Cardiac CT for therapeutic stratification in low gradient presumed severe aortic stenosis with preserved left ventricular ejection fraction

Published: 30-12-2019
Last updated: 21-12-2024

Primary objective: The primary objective of this non-randomized intervention trial is to investigate whether TAVR improves exercise capacity in patients with preserved LVEF and NF/LG or LF/LG severe AS reclassified based on hybrid CT/TTE-derived…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac valve disorders
Study type	Observational non invasive

Summary

ID

NL-OMON48239

Source
ToetsingOnline

Brief title
CAPTURE AS

Condition

- Cardiac valve disorders

Synonym
severe aortic valve narrowing

Research involving
Human

Sponsors and support

Primary sponsor: OLVG

Source(s) of monetary or material Support: OLVG en Medtronic

Intervention

Keyword: Aortic stenosis, CT, Ejection fraction, Gradiënt

Outcome measures

Primary outcome

The co-primary endpoints of this trial are:

Change in exercise capacity assessed by CPET (peak VO2) and 6 minute walk test (6MWT) from baseline to 6 months in patients with NF/LG and LF/LG severe AS with preserved LVEF reclassified from severe to moderate AS with fusion AVA 1.0-1.2 cm2.

Secondary outcome

The secondary endpoints of this trial in patients with NF/LG and LF/LG severe AS with preserved LVEF reclassified based on hybrid CT/TTE-derived parameters from severe to moderate AS with fusion AVA 1.0-1.2 cm2 and referred for TAVR are:

*Change in NYHA class and QoL from baseline to 6 months

*Change in echocardiographic structural and functional characteristics from baseline to 6 months, including:

*LV dimensions, volumes (2D and 3D if possible) and wall thickness

*LV systolic and diastolic function parameters

*Left atrial (LA) dimensions and function

*RV dimensions, volumes (2D and 3D if possible) and wall thickness

*RV systolic and diastolic function

*Pulmonary artery systolic pressure

*Change in plasma levels of NT-proBNP from baseline to 6 months

The secondary endpoints of this trial in patients with NF/LG and LF/LG severe AS with preserved LVEF reclassified based on hybrid CT/TTE-derived parameters from severe to moderate AS with fusion AVA >1.2 cm2 and managed conservatively are:

*Change in fusion AVA from baseline to 6 months

*Change in NYHA class and QoL from baseline to 6 months

*Change in echocardiographic structural and functional characteristics from baseline to 6 months, including:

*LV dimensions, volumes (2D and 3D if possible) and wall thickness

*LV systolic and diastolic function

*LA dimensions and function

*RV dimensions, volumes (2D and 3D if possible) and wall thickness

*RV systolic and diastolic function

*Pulmonary artery systolic pressure

*Change in plasma levels of NT-proBNP from baseline to 6 months

*Change in exercise capacity assessed by CPET from baseline to 6 months.

*Change in exercise capacity assessed by 6MWT from baseline to 6 months.

The secondary endpoints of this trial in patients with LG severe AS with

preserved LVEF in whom fusion AVA remains <1.0 cm2 and referred for TAVR are:

*Change in NYHA class and QoL from baseline to 6 months

*Change in echocardiographic structural and functional characteristics from

baseline to 6 months, including:

*LV dimensions, volumes (2D and 3D if possible) and wall thickness

*LV systolic and diastolic function

*Left atrial (LA) dimensions and function

*RV dimensions, volumes (2D and 3D if possible) and wall thickness

*RV systolic and diastolic function

*Pulmonary artery systolic pressure

*Change in plasma levels of NT-proBNP from baseline to 6 months

*Exercise capacity assessed with CPET only at 6 months

*Change in exercise capacity assessed by 6MWT from baseline to 6 months.

Study description

Background summary

Calcific aortic stenosis (AS) has become the most frequent valvular heart disease encountered in Europe and North America affecting approximately 2% to 4% of people over 65 years of age(1-3). This corresponds to approximately 3 million people with AS in Europe alone. One in five will eventually progress to

symptomatic AS representing 600.000 patients. Left untreated, severe AS is associated with a dismal prognosis with median survival averaging only 2, 3 and 5 years after symptom onset of angina, syncope and heart failure (4).

