IcoSApent ethyL to slow down aortic VAlve stenosis proGrEssion

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This study has been transitioned to CTIS with ID 2024-517342-33-01 check the CTIS register for the current data. The primary objective is:• to study the effect of icosapent ethyl on progression of aortic valve calcification.The secondary objectives...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac valve disorders
Study type	Interventional

Summary

ID

NL-OMON51414

Source
ToetsingOnline

Brief title
SALVAGE

Condition

- Cardiac valve disorders

Synonym
aortic valve calcification, aortic valve narrowing

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Amarin Switzerland GmbH,farmaceutisch bedrijf

Intervention

Keyword: Aortic valve stenosis, Icosapent ethyl

Outcome measures

Primary outcome

The primary outcome is the change in aortic valve calcium (AVC) at 24 months, calculated as follows: (final visit AVC - baseline visit AVC) / (days from baseline visit to final visit / 730).

Secondary outcome

The secondary outcomes are:

• Change in peak aortic jet velocity at 24 months, calculated as follows: (final visit peak aortic jet velocity - baseline peak aortic jet velocity) / (days from baseline visit to final visit / 730).

• Change in calculated aortic valve area (AVA) at 24 months, calculated as follows: (final visit calculated AVA - baseline calculated AVA) / (days from baseline visit to final visit / 730).

• Total coronary plaque volume progression (mm2), calculated as follows: final total coronary plaque volume (mm2) - baseline total coronary plaque volume (mm2).

• Non-calcified coronary plaque volume progression (mm2), calculated as follows: final non-calcified coronary plaque volume (mm2) - baseline non-calcified coronary plaque volume (mm2).

Study description

Background summary

Aortic valve stenosis (AVS) is the most prevalent form of valvular heart disease in developed countries. Due to changing demographics, the incidence is expected to rise considerably over the next decades. AVS is characterized by a long asymptomatic period, in which valvular fibrosis and calcification occurs, but subsequent dysfunction of the valve often remains undetected. Once stenosis becomes severe, it may lead to clinical manifestations including angina, heart failure, or syncope. For symptomatic severe AVS, the only treatment option is surgical or transcatheter valve replacement. Therefore, medical treatment to slow down the progression of AVS is a large unmet clinical need.

The pathophysiology of AVS has long been considered degenerative, but in recent years it has become clear that development and progression of AVS is an active disease process. Current understanding is that its pathophysiology consists of two stages; an initiation phase of aortic valve sclerosis, akin to atherosclerosis, where traditional cardiovascular risk factors such as LDL-cholesterol (LDL-c), obesity and diabetes mellitus play a role. Once a certain degree of valve sclerosis, stiffening and microcalcification has developed, a second propagation stage sets in where progressive valve dysfunction and shear stress lead to accelerated macrocalcification and further stenosis. Nevertheless, statins, the quintessential class of anti-atherosclerotic medication were ineffective in slowing down disease progression among patients with moderate AVS. It is hypothesized that this was caused by the fact that the typical patient population to be targeted in AVS trials, i.e. those with mild to moderate AVS detected as an incidental finding during echocardiography that is performed for other reasons, is already in the second stage of progressive calcification where lipid-lowering therapies are no longer able to modify disease progression. In order to be effective in this disease stage, treatment strategies should target the progressive procalcification pathways ensuing in the aortic valve. Until now, no such treatment exists.

Genetic association studies have identified the rs174547 variant at the FADS1/2 locus as a potentially causal risk factor for AVS. FADS1 and FADS2 encode enzymes that regulate desaturation steps in both *-3 and *-6 fatty acid metabolism. In the *-6 pathway, these steps lead to the formation of arachidonic acid (AA), a precursor of a range of proinflammatory mediators such as tromboxanes, prostaglandins, and leukotrienes. In the *-3 pathway, FADS1 and 2 facilitate the formation of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which can initiate a number of anti-inflammatory pathways, including the formation of resolvins. FADS1 variants associate with inflammation, type 2 diabetes mellitus, and coronary artery disease, and it is hypothesized that this is mediated by affecting inflammatory pathways. For the FADS1/2 variant rs174547, the protective C allele was associated with higher FADS2 transcripts contributing to, overall, higher DHA content in human aortic

valves.11 However, within the same valve, DHA was decreased in calcified versus noncalcified tissue. These data suggest that DHA-derived anti-inflammatory mediators such as resolvins protect against calcification in aortic valves. This concept is further supported by the observation that EPA, a precursor of DHA in the *-3 pathway, attenuated arterial calcification in two rat models. Also, DHA-derived resolvin E1 inhibited Chem23-mediated calcification of vascular smooth muscle cells in vitro.14 Furthermore, within the same aortic valve, calcified parts had a lower content of *-3 fatty acids such as EPA and DHA compared to noncalcified parts, and this corresponded with dysregulation of the *-3 pathway-derived anti-inflammatory mediator resolvin E1. Taken together, these data imply that the *-3 fatty acid pathway products EPA and DHA, via anti-inflammatory mediators such as resolving E1, play a pivotal role in protecting the aortic valve from calcification. This potential of EPA and DHA to inhibit calcification pathways is unique compared to other anti-atherosclerotic therapies such as statins, which have been shown to enhance calcification, at least in coronary atherosclerosis.

