Towards understanding the interplay of inflammation, immunity and circulating cells in atherosclerosis development in young adulthood: a magnetic resonance study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational invasive

Summary

ID

NL-OMON40481

Source
ToetsingOnline

Brief title
AMBITYON STUDY

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
arteriosclerosis, hardening of the arteries, induration of the arteries

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: atherosclerosis, biomarkers, inflammation, Interplay

Outcome measures

Primary outcome

The primary endpoints (a) the presence and (b) rate of change in atherosclerosis in the thoracic and abdominal aorta (shown with MR Imaging) over time in young adulthood as predicted by certain biomarkers in order to identify individuals at high risk to develop advanced atherosclerosis over classical risk factors.

The biomarkers that are involved in this study concern:

- biomarkers of circulating cells

- plasma biomarkers of systemic inflammation (including micro particles)

The findings at MR that are of relevance concern:

- aortic wall thickness and volume

- presence and number of aortic atherosclerotic plaques (luminal protrusion of > 1 mm in radial thickness);

- the extent of aortic atherosclerosis (expressed as % of affected aorta as fraction of total aorta depicted).

Secondary outcome

There are other study parameters involved in this study, such as demographic characteristics, established risk factors and potential confounders:

- factors that affect change over time in plasma markers of systemic inflammation and markers of circulating cells;
- aortic pulse wave velocity
- left ventricle function (LVF)
- age
- gender
- ethnicity
- medical history
- medication use
- lifestyle (smoking, alcohol, consumption, dietary intake, social economic status [income and education level], anthropometry [body mass index, waist circumference, blood pressure, lipid- and glucose levels])

Study description

Background summary

Atherosclerosis is a chronic inflammatory condition that causes detectable changes in the arterial wall prior to clinical symptoms in end organs. The disease affects all vascular beds, including the coronary, carotid, aorta and peripheral arteries and is present years before symptoms arise. Although classical risk factors such as age, sex, hypertension, cholesterol levels, smoking and diabetes mellitus have been conclusively linked to induction and promotion of atherosclerosis they do not fully account for clinically manifest disease later in life. This problem presents a diagnostic dilemma: we know there are (asymptomatic) subjects with (rapidly progressing) atherosclerosis, but they cannot be conclusively identified by using traditional risk factor

profiling alone. Conversely, there are also subjects with elevated levels of traditional risk factors who do not harbor atherosclerotic disease, or whose atherosclerotic disease progresses at a much slower pace. When considering the long asymptomatic latent period before symptoms develop, and that there are highly effective preventive therapies available, it is clear there is a need to identify markers that reliably predict the presence and extent of atherosclerosis in individual patients. In fact, the most recent American College of Cardiology / American Heart Association (ACC/AHA) guideline for assessment of cardiovascular risk in asymptomatic adults (published in November 2010) acknowledges this problem and states: "the problem is immense, but the preventive opportunity is also great".

A further problem is the fact that the association between traditional risk factors and clinical symptoms of atherosclerotic occlusive disease in various beds have been established primarily in people older than 40 years of age. Consequently, the ACC/AHA guideline further states that: "with regard to global risk scores...it is important to note that there are limited data from Framingham and other long-term observational studies on 10-year risk in young adults; consequently, it is difficult to estimate 10-year risk in young adults", and "to direct attention to the lifetime significance of coronary risk factors in younger adults, the writing committee considered measurement of a global risk score possibly worthwhile even in persons as young as age 20"

The relevance of the proposed study lies in clarification of the interrelationship between these markers and the presence of early atherosclerosis. The young adult is an especially relevant study subject as the potential gain in quality adjusted life years by early intervention - in the form of both lifestyle changes and pharmacological intervention - is largest (i.e. will lead to the largest gain in quality adjusted life years). Also, young adults are more amenable to life style changes compared to older subjects. The insights obtained in this study will therefore pave the way for initiation of preventive treatment in young patients at highest risk for developing clinically manifest atherosclerosis. Insight into which biomarkers best predict presence and (accelerated) progression of atherosclerosis in the young allows for the most cost-effective use of the inherently limited funds to develop strategies to prevent future cardiovascular events.

In other words, the results of this study will yield improved tools to identify individuals at highest risk of developing clinically manifest atherosclerosis. The most intensive preventive measures can then be directed at these individuals. This is likely to be a more (cost-) effective approach compared targeting preventive measures to subjects based on traditional risk factors alone.

Study objective

The overall objective of this project is to assess the interplay between

classical risk factors (including lifestyle factors), plasma markers, markers of activated circulating cells and atherosclerosis burden at MR imaging (expressed as aortic vessel wall thickness and presence of plaques) in the development of atherosclerosis in young adulthood to further elucidate key drivers of clinically manifest atherosclerosis later in life.

