Early detection of *silent* myocardial ischemia and cardiac dysfunction in asymptomatic individuals with increased coronary artery calcium scores

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Observational non invasive

Summary

ID

NL-OMON55678

Source
ToetsingOnline

Brief title
EARLY-SYNERGY

Condition

- Coronary artery disorders

Synonym
Ischemic heart disease, oxygen deprivation cardiac muscle

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: asymptomatic, cardiac stress perfusion MRI, myocardial ischemia, prevention

Outcome measures

Primary outcome

To determine the prevalence and extent of silent myocardial ischemia by stress MRI perfusion in asymptomatic and/or unrecognized high-risk individuals with proven coronary calcification on CT (CAC >300)

To determine the effect of cardiac MRI and feedback of important incidental findings on the clinical presentation of the natural course of coronary atherosclerosis (occurrence/recognition of symptoms and consequent *late* diagnostic testing).

Secondary outcome

To determine the prevalence and extent of early detected reduced LVEF and valvular dysfunction by cardiac MRI in asymptomatic and/or unrecognized high-risk individuals.

To determine the association of early detected silent myocardial ischemia, reduced LVEF and valvular dysfunction by cardiac MRI with adverse clinical outcome (presentation/perception of symptoms, medical attention seeking, major adverse cardiovascular events (MACE) and quality of life)

To study the predictors of abnormal CMR parameters in data derived from CT, questionnaires and cardiac blood markers.

To establish an imaging dataset to perform analysis on new imaging

biomarkers.

Study description

Background summary

Identification of individuals in the general population with high risk of adverse outcome due to concealed coronary heart disease (CHD), for instance by acute coronary syndrome (ACS) or sudden cardiac death (SCD), is currently based on risk scores incorporating traditional risk factors. However, risk scores have a relatively low predictive accuracy and a substantial proportion of people suffer from CHD-related adverse outcome while not being recognized as high-risk or despite being treated for classical risk factors.

The prognostic value of Coronary Artery Calcium (CAC) scoring on computed tomography (CT) as a measure of coronary atherosclerosis has been extensively studied. A CAC-score of 0 has been shown to be associated with very low risk of adverse outcome, whereas a CAC-score >300 has been associated with high risk. The clinical benefit of CAC-based management decisions with medication is currently under investigation.

The presence of myocardial ischemia has also been shown to be a strong predictor of poor clinical outcome. Treatment strategies based on ischemia detection were shown to improve clinical outcome in symptomatic patients. Current insights on the implications of ischemia detection are mainly derived from studies investigating symptomatic patients and less is known for asymptomatic individuals and smaller areas of ischemia. However, myocardial perfusion imaging by MRI is expensive. Therefore, selection of asymptomatic healthy individuals with high risk of adverse outcome is necessary for further perfusion imaging to be effective in the general asymptomatic public.

An increased CAC-score was associated with the presence of myocardial ischemia in previous studies, with a high prevalence of ischemia in individuals with increased CAC-scores. However, these studies investigated patients with a history of cardiovascular disease by SPECT. MRI was shown to have higher diagnostic accuracy compared to SPECT.A diagnostic strategy engaging two modern cardiac imaging techniques to early detect silent myocardial ischemia might be effective to accurately identify individuals at high risk for adverse outcome.

Study objective

The aim of this study is to evaluate early silent myocardial ischemia detection and other parameters of cardiac dysfunction by cardiac MRI in asymptomatic high-risk individuals. We will study the prevalence and extent of early

detected silent myocardial ischemia by MRI and its association with adverse clinical outcome during 5 years of follow-up in asymptomatic individuals with extensive coronary calcification (CAC>300), who are known to have high risk of CHD-related adverse outcome. MRI findings will only be reported in case of serious incidental findings that require guideline-based management.

From previous studies, it can be expected that *placebo* interventions might alter symptom perception. Feedback of only important incidental findings by MRI might result in the (possibly false) assumption of individuals who receive no feedback that they have no (heart) disease and influence symptom perception and medical attention seeking. The group undergoing MRI will be compared to a group who will not undergo MRI testing, in which the clinical presentation of the *natural* course of coronary atherosclerosis (occurrence/recognition of symptoms and medical attention seeking) is assessed, to evaluate the possible change in perception and medical attention seeking after performing cardiac MRI.

Study design

This is a prospective multi-center observational cohort study. Two cohorts will be created by randomization to allow the evaluation of the potential change in perception of symptoms after performing stress CMR perfusion with feedback of important incidental findings. Participants in cohort 1 will receive stress MRI perfusion imaging to investigate cardiac function. Participants in cohort 2 will not receive MRI but will be followed to assess the clinical presentation of the *natural* course of coronary atherosclerosis.1660 individuals will be randomized to one of the two cohorts. Follow-up will be performed by questionnaire and reviewing the medical file at 1, 2.5 and 5 years. Prior to performing the MRI scan, blood from participants in cohort 1 is drawn and stored to allow evaluation of cardiac blood markers as predictors of MRI findings.

Study burden and risks

Participants in the MRI group will undergo MRI and blood will be drawn during 1 visit to the hospital. Furthermore, participants will be asked to fill out 5 questionnaires in total prior to participation (1x), at baseline (1x) and during follow-up (3x) of approximately 15 minutes per questionnaire. Participants in the group not undergoing MRI will only be asked to fill out the questionnaires and do not have to visit the hospital.

MRI is a safe, commonly used diagnostic tool. A small chance of experiencing mild side effects of the vasodilating agent (adenosine) and contrast medium (gadolinium) is present. Potential side effects of the vasodilating agent include dyspnoe or recognizable chest pain or discomfort during infusion. These side effects are brief (<30 seconds after terminating infusion). Potential side

effects of gadolinium include brief headache, nausea (feeling sick) and dizziness for a brief time following the injection. Allergic reactions for both substances are rare. Serious side effects requiring medical care are very rare. The procedure of drawing blood is also minimally aggravating. A small chance of hematoma or phlebitis as a consequence of drawing blood exists.

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

Asymptomatic individuals with increased coronary artery calcification scores on CT (executed prior to participation in this study)

Exclusion criteria

Known history of cardiac disease
Contra-indications to cardiac MRI
Pregnancy
Severe comorbidity and/or life expectancy < 1 year
Unable to provide written informed consent

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-05-2019
Enrollment:	1392
Type:	Actual

Ethics review

Approved WMO Date:	23-07-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
CCMO	NL64860.042.18