Both, the ESC and ACC/AHA cardiology societies have endorsed guidelines on valvular heart disease emphasizing the need for aortic valve replacement (AVR) once symptoms develop or in case of impaired left ventricular (LV) function (5,6). Surgical replacement of the aortic valve reduces symptoms and improves survival in patients with severe AS (7,8) and in the absence of serious comorbidities, the procedure is associated with low operative mortality (9). However, in clinical practice, at least 30% of patients with severe symptomatic AS do not undergo surgical AVR because of advanced age, LV dysfunction or the presence of multiple comorbidities (10-12).

Transcatheter aortic valve replacement (TAVR) represents a less invasive procedure than surgical AVR (13,14) with similar 1 year survival rates (15). Doppler echocardiography is the preferred technique for assessing AS severity providing transvalvular jet velocities, pressure gradients and aortic valve area (AVA) (6,16).

According to current guidelines severe AS is defined as an AVA <=1 cm2 (AVA indexed to body surface area (BSA) <=0.6 cm2/m2), a transaortic mean gradient >= 40 mmHg or a peak velocity >= 4 m/s (5,6). However, approximately 30-45% of patients with preserved LVEF present with paradoxically discordant low mean transvalvular pressure gradients (<40 mmHg), despite AVA <=1 cm2, posing significant diagnostic and therapeutic challenges (17-19). Indeed, in a recent substudy of the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial, Jander et al. reported that patients with low mean gradient (LG) (<40 mmHg) severe AS (AVA <=1 cm2) and normal LVEF (>=50%) had similar outcome compared to patients with moderate AS (20).

Paradoxical LG severe AS with preserved LVEF can occur in the presence of both normal flow (NF) with LV stroke volume index (SVI) > 35 ml/m2 and low flow (LF) with LV SVI <= 35 ml/m2 (21,22). A recent study of 1704 consecutive severe AS patients stratified by gradient and SVI demonstrated that patients with NF/LG severe AS with preserved LVEF had a favorable outcome with medical management with no survival benefit associated with AVR (23). Indeed, peroperative aortic valve (AV) inspection frequently reveals only minor AV calcifications in patients with LG severe AS and preserved LVEF, while these patients frequently suffer a protracted postoperative course, including increased risk of heart failure and mortality. The entity of paradoxical LG (<40 mmHg) severe AS (AVA <=1 cm2) with preserved LVEF (>=50%) (24) is associated with small ventricular size, marked LV hypertrophy, a history of hypertension (6), higher LV hemodynamic afterload, increased concentric remodeling (25,26), decreased ventricular cavity size (23), reduced LV longitudinal function (27-29), increased myocardial fibrosis (28) and elevated brain natriuretic peptide level (29).

Previous studies have indicated that the average rate of progression of calcific AS is a reduction in valve area of about 0.1 cm2 per year and an average increase in mean gradient of 7 mmHg (30-32). Recently, the natural progression of AVA and mean gradient was assessed after two years follow up in 116 patients with either mild, moderate or severe AS with the severe AS group subdivided in patients with low and high mean gradient (33). Annual decreases in AVA were -0.16 ± 0.15 cm2 for mild AS, -0.08 ± 0.15 cm2 for moderate AS, -0.03 ± 0.07 cm2 for low gradient severe AS and -0.03 ± 0.07 cm2 for high gradient severe AS (p=0.004 between groups). Annual increases in mean gradient were 1 ± 3 mmHg for mild AS, 1.8 ± 5 mmHg for moderate AS, 4.8 ± 9 mmHg for low gradient severe AS and 1.5 ± 7 mmHg for high gradient AS. At 2 years follow up no patients had died and 25% of patients in the LG severe AS group progressed to high gradient severe AS (33). In the moderate AS group, 24% progressed to low gradient and 13% progressed to high gradient severe AS respectively. From the perspective of progression to high gradient severe AS, low gradient AS patients appeared to be more advanced than moderate AS patients, which suggests that low gradient severe AS might represent an intermediate stage between moderate AS and high gradient severe AS (33).

