“Transcatheter aortic valve replacement in severe low flow low gradient aortic stenosis: the multicenter LOW-TAVR registry”

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STUDY PROTOCOL

Title:
Transcatheter aortic valve replacement in severe low flow low gradient aortic stenosis: the multicenter LOW-TAVR registry

Clinical Phase:
Observational registry

Coordinating Center:
A.O.U. San Giovanni di Dio e Ruggi d'Aragona, Salerno

Principal Investigator:
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Study Duration:
20 years (01.01.2017 – 31.12.2037)

GCP Statement:
The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and is compliant with ICH Good Clinical Practice and regulatory requirements.

Funding:
The study will be conducted without financial contributions from public or private funds.

SYNOPSIS

Title of the Study:
Transcatheter aortic valve replacement in severe low flow low gradient aortic stenosis: the multicenter LOW-TAVR registry

Study Duration:
20 years (01.01.2017 – 31.12.2037)

Study Design:
Retrospective and partially prospective registry

Study Objectives:
To investigate the clinical characteristics and outcomes of patients with severe low flow low gradient aortic stenosis (SA-LFLG) undergoing TAVR.

The primary objective is to evaluate the rate of all-cause mortality or new hospitalizations due to heart failure exacerbation at the 1-year follow-up.

Secondary objectives include the evaluation of periprocedural complications, in-hospital adverse events, and both short-term and long-term adverse events (30 days, 1 year, 2 years, and 5 years).

Primary Endpoint:
Composite endpoint of all-cause mortality and new hospitalizations for heart failure exacerbation at 1 year.

Secondary Endpoints:

- Periprocedural complications: complete atrioventricular block, stroke, acute myocardial infarction, acute aortic insufficiency, cardiogenic shock, acute pulmonary edema, cardiac tamponade, aortic rupture.
- In-hospital adverse events: major and minor bleeding, major and minor vascular complications, permanent pacemaker implantation, cardiogenic shock, myocardial infarction, stroke, and death.
- Adverse events at 1-year follow-up: all-cause mortality, new hospitalizations for heart failure exacerbation, cardiovascular mortality, myocardial infarction, stroke, major and minor bleeding at 30 days, 1 year, 2 years, and 5 years.

Number of Subjects:
1500

Number of Centers:
6

ABBREVIATIONS LIST

AS: Aortic stenosis
AVA: Aortic valve area
BNP: B-type natriuretic peptide
BSA: Body surface area
CK: Creatine kinase
CK-MB: Creatine kinase – myocardial type
ECG: Electrocardiogram
EuroSCORE: European System for Cardiac Operative Risk Evaluation
WBC: White blood cells
HDL: High-density lipoproteins
HF: Heart failure
LDL: Low-density lipoproteins
LFLG-AS: Low flow low gradient aortic stenosis
LVEF: Left ventricular ejection fraction
sPAP: Systolic pulmonary arterial pressure
SVi: Stroke volume index
NYHA: New York Heart Association
TAVR: Transcatheter aortic valve replacement
VARC: Valve Academic Research Consortium
CRF: Case report form
GMP: Good manufacturing practice
ICH: International Conference on Harmonization

STUDY BACKGROUND

According to current guidelines, severe low flow low gradient aortic stenosis (LFLG-AS) is defined by echocardiographic parameters as an aortic valve area (AVA) <1 cm^2 or an indexed AVA (AVAi) ≤0.6 cm^2/m^2, a mean aortic gradient <40 mmHg, and a stroke volume index (SVi) <36 mL/m^2. Additionally, based on left ventricular ejection fraction (LVEF), patients with LFLG-AS can be classified into a classic form (LVEF <50%) or a paradoxical form (LVEF ≥50%).

Patients with LFLG-AS are estimated to account for approximately 15% of the overall population with severe aortic stenosis and are characterized by multiple comorbidities and high mortality, making this subgroup at high risk for traditional surgery.

Currently, transcatheter aortic valve replacement (TAVR) is a safe and less invasive procedure than surgery and is recommended for patients at high surgical risk. However, in patients with LFLG-AS, TAVR may have a less favorable risk-benefit ratio compared to high-gradient aortic stenosis.

The purpose of this study is to improve risk stratification and prognostic evaluation in this high-risk population following TAVR through the creation of a large registry.

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STUDY OBJECTIVES

Although criteria for the diagnosis of LFLG-AS have been established, the clinical and anatomical characteristics, procedural strategy, and possible short- and long-term complications of LFLG-AS treated with TAVR in large patient cohorts are still not well defined. There remain many questions regarding risk stratification, accurate selection of patients for TAVR, and the prognostic framework for this specific high-risk population. Observing the natural history of patients with LFLG-AS who undergo TAVR may help us better understand this pathology and identify factors associated with poor prognosis.

Therefore, we aim to study the clinical characteristics, incidence, risk factors, comorbidities, anatomical characteristics, procedural strategy, in-hospital complications after TAVR, gender differences, and prognosis (short- and long-term) of patients with LFLG-AS who undergo TAVR, as well as the peculiar characteristics of different forms of LFLG-AS.

STUDY POPULATION

We intend to enroll 1500 patients diagnosed with LFLG-AS undergoing TAVR admitted to participating centers in Italy.