Icosapent ethyl is a highly purified (>96%) form of EPA. In the REDUCE-IT trial, high dose icosapent ethyl resulted in a 25% reduction in ischemic cardiovascular events.18 Interestingly, Interestingly, this benefit is considered to be only partly attributable to the moderate triglyceride-lowering effect of EPA, with a substantial part of the cardiovascular benefit potentially related to the anti-inflammatory effects of EPA. The subsequent EVAPORATE trial investigated the effect of icosapent ethyl on coronary plaque volume and composition, as captured by coronary computed tomography angiography (CCTA) in 80 patients with atherosclerosis and elevated triglyceride levels. Interestingly, icosapent ethyl resulted in remarkable reductions in plaque volume, predominantly in high-risk non-calcified, low-density plaque volume. It remains unknown whether icosapent ethyl also reduces plaque volume and improves plaque composition in patients without hypertriglyceridemia.

We hypothesize that EPA administration results in upregulation of anti-inflammatory mediators in the aortic valve, leading to inhibition of pro-calcific pathways. We designed a proof-of-concept randomized, double-blind, placebo-controlled trial to test the efficacy of icosapent ethyl in slowing down the progression of aortic valve calcification and stenosis among patients with mild to moderate AVS. As secondary and exploratory outcomes, we will test the effect of icosapent ethyl on coronary plaque volumes and plaque composition.

Study objective

This study has been transitioned to CTIS with ID 2024-517342-33-01 check the CTIS register for the current data.

The primary objective is:
• to study the effect of icosapent ethyl on progression of aortic valve

calcification.

The secondary objectives are:
• to study the effect of icosapent ethyl on progression of aortic valve stenosis.
• to study the effect of icosapent ethyl on coronary plaque volumes and plaque composition.

Study design

This study is designed as a randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of icosapent ethyl in slowing down the progression of aortic valve calcification (AVC) and stenosis among people with mild to moderate AVS. Potentially eligible participants will be recruited at the Amsterdam UMC Department of Cardiology or at Cardiologie Centra Nederland, a network of independent outpatient clinics cooperating with Amsterdam UMC. Potentially eligible participants will be invited to visit CURIUS, the clinical trial unit of the Heartcenter Amsterdam UMC for a screening visit (screening inclusion and exclusion criteria, signing informed consent). Eligible participants who have signed informed consent will be invited for a first visit which will comprise baseline echocardiography and cardiac CT, as well as blood drawing. Subsequently, study participants will be randomized to treatment with either icosapent ethyl or matching placebo (mineral oil capsules, comparable to REDUCE-IT trial) for the duration of 24 months. At 1 month, a follow-up check will be performed by telephone to screen for medication safety issues and compliance. At 1 year, a follow-up visit will be comprise echocardiography and drawing of blood. At 2 years, a closing visit will comprise echocardiography, cardiac CT, and drawing of blood.

Intervention

Patients will be randomized to treatment with either icosapent ethyl or matching placebo (in a 1:1 ratio).

Study burden and risks

The study protocol comprises 2 cardiac CT scans, with associated radiation exposure, as well as injection of iodine contrast, which carries a very small risk of an allergic reaction. In addition, the protocol comprises 3 visits for blood sampling and echocardiography, which are considered to carry negligible risk.
Participants will be randomized to either icosapent ethyl or matching placebo. In the clinical trials performed thus far, icosapent ethyl was not associated with an increased risk of side-effects compared to placebo, although it must be stated that placebo consisted of mineral oil (an FDA requirement, in order to mimic the color and consistency of icosapent ethyl). In absolute

terms, there was a high rate of treatment-emergent gastrointestinal side-effects (icosapent 33,0% vs placebo 35,1%), which included diarrhea (9,0% vs 11,1%), constipation (5,4% vs 3,6%), and nausea (4,6% vs 4,8%). Adverse events that occurred more frequently in participants taking icosapent ethyl versus placebo were atrial fibrillation (5,3% vs 3,9%) and peripheral edema (6,5% vs 5,0%). Serious adverse bleeding events occurred in 2.7% of participants in the icosapent ethyl group vs 2.1% in the placebo group (P=0.06). The rates of serious adverse events leading to discontinuation of the trial drug or placebo did not differ significantly between the trial groups. Importantly, in the REDUCE-IT trial icosapent ethyl was shown to reduce the risk of cardiovascular events, including cardiovascular death, myocardial infarction, and stroke, by 25%. Also, if the study hypothesis turns out to correct, participants may benefit from delaying the progression of AVS, thereby postponing the need for open heart surgery. Finally, the yield for participants lies in the contribution to the development of a potentially effective treatment option for AVS.

Contacts

Public
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age > 50 years
2. Mild to moderate AVS, defined as:
(a) aortic valve maximum velocity by continuous wave doppler > 2,0 m/sec, and
(b) aortic valve area >1,0 cm2 as calculated by continuity equation, and
(c) morphologic evidence of aortic valve thickening, sclerosis or calcification.

Exclusion criteria

1. Bicuspid aortic valve
2. History of chest radiotherapy
3. History of rheumatic fever
4. Moderate to severe renal failure, defined as eGFR < 30 ml/min
5. Hyperparathyroidism
6. Paget*s disease
7. Diagnosis of (active) malignancy in last 5 years
8. Anticipated or planned aortic valve surgery in the next 6 months
9. Life expectancy <2 years
10. Chronic atrial fibrillation
11. Use of anticoagulant medication or dual antiplatelet therapy
12. Known hypersensitivity to fish and/or shellfish
13. Known hypersensitivity to soya
14. Malabsorption syndrome and/or chronic diarrhea
15. Any other treatment or clinically relevant condition that could interfere with the conduct or interpretation of the study in the opinion of the investigator
16. Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study

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):	07-06-2023
Enrollment:	110
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	vazkepa
Generic name:	icosapent ethyl
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	31-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2022
Application type:	First submission
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214

	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	12-04-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl

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
EU-CTR	CTIS2024-517342-33-01
EudraCT	EUCTR2022-002135-56-NL
CCMO	NL81780.018.22