Apart from representing a distinct entity, inconsistent grading of AS severity with low gradient severe AS can also result from several mechanisms, including small body size and the tendency of Doppler measurements to underestimate flow, resulting in eventual underestimation of AVA and erroneous assumption of *low flow conditions*. In addition, severity thresholds for AVA and mean pressure gradient recommended in current guidelines are inherently inconsistent and generation of a mean gradient of 40 mmHg requires a valve area closer to 0.8 cm2 than 1.0 cm2 (24). Discordantly low mean transvalvular pressure gradients and severe AS according to AVA <=1 cm2 can also result from an underestimation of AVA due to the erroneous assumption of a circular shape of the LV outflow tract (LVOT) with 2-dimensional echocardiography (16,34). Using the continuity equation, the AVA is calculated based on the ratio between the Doppler stroke volume and the post-aortic valve flow. Doppler stroke volume relies crucially on accurate estimation of the LVOT area (LVOT area) according to the formula: Doppler stroke volume = LVOTarea x LVOT flow. On 2-dimensional echocardiography, the LVOT area is derived from LVOT diameter measurements made on the parasternal long axis view and the assumption that the LVOT is circular. However, recent computed tomography (CT) studies demonstrate that the LVOT is elliptical and not circular, and as a consequence, measurements made using echocardiography underestimate the true LVOT area and hence also LV stroke volume and AVA (35,36).

Initial studies in AS patients, using 3-dimensional echocardiography or CT demonstrated that the introduction of the planimetered LVOT area in the continuity equation leads to a significantly larger AVA compared with the use of 2-dimensional echocardiogarphy derived LVOT diameter (37,38). Importantly, Kamperidis et al. recently demonstrated that incorporation of CT-derived LVOT area into the echocardiographic continuity equation (fusion AVAi) reclassified

52% of NF/LG and 12% LF/LG severe AS into moderate AS (21). Additionally, assessment of AV calcium burden using coronary calcium computed tomography recently discriminated between patients with true severe AS among patients with inconsistently graded severe AS with low mean transvalvular pressure gradients (21,39,40).

It is currently unknown whether it is safe to cancel or postpone AVR in patients who are reclassified from severe to moderate AS based on incorporation of CT-derived LVOT area into the continuity equation (fusion AVAi). It is also unknown whether a less invasive AVR using TAVR improves exercise capacity in patients with echocardiographically NF/LG and LF/LG severe AS with preserved LVEF reclassified to moderate AS by CT derived LVOT area. Recently, TAVR was shown non-inferior to surgery in patients with severe AS at intermediate surgical risk (41).

Therefore, the CAPTURE-AS trial will allocate patients with NF/ LG and LF/LG severe AS with preserved LVEF and fusion AVA-derived reclassification from severe to moderate AS with fusion AVA in the range of 1.0-1.2 cm2 to TAVR in

Study objective

Primary objective: The primary objective of this non-randomized intervention trial is to investigate whether TAVR improves exercise capacity in patients with preserved LVEF and NF/LG or LF/LG severe AS reclassified based on hybrid CT/TTE-derived parameters from severe to moderate AS with fusion AVA of 1.0-1.20 cm2.
In addition, this trial will investigate whether conservative management is safe in patients with preserved LVEF and NF/LG or LF/LG severe AS reclassified based on hybrid CT/TTE-derived parameters from severe to moderate AS with fusion AVA >1.20 cm2.
Furthermore, exercise capacity will be compared between patients referred for TAVR based on fusion AVA <1.0 cm2 (6 minute walk test (6 MWT) and cardiopulmonary exercise test (CPET) only to be performed at 6 months follow up) and 1.0-1.2 cm2 (6 MWT and CPET and patients managed conservatively with fusion AVA >1.2 cm2 (6 MWT and CPET).

Secondary objective: The secondary objectives of this trial are to assess in all 6 groups of patients:
The change from baseline to 6 months in quality of life (QoL)(Kansas City Cardiomyopathy Questionnaire), symptoms (New York Heart Association (NYHA) class and cardiac structural and functional characteristics assessed with TTE and biomarkers.