Inclusion Criteria

Patients diagnosed with LFLG-AS as defined by the criteria in the current European guidelines who undergo TAVR:

Echocardiographic criteria for LFLG-AS:

Aortic valve area <1 cm^2 or aortic valve area indexed to BSA ≤0.6 cm^2/m^2

Mean aortic valve gradient <40 mmHg

Maximum aortic valve velocity <4 m/s

Stroke volume indexed to BSA <36 ml/m^2

The classical form is defined by a left ventricular ejection fraction (LVEF) <50%

The paradoxical form is defined by preserved LVEF (≥50%)

In patients with LVEF <50%, the diagnosis of LFLG-AS is confirmed by dobutamine stress echocardiography to rule out the possibility of pseudo-severe aortic stenosis.

In patients with LVEF ≥50%, the severity of aortic stenosis is confirmed through the evaluation of the calcium volume of the native aortic valve via computed tomography (CT).

Patients with LFLG-AS are candidates for TAVR through a multidisciplinary decision-making process (Heart Team) based on a comprehensive assessment of surgical risk according to the "European System for Cardiac Operative Risk Evaluation" (EuroSCORE II), as well as clinical, echocardiographic, and CT parameters.

Modified from Vahanian A et al. ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022 Feb 12;43(7):561-632. doi: 10.1093/eurheartj/ehab395.

Exclusion Criteria

Pseudo-severe LFLG-AS or failure to confirm the severity of aortic stenosis according to the current criteria of the European guidelines

LFLG-AS directed to medical therapy or subjected to surgery

Pregnant or breastfeeding women

STUDY DESIGN

This is a spontaneous observational "non-profit" retrospective and partly prospective registry that aims to enroll patients with a previous diagnosis (retrospective) and newly diagnosed (prospective) LFLG-AS treated with TAVR.

METHODS

Study Population

At least 1500 patients diagnosed with LFLG-AS treated with TAVR and admitted to participating centers.

This population includes patients with a previous diagnosis made based on the diagnostic criteria according to the current European guidelines mentioned above, or patients with a new diagnosis.

Parameters

We intend to collect parameters from the clinical history, the TAVR procedure, and the subsequent clinical course of patients with LFLG-AS treated with TAVR. This information will be included in a specific data collection sheet. We will collect data on medical history, physical examination, laboratory parameters, and results from instrumental tests such as ECG, echocardiogram, coronary angiography, cardiac MRI, and/or cardiac CT, as well as the characteristics of the TAVR procedure.

The accompanying symptoms will be classified according to the NYHA scale. The medical history will include classic cardiovascular risk factors (family history, obesity, smoking, hypertension, diabetes mellitus, lipid profile), and known patient comorbidities will be documented. Regarding laboratory parameters, routine cardiac enzymes (troponin, BNP, CK, CK-MB), blood count (hemoglobin, WBC), electrolytes (sodium, potassium), renal function indices (creatinine, EGFR, and BUN), and lipid profile (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol) will be considered. ECGs and echocardiograms at hospital admission and during the subacute period following TAVR will be analyzed. Coronary angiography parameters will be used for better characterization and extent of any concomitant coronary artery disease, according to the SYNTAX score. Pre-TAVR CT parameters will be collected to analyze anatomical factors, the TAVR procedural strategy, hemodynamic parameters, and details of acute phase management (resuscitation, aortic counterpulsation, respiratory failure), as well as in-hospital complications after TAVR, according to the Valve Academic Research Consortium (VARC) 3 criteria.

All the parameters mentioned above are already part of routine clinical practice for this type of pathology, regardless of the study's objectives. In fact, the patient will not undergo additional tests, nor will there be any modifications in clinical and/or therapeutic management compared to current clinical evidence and care standards.

The follow-up analysis will be conducted using a hospital database. We intend to subsequently contact the patients for telephone interviews to gather information on major adverse cardiac events (death, acute heart failure, myocardial infarction, stroke/transient ischemic attack, atrioventricular blocks, and permanent pacemaker or defibrillator implantation, malignant ventricular arrhythmias) according to VARC 3 criteria, current pharmacological therapy, and cardiac, neurological, psychiatric, and oncological

comorbidities. The first clinical and instrumental follow-up (ECG and echocardiography) will be conducted one month after the TAVR procedure and then every six months.

All data will be collected using a specific data collection sheet and saved in an online data collection system approved according to GMP. All stored data, both related to the baseline enrollment time and the telephone and/or clinical follow-up, will be completely anonymized, and only the PI and authorized investigators will have access and use them.

Cooperation

In this project, the reference center (A.O.U. San Giovanni di Dio e Ruggi d'Aragona) will collaborate with several cardiovascular centers throughout Italy. The local ethics committees of each center will be responsible for patient participation in this partly retrospective and partly prospective analysis.

Data Analysis

The baseline and follow-up data of enrolled patients will be analyzed using descriptive statistics. Categorical variables will be analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed for normality using the Shapiro-Wilk test. Depending on their distribution, continuous variables were expressed as mean ± standard deviation, or median and interquartile range (25th-75th IQR), as appropriate. An unpaired two-tailed t-test will be used to compare continuous variables between groups, and the chi-square test for comparison of categorical variables.

A p-value <0.05 will be considered statistically significant.

The independent association with primary and secondary endpoints will be evaluated using binary logistic regression analysis.

Statistical analyses will be performed using RStudio software (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

PRIVACY PROTECTION

All results will be used for the purposes of the study objectives. All data will be anonymized using a code for each patient.

Ver 1.0 of 12/02/2024

Study title: "Transcatheter aortic valve replacement in severe low flow, low gradient aortic stenosis: the multicenter LOW-TAVR registry."

The researchers declare no conflict of interest for this observational "non-profit" study/registry and that no insurance coverage is required.

Date, 12/02/24

Approved with signature by:

Gennaro Galasso MD, PhD