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Low-flow low-gradient aortic stenosis: outcomes after aortic valve replacement

Ana Lopez Marco

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Universitat de Barcelona

DOCTORAL THESIS

**LOW - FLOW LOW - GRADIENT AORTIC STENOSIS:
OUTCOMES AFTER AORTIC VALVE REPLACEMENT**



Universitat de Barcelona
Facultat de Medicina i Ciències de la Salut
Programa de Doctorat de Medicina i Recerca Translacional

**LOW - FLOW LOW - GRADIENT AORTIC STENOSIS:
OUTCOMES AFTER AORTIC VALVE REPLACEMENT**

Doctoral Thesis presented by Miss Ana Lopez Marco,
aspiring to the degree of Doctor in Medicine

Thesis Director: Dr. Ricard Ramos Izquierdo

Barcelona, March 2019

“ I am thankful for all of those who said NO to me.

It’s because of them I’m doing it myself”.

– Albert Einstein -

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This doctoral thesis is presented as a compendium of publications.

The original articles in which this work is based on are:

1. Low-flow low-gradient aortic stenosis: surgical outcomes and mid-term results after isolated aortic valve replacement.

A. Lopez-Marco, H. Miller, A. Youhana, S. Ashraf, A. Zaidi, F. Bhatti, P. Kumar.

[Eur J Cardiothoracic Surg 2016; 49:1685-90.](#)

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2. Outcome of isolated aortic valve replacement in patients with classic and paradoxical low-flow, low-gradient aortic stenosis.

A. Lopez-Marco, H. Miller, P. Kumar, S. Ashraf, A. Zaidi, F. Bhatti, A. Ionescu, A. Youhana.

[J Thorac Cardiovasc Surg 2017;154:435-42.](#)

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1. INTRODUCTION

1. INTRODUCTION

Aortic stenosis (AS) is the most common valve disorder in the Western World and the most frequent indication for aortic valve replacement (AVR) in adults. The earliest description of calcific AS is attributed to the French physician Lazare Riviere, who in 1663 reported the necropsy findings of large caruncle-like masses obstructing the left ventricular outflow to the aorta in a patient who presented with progressive dyspnea and loss of pulses [1].

The aortic valve, already drawn by Leonardo Da Vinci in 1512 [2] (Figure 1), is one of the semilunar valves of the heart, and it is located between the end of the left ventricular outflow tract and the aorta. It usually has three leaflets, although 1-2% of the population is born with a bicuspid aortic valve, and very rarely with unicuspid or quadricuspid aortic valve.

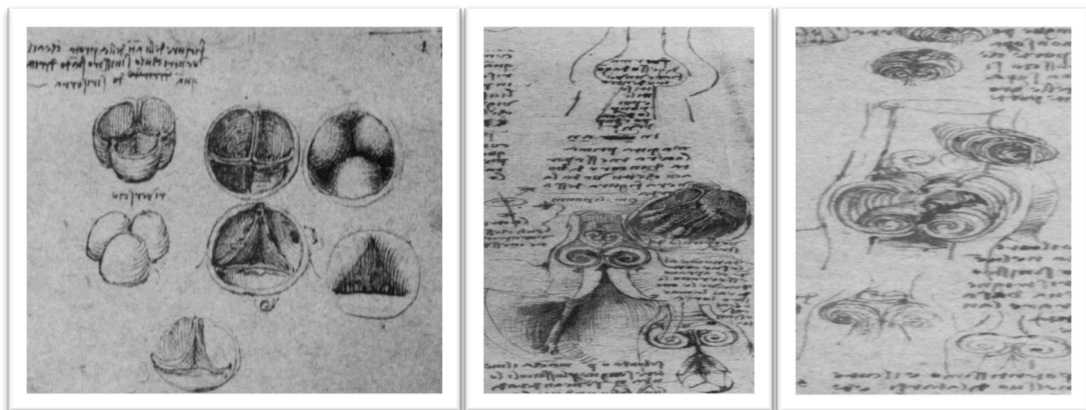


Fig 1. Details of Leonardo Da Vinci's drawings of the aortic valve, left ventricular outflow tract and sinuses of Valsalva from Leonardo's notebook (pages 19079 Verso, 19082 Recto and 19083 Verso). Original source: Royal Library, Windsor Castle. Copyright reserved by Her Majesty Queen Elizabeth II.

The aetiology of AS in the developed countries includes, by decreased frequency, calcific degenerative AS, congenital AS (including bicuspid aortic valve), rheumatic fever and other rare causes such as radiation to the chest.

Its pathophysiology consists of a reduction of the effective orifice of the aortic valve, creating a pressure gradient between the left ventricular cavity and the aorta. Initially, the heart uses compensatory mechanisms to maintain normal hemodynamics such as the muscular hypertrophy of the left ventricle (LV) by effectively maintaining the stroke volume. In later stages, the compensatory mechanisms fail and the LV dilates, the LV wall thins and the systolic function deteriorates, resulting in the LV being unable to pump blood forward effectively. Once this happens the patients starts having symptoms of dyspnoea and/or angina and general tiredness, eventually leading to severe LV failure and failure if not treated.

The classical clinical symptoms of AS are angina, syncope and breathlessness generally associated with progressive reduction in physical activity. They do occur after a latent period, as initially patients remain asymptomatic for a period of time due to the compensatory mechanism until the reduction in the valve area becomes significant. If AS remains untreated, symptoms of congestive heart failure, such as dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea and signs like peripheral oedemas will occur eventually leading to death due to intractable congestive cardiac failure [3-5].

