocker	53 (29%)	54 (30%)	0.99
Mineralocorticoid receptor antagonist	6 (3%)	12 (7%)	0.23
Antiplatelet therapy	126 (69%)	124 (68%)	0.82
DOAC	20 (11%)	20 (11%)	0.99
Statin therapy	135 (74%)	142 (78%)	0.47

Numbers are mean (SD), median (interquartile range), or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; AU, arbitrary unit; AVC, aortic valve calcification; DOAC, direct-acting oral anticoagulant; dp-ucMGP, dephosphorylated-undercarboxylated matrix Gla-protein; GFR, glomerular filtration rate; MK-7, menaquinone-7; and V_{max}, peak aortic jet velocity.

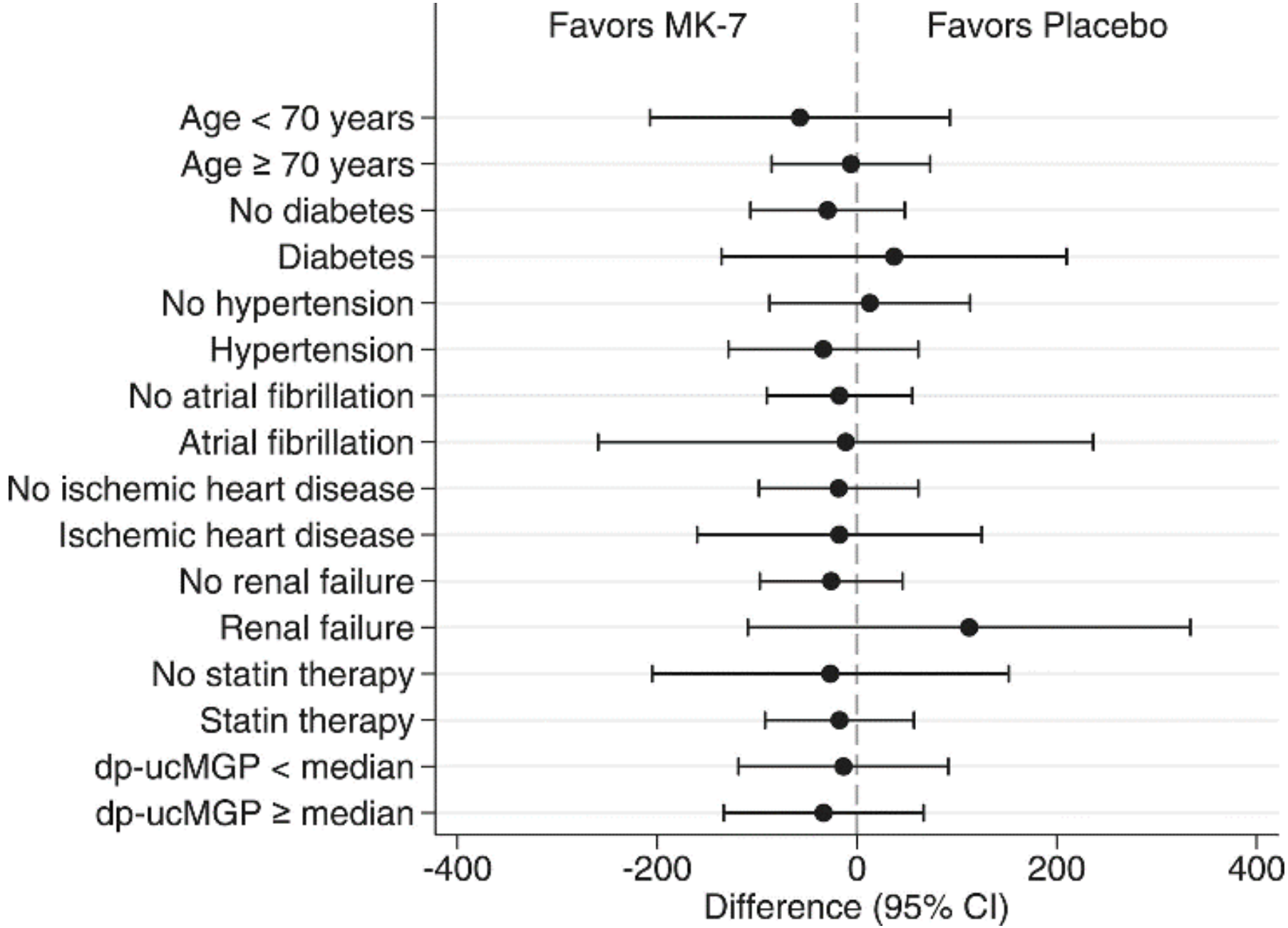

A
Placebo
MK-7 and Vitamin D
AVC<600
P=0.65
Change in AVC score
0
100
200
300
400
500
600
0
12
24
Months
Number at risk
183
177
162
181
175
170





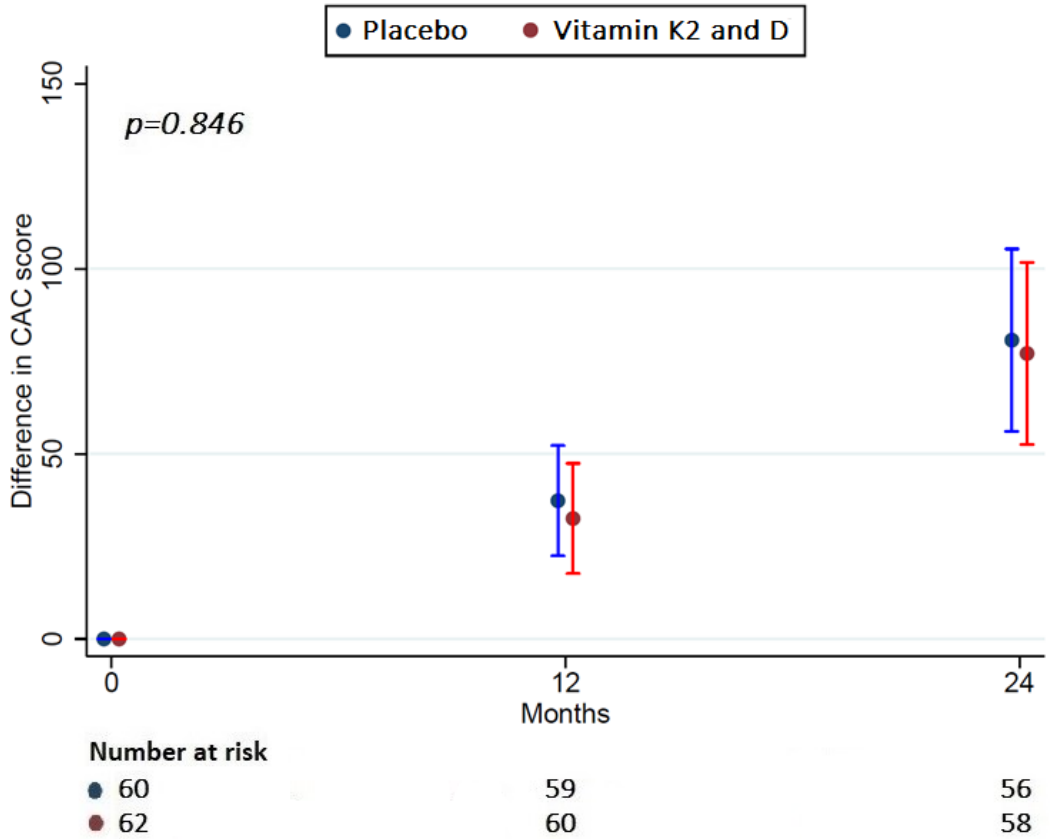
- Potential trend to a difference in the highest calcification strata?