Study design

This study is a single center, non-randomized, intervention trial designed to evaluate the efficacy of TAVR in improving exercise capacity in patients with NF/LG and LF/LG severe AS with preserved LVEF reclassified based on hybrid CT/TTE-derived parameters from severe to moderate AS with fusion AVA 1.0-1.20 cm2.

Patients with NF/LG and LF/LG severe AS with preserved LVEF reclassified based on hybrid CT/TTE-derived parameters from severe to moderate AS with fusion AVA >1.2 cm2 will be managed conservatively with echocardiographic follow up at 6 months.

Patients with NF/LG and LF/LG severe AS with preserved LVEF in whom fusion AVA remains <1.0 cm2 will be referred for TAVR.

Study burden and risks

Included patients will be referred once for a cardiac CT. Even in the case a patient does not want to participate, it may be necessary to conduct a cardiac CT for diagnostic purposes.

During the study the following measurements will be conducted at baseline and at 6 months: Echocardiography, blood sampling, exercise tests (CPET and 6 MWT) and quality of life questionnaire.

In case aortic valve replacement is necessary, this will be conducted through TAVI instead of surgery. TAVI is associated with lower periprocedural risk of morbidity and mortality than surgery in this population.

Patients who are allocated to a conservative strategy based on fusion-AVA >1.2 cm2 could experience symptomatic deterioration in case of progressive AS. Conservatively managed patients will closely be followed up by outpatient visits and echocardiography and in the setting of rising mean gradient >40mmHg will be referred for TAVI.

This study includes the following safety endpoints:

*Major Adverse Cardiovascular and Cerebral Events (MACCE-) free survival at 6 months.
*Occurrence of individual MACCE components from baseline to 6 months.
*Major Adverse Events (MAE) from baseline to 6 months.
*Conduction disturbances leading to pacemaker implantation after TAVI from baseline to 6 months.
*Aortic valve related hospitalizations from baseline to 6 months.
*Cardiovascular mortality.
*Periprocedural neurological injury (TIA, CVA).

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

1. Written informed consent
2. Echocardiographic severe aortic valve stenosis with aortic valve area <1.0 cm2
3. Preserved left ventricular ejection fraction (LVEF), defined as LVEF at least 50%
4. Low mean transvalvular aortic pressure gradiënt (<40 mmHg)
5. Age at least 60 years
6. Patient has suitable anatomy to allow transcatheter aortic valve implantation
7. Patient demonstrates symptoms suspicious of heart failure or severe aortic valve stenosis

Exclusion criteria

1.Hypersensitivity or contraindication to aspirin, heparin, clopidogrel or sensitivity for contrast media which cannot be adequately pre-medicated
2.Blood dyscrasias as defined: leukopenia (WBC <1000 mm3), thrombocytopenia (platelet count <50,000 cells/mm3), history of bleeding diathesis or coagulopathy
3.Concomitant valvular disease, defined as more than moderate aortic valve regurgitation, and/or more than moderate mitral valve regurgitation and/or stenosis.
4.Ongoing sepsis, including active endocarditis
5.Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 6 weeks of inclusion
6.Active gastrointestinal (GI) bleeding within the past 3 months
7.Subject refuses blood transfustion
8.Severe dementia
9.Estimated life expectancy of less than 24 months due to associated non-cardiac comorbidities
10.Other medical, social, or psychological conditions that in the opinion of the investigator precludes the subject form appropriate consent or adherence to the protocol required follow-up exams
11.Reduced LV function (LVEF <50%)
12.Native aortic annulus size <18 mm or >30 mm per baseline diagnostic imaging
13.sinus of valsalva diameter <25 mm or sinus of valsalva height <15 mm
14.Concomitant planned coronary artery bypass graft or additional valve intervention
15.Hypertrophic obstructive cardiomyopathy
16.Echocardiographic or CT evidence of intracardiac mass, thrombus or vegetation
17.Transarterial access not able to accommodate an 18Fr sheath
18.Patient not being able to exercise or perform 6 MWT

Study design

Design

Study phase:	2
Study type:	Observational non invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-11-2020
Enrollment:	60
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	30-12-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-11-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL68906.100.19