

Discordant Echocardiographic Grading in Low Gradient Aortic Stenosis (DEGAS Study) From the Italian Society of Echocardiography and Cardiovascular Imaging Research Network: Rationale and Study Design

Background: Low-gradient aortic stenosis (LG AS) is characterized by the combination of an aortic valve area (AVA) compatible with severe stenosis and a low transvalvular mean gradient with low flow state (i.e. indexed stroke volume $<35\text{mL}/\text{m}^2$) in the presence of reduced (classical low-flow AS) or preserved (paradoxical low-flow AS) ejection fraction. Also, the occurrence of a normal flow LG AS is still advocated by many authors. Within this diagnostic complexity, the diagnosis of severe AS remains challenging given the discrepant results at transthoracic echocardiography with a substantial proportion of patients misevaluated in common practice and thus not receiving the optimal therapy.

Objective: The general objective of the **Discordant Echocardiographic Grading in Low Gradient Aortic Stenosis (DEGAS Study)** study will be to assess the prevalence of true severe AS in this population and validate new parameters to improve the assessment and the clinical decision making in patients with LG AS presenting to cardiology centers in Italy who will be interested in taking part in the study.

Methods and analyses: The DEGAS Study of the Italian Society of Echocardiography and Cardiovascular Imaging (SIECVI) is a prospective, multicenter, observational diagnostic study that will enroll consecutively adult patients with LG AS over 2 years. AS severity will be confirmed by a multimodality approach including low dose dobutamine stress echocardiography and aortic valve calcium score at multidetector computed tomography (MDCT) according to investigators' experience. However, only one of them (MDCT) will be mandatory and enough for including a patient in case it performs convincing results. Clinical follow-up will be performed by scheduled cardiology visits or phone interview at 12 months. The primary clinical outcome variable will be 12-months all-cause mortality. Secondary outcome variables will be: i) 30-day mortality (for patients treated by SAVR or TAVR), ii) 12-months cardiovascular mortality, iii) 12-months new major cardiovascular events: myocardial infarction, stroke, vascular complications, and re-hospitalization for heart failure; iv) composite end-point of cardiovascular mortality and hospitalization for heart failure. Data collection will take place through a web platform (REDCap), absolutely secure based on current standards concerning the ethical requirements and data integrity. The study protocol will

be submitted for approval to each institutions' Medical Ethical Committee. Patients eligible for inclusion will be asked for their consent.

Study design and sample size

The Discordant Echocardiographic Grading in Low Gradient Aortic Stenosis (DEGAS Study) of the Italian Society of Echocardiography and Cardiovascular Imaging (SIECVI) is a prospective, multicenter, observational study that will enroll consecutively adult patients with LG AS over 2 years. The follow-up period will last 12 months for the last included patient up to 36 months for the first included patient. Fifteen to twenty centers will be appointed and accepted voluntarily. It is expected that 15-20 consecutive patients with discordant echocardiographic findings and suspected SAS will be observed per center per year. Accordingly, ~300 patients should be enrolled for over 12 months. This sample size should allow us to generate hypotheses to improve our therapeutic approach to AS.

The IBM-Sample Power™ ver. 3.0 software will be used to calculate the sample size; sampling tests will be accepted at the power level $\beta > 80\%$, $\alpha = 5\%$, and tests with two tails.

Aims

The DEGAS registry aims to derive a data set of unselected patients with LG AS, reaching the largest population ever reported on a national scale. The specific aims are:

- Identify the occurrence of true SAS according to EF/flow pattern
- To validate the use of aortic valve calcification as measured by MDCT
- To assess the interest of flow rate, global longitudinal strain and diastolic dysfunction in LG AS patients
- To assess the usefulness of NT pro-BNP and high-sensitive troponin
- To assess the interest of valvuloarterial impedance in LG AS patients

Endpoints

- Prevalence of true AS severity: AS severity will be confirmed by a multimodality approach including DSE and aortic calcium score at MDCT according to investigators' experience. However, one of them (MDCT) will be enough for including a patient in case it performs convincing results

- Clinical outcomes: the primary clinical outcome variable will be 12-months all-cause mortality as recommended by the VARC. Secondary outcome variables will be: i) 30-day mortality (for patients treated by SAVR or TAVR), ii) 12-months cardiovascular mortality, iii) 12-months new major cardiovascular events as defined by VARC: myocardial infarction, stroke, vascular complications, and re-hospitalization for heart failure; iv) composite endpoint of cardiovascular mortality and hospitalization for heart failure.