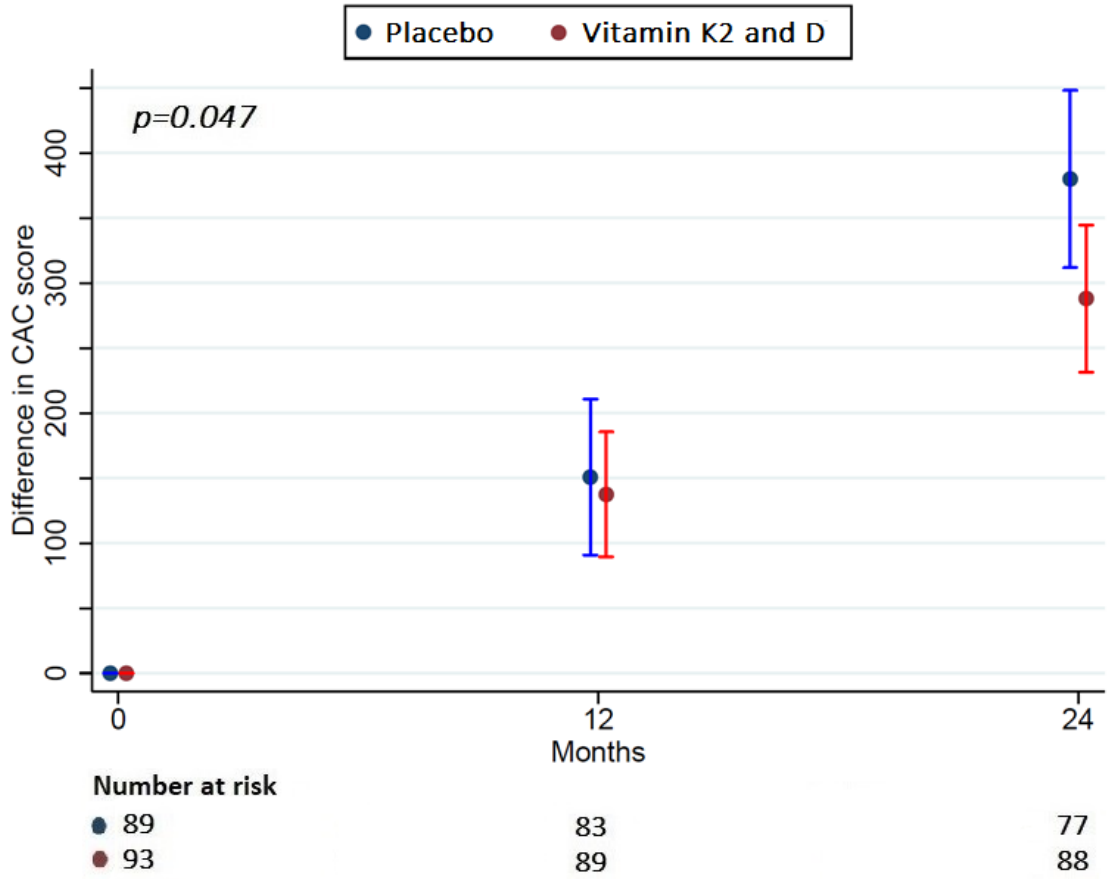
Stratified analyses of the primary outcome



Secondary analyses

- No differences apart from higher dp-ucMGP in the treatment arm.
- However regarding stratified analyses showed significantly less increase of coronary calcification in the highest strata of coronary calcification





Conclusion

- The combination of MK-7 plus vitamin D resulted in no difference in progression in AVC measured by noncontrast CT during a period of 2 years.
- Apparently neither in any secondary outcome, except improving the level of activated MCP showing the dose did what it was surposed to do
- Was it too short a treatment duration? Was the calcification too severe, or doesn´t it just not work
- Nevertheless, a subgroup analysis in a secondary outcome indicates, but it might be a target group for people with clinical relevant coronary calcification

As danes say: ”We got a long nose, we had expected more”