The effects of Vitamin K2 supplementation on the progression of Coronary Artery Calcification

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON46941

Source
ToetsingOnline

Brief title
VitaK-CAC

Condition

- Coronary artery disorders
- Vascular hypertensive disorders

Synonym
coronary atherosclerosis, coronary calcification

Research involving
Human

Sponsors and support

Primary sponsor: Interne Geneeskunde
Source(s) of monetary or material Support: Ministerie van OC&W,Nederlandse

Hartstichting en NattoPharma levert de placebo en Vitamine K2 capsules;

Intervention

Keyword: calcification, coronary arteries, trials, vitamins

Outcome measures

Primary outcome

Progression of Coronary Artery Calcification (CAC) expressed in Agatston units

and Mass-score; measured by 128-slice Multidetector CT after 12 and 24 months.

Secondary outcome

- Evaluation of calcified coronary atherosclerotic lesions after 24 months of

follow-up measured by Coronary CT-angiography.

- Change in parameters of arterial stiffness: Pulse-Wave Velocity, central

Aortic Blood-pressure and systolic blood-pressure.

- Change in the carotid Intima Media Thickness after 12 and 24 months of

follow-up.

- Biochemical changes in blood-markers of calcification such as Matrix Gla

Protein and Osteocalcin

Study description

Background summary

Coronary Artery Calcification (CAC) is a strong predictor of cardiovascular events. Not only CAC in itself, but also its annual progression is independently associated with cardiovascular events and mortality. There is increasing evidence that arterial calcification in atherosclerotic disease is not merely a passive epiphenomenon of atherosclerosis, but actually plays an active role in further atherogenesis and plaque-stability. The development of arterial calcification results from imbalance between calcification-promoting and inhibiting factors. An important inhibitor of calcification is Matrix Gla

Protein (MGP), a protein present in the vascular wall where it is synthesized by Vascular Smooth Muscle Cells (VSMC). MGP requires Vitamin K-mediated carboxylation to function properly. Deficiency of Vitamin K has been demonstrated to cause arterial calcification and in observational studies, a diet containing large amounts of Vitamin K2 was associated with lower CAC and cardiovascular risk. In animal studies, active supplementation of Vitamin K2 caused regression of existing arterial calcification. To date, no controlled trials with Vitamin K2 have been performed in humans.

Study objective

The primary objective of this study is to determine whether daily oral supplementation of Vitamin K2 will slow down or arrest CAC-progression after 12 and 24 months in comparison to placebo in patients with established CAC. Secondary, we wish to determine whether oral vitamin K2 supplementation will inhibit the development of new calcified coronary lesions, alter parameters of arterial stiffness, such as the carotid-femoral Pulse-Wave Velocity (PWV) and central Aortic blood-pressure and parameters of non-coronary atherosclerosis such as the carotid Intima Media Thickness. Finally, we will study the effects of Vitamin K2 supplementation on the blood-concentrations of Osteocalcin and MGP and assess whether changes in MGP concentrations are correlated with changes in CAC-progression

Study design

Randomized, placebo-controlled, double-blind clinical trial. Subjects will be followed-up for 24 months with measurements of the primary and secondary outcomes at 0, 12 and 24 months.

Intervention

Daily oral capsule containing 360 micrograms of menaquinone-7 (Vitamin K2) or a daily placebo-capsule that is identical to the other intervention except for the presence of menaquinone-7.

Study burden and risks

The most important risks and disadvantages of this study are:
- Radiation exposure due to CT-scanning
- Possibly adverse reaction to iodine-contrast agents
- Blood-sampling by venipuncture
- The requirement to take one capsule per day
- Time-investment for follow-up visits.

The radiation-exposure per CT-scan varies between 2 and 6 mSv. Since we aim to use dose-reduction techniques, the mean effective radiation dose is estimated

to be 1- 3 mSv per CT-scan. We estimate that we can apply these reduction-techniques in 90% of all study-participants. In total, two CT-scans will be made for the purpose of this study (after 12 and 24 months of follow-up). The first follow-up scan will only consist of calcium scoring (0.9 mSv) In a study on the lifetime attributable risk on cancer after a standard 64-slice coronary CT-scan, the risk was 0.35% and 0.22% for a 40-year-old and a 80-year-old woman respectively (Einstein et al.). The mean effective dose was 9 * 29 mSv and no dose-reduction techniques have been applied in this study. In our proposed study, the effective radiation-dose will therefore be 7 to 23 mSv lower than in the study mentioned above.
We will use iodine-contrast in our study. In rare cases (0.1%), an allergic reaction may occur after administration of iodine contrast. Since we will not include patients with renal insufficiency, we estimate the risk of contrast-induced nephropathy to be very low.

In all subjects, 25 ml of blood will be obtained three times by venipuncture. This possibly may cause a small hematoma.
Finally, we will require participants to take a capsule every day for 24 months and to visit the hospital every six months for follow-up. On the first visit and after 12 and 24 months, the visit will consist of physical examination, ultrasonography, blood-sampling and the follow-up CT-scan (at 12 and 24 months). These investigations will take approximately 2 hours. The remaining follow-up visits after 6 and 18 months will only take 15 * 20 minutes and consist of a short interview about the study and medication, measurement of the blood-pressure and providing the capsules for the next period.

In our opinion, this study can be justified with regards to risks and burdens because this study may lead to a new (additional) therapy for calcified coronary atherosclerotic disease; a condition that is associated with a high morbidity and mortality. In addition, the role of calcification in atherosclerosis and plaque-stability is not yet fully understood. This study will provide more insight into these matters.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- age 18 years or older
- Baseline Coronary Computed Tomographic Angiography (CCTA) of sufficient quality
- Baseline Agatston calciumscore 50 - 400

Exclusion criteria

- Baseline-scan of insufficient quality (due to the presence of motion artefacts, breathing artefacts or high noise-levels)
- Heart rate greater than 70 beats per minute during first scan.(despite adequeate treatment with metoprolol)
- Chronic or paroxysmal Atrial Fibrillation
- Presence or scheduled coronary revascularization procedure (balloon-dilatation or stent-placement in more than one artery or bypass-grafting).
- History of myocardial infarction or stroke within the last 6 months before CT-scan.
- Presence of Diabetes Mellitus type 1
- Known kidney disease or a Glomerular Filtration Rate (GFR) < 60 ml/min/1.73m2 calculated by the MDRD-formula (Levene; 2001).
- Malignant disease (exception: treated basal-cell or squamous cell carcinoma).
- Use of Vitamin K antagonists.
- A life-expectancy < 2 years
- Pregnancy or wish to become pregnant in the near future.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-09-2011
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO Date:	14-10-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-01-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	28-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01002157
CCMO	NL27372.068.09