Primary study hypotheses

- Fifty percent or more of patients with LG AS have a SAS. This proportion will be higher in low EF patients
- Aortic valve calcification will be predictive of events in patients with LG AS

Secondary study hypotheses

- Global longitudinal strain and diastolic dysfunction parameters will be predictive of events in LG AS patients
- The AVA_{Proj} measured by DSE will be superior to the conventional indices of stenosis severity (rest or peak stress AVA & gradient) for the discrimination of true severe vs. pseudo severe AS (determined by calcification) and the prediction of hemodynamic/ functional/ clinical outcomes in LF-LG AS patients
- The valvuloarterial impedance will be useful to predict an adverse event in LF-LG AS patients and will correlate with NT pro-BNP
- LV pump reserve (stress-induced increase in SV) will not be able to predict operative/procedural risk and hemodynamic/functional/clinical outcomes in LF-LG AS opposed when measured by an increase in flow rate.

Inclusion criteria

1) age > 21 years; 2) suspected SAS defined by an $AVA \leq 1.0 \text{ cm}^2$ and indexed $AVA \leq 0.6 \text{ cm}^2/\text{m}^2$; 3) low transvalvular gradient defined by a mean gradient <40 mmHg.

Exclusion criteria

1) > mild aortic regurgitation, > mild mitral stenosis, > moderate mitral regurgitation; 2) end-stage renal disease; 3) pregnant or lactating women; 4) unwillingness to provide informed consent.

Patients diagnosed with transthyretin amyloidosis can be included. Patients having a coronary artery disease that is requiring revascularization at the time of baseline echocardiography can be included. But for all the patients, it is mandatory to identify possible causes of low-flow (e.g. atrial fibrillation, significant mitral regurgitation) and to optimize anti-hypertensive medical therapy and re-assess parameters of stenosis before to proceed with inclusion.

Current or previous participation in cardiovascular or non-cardiovascular trials is not excluding the patient from participation in the DEGAS study.

Baseline studies

Medical history, physical examination, and functional capacity

Medical history, concomitant risk factors and diseases, current medication, weight, height, blood pressure, symptoms, and functional status (NYHA class) will be determined. A 6-min. walk test (6MWT) will also be performed to provide a more objective assessment of the patient's functional capacity.

Biomarkers (optional)

Plasma levels of NT pro-Brain Natriuretic Peptide (NT proBNP) and high-sensitive troponin will be measured using established radioimmunoassay.

Doppler-echocardiography

The echocardiographers at each site will use the standardized acquisition of the echocardiograms. Left ventricular systolic function will be assessed by biplane Simpson's EF. Left ventricular pump function: SV will be measured in the LVOT (at the aortic annulus, using the midsystolic image that bisects the largest dimension of the aortic annulus (i.e., the plane that bisects the right coronary cusp point hinge point anteriorly and the interleaflet triangle between the left and noncoronary cusps posteriorly), mean transvalvular flow rate (Q) will be calculated by dividing SV by LV ejection time. LV diastolic function will be assessed as previously described. Aortic valve function: peak

aortic jet velocity, AVA by continuity equation, peak and mean transvalvular gradients by Bernoulli formula. Post-extrasystolic potentiation-associated augmentation in peak and mean transvalvular gradients should be evaluated in case of incidental premature ventricular contraction during resting echocardiography. The global LV hemodynamic load resulting from the valvular and arterial loads will be assessed using the valvuloarterial impedance. Global longitudinal strain (optional) will be assessed as previously described. 3D echo (optional): 3D EF and 3D SV will be recorded.

Dobutamine stress echocardiography (optional)

Classical LG AS patients will undergo a DSE to assess 1) LV pump reserve (i.e. stress-induced increase in SV and mean flow rate); 2) stenosis severity. The dobutamine infusion protocol consists of 5 minutes increments of 5 $\mu\text{g}/\text{kg}/\text{min}$ up to a maximum dosage of 20 $\mu\text{g}/\text{kg}/\text{min}$ and echo measurements are performed at each stage. The end-points for terminating DSE are: 1) heart rate >220 -age; 2) systolic blood pressure <80 or >220 mmHg; 3) significant increase in the LV outflow tract gradient; 4) ischemia detected by ECG (>5 mm of flat or downsloping ST depression); 5) complex ventricular arrhythmias or rapid new atrial arrhythmias; 6) breathlessness, angina, dizziness, or syncope, and 7) maximum dose reached (20 $\mu\text{g}/\text{kg}/\text{min}$). After each increment in dobutamine dose, a period of 5 min is allowed to ensure the stabilization of hemodynamic status before starting the measurements that include: SV, mean flow rate, AVA, gradients, systolic/diastolic blood pressures, and Z_{va} . The AVA_{proj} is determined as described.

