Risk factors for progression of aortic valve stenosis

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- To document the average progression of AVS in a large population of patients with mild to moderate AVS.- To assess the prevalence of elevated Lp(a) among patients with mild to moderate AVS.- To identify lipid and genetic risk factors for AVS.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac valve disorders
Study type	Observational invasive

Summary

ID

NL-OMON47413

Source
ToetsingOnline

Brief title
Risk factors for progression of aortic valve stenosis

Condition

- Cardiac valve disorders

Synonym
Aortic valve stenosis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO

Intervention

Keyword: Aortic valve stenosis, Cholesterol, Lipoprotein (a)

Outcome measures

Primary outcome

The main study parameter is progression of AVS over time. In addition, a number of candidate risk factors for AVS progression will be recorded, including a traditional lipid spectrum, lipoprotein(a) and a blood sample for DNA isolation.

Secondary outcome

The following parameters will be recorded for each participant:

- Identifying information (name, sex, date of birth, contact details)

- Anthropometric data (height, weight)

- Comorbidities (hypertension, dyslipidemia, diabetes, coronary artery disease)

- Medical history

- Medication use

- Laboratory parameters (traditional lipid spectrum, lipoprotein(a), fasting glucose, eGFR)

- Echocardiography parameters:

Bicuspid / tricuspid aortic valve morphology

Aortic valve calcification score

Stroke volume, mL

Aortic valve maximum velocity, m/sec

Maximum transvalvular gradient, mmHg

Mean transvalvular gradient, mmHg

Aortic valve area, cm2

Indexed aortic valve area, cm^2/m^2 body surface area

LV mass index, g/m^2 body surface area

LV ejection fraction, %

Study description

Background summary

Aortic valve stenosis (AVS) is already the most common form of valvular heart disease in the Western world affecting 25% of individuals over 65 years old. As our population ages, the burden of AVS is expected to double within the next 50 years. To date, the only effective treatment for severe AVS is surgical or percutaneous aortic valve replacement, both associated with considerable perioperative morbidity and mortality, as well as substantial costs. Importantly, the implanted aortic valve prosthesis and obligatory use of anticoagulant therapy are also associated with additional long-term morbidity and mortality. Understandably, a pharmacological intervention to prevent the development and/or progression of AVS has been a holy grail in cardiovascular medicine for decades. The feasibility of such an approach depends on the identification of causal risk factors that can be used as therapeutic targets. AVS shares many risk factors with atherosclerotic cardiovascular diseases such as myocardial infarction and stroke. However, therapeutic strategies that are successful in atherosclerosis including ACE-inhibitors and LDL cholesterol lowering with statins have not been successful in AVS. Interestingly, recent new insights have implicated lipoprotein(a), and not LDL cholesterol, as a causal risk factor in the development of AVS. A large-scale meta-analysis of genome-wide scans identified rs10455872 at the LPA locus as a susceptibility single nucleotide polymorphism for aortic valvular calcium. Because this variant defines a genetic predisposition to elevated lipoprotein(a) plasma levels, these data support a causal role for lipoprotein(a) in the development and/or progression of AVS. The associations between rs10455872 as well as lipoprotein(a) levels, and clinically diagnosed AVS were confirmed in two Danish population-based studies. In addition, we have confirmed in the EPIC-Norfolk prospective population study that rs10455872, as well as elevated lipoprotein(a) levels, were associated with an increased risk of AVS. In summary, these data show that elevated lipoprotein(a) levels are associated with severe end-stage calcified AVS, and suggest that lipoprotein(a) is involved in development of aortic valve sclerosis and/or its slow progression to severe calcified end-stage AVS over the years. Interestingly, inhibition of proprotein convertase subtilisin/kexin

type 9 (PCSK9) by alirocumab or evolocumab as well as inhibition by an apo(a) antisense oligonucleotide have recently been shown to be effective in lowering lipoprotein(a) levels. This prompts the hypothesis that therapeutic lipoprotein(a) lowering may reduce AVS development and/or progression. In order to identify the potential for such an approach, this study aims to characterize a cohort of patients with mild to moderate AVS, who are at risk of progressing to severe, calcified end-stage AVS.

Study objective

- To document the average progression of AVS in a large population of patients with mild to moderate AVS.
- To assess the prevalence of elevated Lp(a) among patients with mild to moderate AVS.
- To identify lipid and genetic risk factors for AVS.

Study design

This study is designed as a single center cross-sectional pilot study. We will identify patients with mild to moderate AVS by screening the echocardiography database of the Department of Cardiology, AMC. The study will require one visit to the Academic Medical Center (AMC) hospital for questionnaire and blood sampling. Prior to the visit, in- and exclusion criteria will be confirmed using a questionnaire. The total duration of the visit will be approximately one hour.

Study burden and risks

Considering that this is a study that requires only one blood drawing, we do not expect any associated risk for participating patients other than the risk of a small hematoma at the puncture site.

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

- Men and women aged between 18 and 80 years of age.
- Able to provide written informed consent.
- Mild to moderate aortic valve stenosis, defined as an aortic valve maximum velocity 2.0-4.0 m/sec.
- Both bicuspid and tricuspid aortic valve morphology.

Exclusion criteria

- Severe aortic valve stenosis (AVA <1.0 cm2 or <0.6 cm2/m2 body surface area).
- History of radiotherapy of the thorax.
- History of rheumatic fever.
- Renal insufficiency, defined as eGFR < 30 ml/min.
- Hyperparathyroidism.
- Paget*s disease of the bone.

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):	14-12-2017
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO

Date:	31-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL58541.018.16