The 4 objectives of this project are to assess:

1. Which markers of circulating cells relate to presence and rate of change in atherosclerosis over time in young adulthood?
2. Which plasma markers of systemic inflammation (including micro-particles) relate to (a) presence and (b) rate of change in atherosclerosis over time in young adulthood?
3. Which plasma markers of systemic inflammation and markers of circulating cells can best identify individuals in young adulthood that are at high risk of developing advanced atherosclerosis, over classical cardiovascular risk factors (including lifestyle factors)?
4. What are the factors that affect change over time in plasma markers of systemic inflammation and markers of circulating cells in young adulthood?

Atherosclerosis burden is measured with MR imaging (expressed as aortic vessel wall thickness and presence of plaques)

Study design

This is a prospective, single center study. It will be a collaboration between the Departments of Experimental Cardiology, the Julius Center for Health Sciences and Primary care and the department of Radiology at the University Medical Center Utrecht, The Netherlands. The cooperating study subjects will sign an informed consent prior to any study related procedure. The study subjects will be included and examined. Subsequently, these individuals will be re-examined 3 years after the first examination. In total 520 patients will be included.

Permission to use the Utrecht Health Project as a sampling frame for our study has been permitted by the Julius Huisartsen Netwerk (JHN). Invitations will be sent to the potential participants on behalf of the project group and with consent from the JHN. If this method would not lead to enough participants, we will furthermore recruit participants via advertising. When participants are willing to participate, a visit at the UMC Utrecht will be planned. Before that visit, all participants have to give written informed consent . During the visit at the UMC Utrecht, participants will undergo a physical examination, blood sampling and MR imaging. All these tests will be performed within 2 hours. Afterwards, participants will receive a questionnaire at home that they have to complete.

Study burden and risks

The risks of this study are minimal. The infusion, the blood withdrawal, the infusion of contrast agent and the MR Imaging are procedures that are safe, innocent, without (long term) side effects and do no potential harm to the subject. Gadovist is a safe and innocent contrast agent that is routinely used daily in usual patient care. Side effects of Gadovist are very rare, if a side effect (i.e. an allergic reaction) occurs, this reaction is easy to treat, health risks are minimal. The most prevalent side effects of Gadovist contrast are headache, nausea, a warm feeling and local reactions at the injection site (i.e. swelling and pain). However, the frequency of these side effects is very low. Adjacent to that, the study population consists of an ongoing cohort of healthy young adults in whom it is very unlikely that adverse events will occur. However, this study has the potential to have enormous benefits as well for its participants as for the general population. This multidisciplinary proposal is aimed at decreasing cardiovascular disease burden. A highly innovative element of this proposal is assessment of the presence and extent of atherosclerosis in the young, including changes over time, which is an area where very little data is available. The project may open horizons by enhancing insight in development of atherosclerosis in humans at a young age (25-35 years) and its determinants. Furthermore, it may open opportunities to find specific markers for identification of those at high risk of development of atherosclerosis and opens ways for evaluation of interventions targeted to these markers. Serial magnetic resonance imaging will boost opportunities for studying the rate of aortic atherosclerosis over time in response to both non-pharmacological and pharmacological interventions. The young adult is an especially relevant study subject as the potential gain in quality adjusted life years by early intervention - in the form of both lifestyle changes and pharmacological intervention - is largest (i.e., will lead to the largest gain in quality adjusted life years). Also, young adults are more amenable to life style changes compared to older subjects. The insights obtained in this study may therefore pave the way for initiation of preventive treatment in young patients at highest risk for developing clinically manifest atherosclerosis. Insight into which biomarkers best predict presence and (accelerated) progression of atherosclerosis in the young may allow for the most cost-effective use of the inherently limited funds to develop strategies to prevent future cardiovascular events.
Hence, the results of this study potentially may yield improved tools to identify individuals at highest risk of developing clinically manifest atherosclerosis. The most intensive preventive measures can then be directed at these individuals. This is likely to be a more (cost-)effective approach compared targeting preventive measures to subjects based on traditional risk factors alone.

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

- cardiovascular healthy subjects (no medical history of cardiovascular disease and no cardiovascular preventive medication);
- between 25-35 years of age
- willing and be able to sign informed consent.

Exclusion criteria

- subjects with claustrophobia;
- subjects with a history of allergic reactions to contrast fluids;
- subjects with implanted electronic devices (i.e. pacemaker, internal cardioverter-defibrillator, cochlear implants, nerve- and bone stimulators);

- subjects with ferromagnetic clips in brain, eyes or lungs;
- subjects with a known reduced kidney function (GFR< 60 ml/min)
- subjects who are pregnant
- subjects who do not wish to be informed of abnormal results

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2014
Enrollment:	520
Type:	Actual

Ethics review

Approved WMO Date:	04-02-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25569
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL44603.041.13
OMON	NL-OMON27711
OMON	NL-OMON25569