Multidetector computed tomography

Image analysis will be performed locally using a range of different software packages. At the initiation of the study, the consensus will be achieved on the optimum method for calcium scoring, and this will be then applied at each of the centers, ensuring consistency of approach. The typical radiation dose associated with this study will be 0.8-1.0mSv, less than the yearly radiation exposure from natural sources as reported by the Princeton group. Off-line image analysis will be conducted on dedicated workstations using validated software by modified Agatston. Total valve calcium score will be calculated by summing the per-slice lesion scores for all sections containing calcium and excluding coronary and non-valvular calcifications. The calcium score will be indexed to the aortic annulus cross-sectional area measured by MDCT to assess the “calcification density”.

Therapeutic decision, management and follow-up

Decisions on drug prescriptions and indications to perform diagnostic and therapeutic procedures will be left to participating cardiologists who will know the baseline measures of traditional parameters of disease severity, according to international guidelines and good clinical practice. No specific protocols or recommendations for treatment will be made during this observational study. Therefore, there will be no attempt to interfere with the routine clinical care of the patient who, according to the disease's condition, will be expected to attend at least one visit during the follow-up. A visit close to 12 ± 3 months after the in- or outpatient entry visit will be recommended to collect information on morbidity and mortality. A phone call can replace the follow-up clinical visit in cases where the patient cannot attend the center for clinical or logistical reasons.

Statistical analyses

Data will be expressed as mean \pm SD, median/range, or as proportions. Categorical data will be analyzed using Chi-Square or Fisher's exact test. Correlations between variables will be expressed using the Pearson's or Spearman's correlation coefficients. Continuous variables will be analyzed using a t-Student or ANOVA followed by Tukey's test. The normality assumption will be verified using the Shapiro-Wilk test. Data will be investigated for log-transformed to satisfy this assumption. Multivariable linear (continuous variables) or logistic (dichotomous variables: e.g. MAS vs. SAS; presence vs. absence of LV pump reserve; global longitudinal strain) regression analyses and multivariable Cox regression analysis will be used. Variables previously reported as being associated with the studied endpoints and those with a p value <0.1 on univariate analysis will be entered into the models. We will also analyze the interactions between the following variables to their impact on outcomes: age, sex, stenosis severity (SAS vs. MAS), degree of myocardial impairment (i.e. LV pump or contractile reserve; global longitudinal strain), and type of treatment.

Ethical issues

All centers will require local ethics approval. All patients will be approached by the center investigator and will be asked for their written informed consent to participate in the DEGAS study on AS. No data will be collected before written detailed information is given to the patient and signed informed consent is obtained.

In centers where written informed consent is not mandatory for patient participation in a registry, written informed consent will not be required but this should be documented in the ethics application and approved by the ethics board, according to the local rules.

For those patients who will be admitted with the severe clinical conditions and not able to consent at the time of admission, information and written consent will be obtained from a legally authorized representative if allowed by the ethics board. Patients will have to give consent as soon as more favorable clinical conditions allow them to receive appropriately the study information. The patient or legally acceptable representative will be given a copy of the signed informed consent.

Protection of human subjects

The DEGAS registry will not require the transmission of identification data outside the participating centers. The data collected will be anonymous. Each patient will be assigned a unique identification number and no other identification variables will be entered. The identity of the patient will remain at the participating center as confidential information. Information aimed at identifying the individual patients of the study will not be collected or stored in the database. All confidential information will be password protected for electronic data or stored in secure places for paper data. For these reasons, a high level of security will be assured. To maintain these high levels of security at the same time as data reliability, each researcher will have a single personal login and password to access patient information. There will not be a collection of data outside the collection tools, which will take place through a web platform (REDCap), absolutely secure based on current standards concerning the ethical requirements and data integrity.

Pharmacovigilance

In this observational study, there are no diagnostic or therapeutic interventions other than those already recommended by contemporary guidelines.

Quality control of enrolling centers

As with any imaging modality, the quantification of valve calcification by MDCT is not a perfect method to assess AS severity. However, the use of different scanners for image acquisition and different software for image analysis is reported not to have any significant effect on thresholds levels or accuracy of valve calcification (AUC: ≥ 0.89) to identify severe AS. Nevertheless, quality control of MDCT diagnostic performance among the enrolling centers will be of critical importance to acquire meaningful information into the data bank and to reduce interobserver variability. For this purpose, a video tutorial prepared by the steering committee will be available on <https://www.siec.it/ricerca> which elucidates questions concerning the quantification of valve calcification by MDCT and the methods of measurement. The second criterion will consist in random

sampling of 5 consecutive studies from each contributing center. These 5 studies will be examined in a blinded fashion by two members of the steering committee who will verify the adequacy and congruence of the data entered in the database.

Timeline

An invitation letter will be sent to all members of the SIECVI. In case of preliminary interest, you must notify us by email (ricerca@siecvl.it) by 31 August 2020 providing the following information: institute name, name of the local PI, Email and telephone contact. After the promoting center and local ethics approval we will start recruiting patients.