At physical examination, aortic stenosis presents with an ejection systolic murmur, heard loudest at the second right intercostal space and radiating to the carotid arteries. There is also a low volume arterial pulse due to the reduced upstroke, classically

described as ‘pulsus parvus et tardus’.

Diagnosis of the aortic stenosis is made by a combination of clinical evaluation involving history taking and physical examination confirmed by complementary tests, with the echocardiogram being the gold-standard non-invasive test for assessment of the valve anatomy. The echocardiogram also identifies the likely aetiology and grades the severity of the stenosis according to the valve area and the gradients generated between the LV and the aorta.

The natural history of AS was already reported in the late 1960s and early 1970s by Ross and Braunwald, Frank and Rapaport [3-5]. They demonstrated that once symptoms related to the AS become manifest, the survival of the patient is shortened significantly, with a mortality rate of 50% at 2 years after developing breathlessness, 50% mortality at 3 years after the appearance of syncope and 50% mortality at 5 years when presenting with angina (Figure 2).

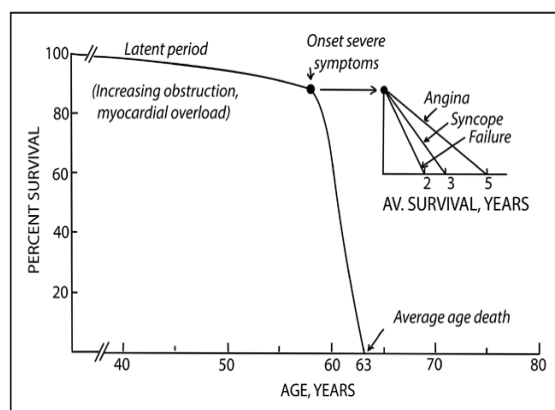


Fig 2. Average course of patients with aortic stenosis from postmortem data. © Ross J Jr, Braunwald E. *Circulation* 1968; 37-61.

The first attempt to open a stenotic aortic valve was performed by Tuffier in 1912 by invaginating the ascending aortic wall with a finger and pushing the aorta through the valve [6]. Several methods for dilating calcified aortic valves were conducted from the late 1940s, all of them abandoned due to the high mortality [7,8].

The first AVR was conducted in 1961 using the Starr-Edwards mechanical prosthesis, consisting of a silastic ball caged in a titanium frame and a sewing ring covered by Teflon [9]. In 1969, in an attempt to reduce the high profile of the cage ball prosthesis, the tilting disc prosthesis were introduced; the Bjork-Shiley was the first tilting disc prosthesis implanted and consisted of a stellite housing, a pyrolytic disc and two inlet and outlet struts. However, reports of fractures of the struts in the late 70's made them unpopular [10,11]. In 1977 the first bileaflet model valve, consisting of two semicircular leaflets made from pyrolytic carbon that rotate about struts attached to the valve housing, was implanted [12]. This valve has undergone a number of modifications until the current era of mechanical prosthesis that offer greater effective orifice areas and reduced thrombogenicity.

The first porcine bioprosthesis, the Hancock, was implanted in aortic position in 1970 [13], and the first bovine pericardial prosthesis, the Ionescu-Shiley Pericardial Xenograft was introduced in 1971 [14]. The Carpentier-Edwards pericardial valve prosthesis was first implanted in 1980 [15], and underwent several modifications that has made it the most common used pericardial valve at present.

Other options for AVR include the stentless porcine bioprosthesis, first introduced by David in 1990 (St Jude Toronto Stentless porcine valve) [16], offering an increased effective orifice area compared to the stented bioprosthesis and homografts. The first homograft aortic tissue was used in 1962 using a freeze-dried aortic valve [17, 18]

and in 1967 the first Ross procedure, consisting of replacing the aortic valve with a pulmonary autograft and using a homograft for pulmonary valve reconstruction, was performed [19].

There is currently no medical therapy available to reduce the natural progression of the AS. The operation AVR has been accepted as the standard of care treatment for symptomatic AS for the last several decades.

Trans aortic valve implantation (TAVI) was first performed in 2002 [20], and has merged as alternative to AVR, being currently offered to patients with high or prohibitive surgical risk, after thorough evaluation of candidates by the local Heart Team composed of surgeons and cardiologists.

1.1. Normal-flow high-gradient aortic stenosis, NFHG AS.

Most commonly, severe AS presents with normal flow and thus generates high gradients through the stenotic valve. The normal-flow high-gradient AS (NFHG AS) has been defined with aortic valve area (AVA) $< 1.0 \text{ cm}^2$, mean transvalvular gradient $> 40 \text{ mmHg}$ and peak flow velocity $> 4.0 \text{ m/s}$ (Figure 3).

As previously mentioned, the natural history of the disease, its prognosis and therapeutic options have been studied in depth over the last several decades. All the studies have confirmed the symptomatic and prognostic benefit of AVR in this very malignant pathology when left to medical treatment; therefore indications for AVR are well documented in all the guidelines. [21-24] (Figure 3).

The NFHG AS group has an excellent prognosis after AVR, with an in-hospital mortality of 1-2% for first-time isolated AVR [25] and a long-term survival similar to age-matched population [26].

However, it is estimated that up to 50% of patients in whom the AVA meet the criteria of severe AS, have transvalvular gradients in the range of moderate AS ($< 40 \text{ mmHg}$) due to a reduced transvalvular flow (Stroke Volume Index, $\text{SV}_i < 35 \text{ ml/m}^2$). This entity is known as low-flow low-gradient AS (LFLG AS) and is subdivided into two categories depending on the left ventricular ejection fraction (LVEF): True or Classical LFLG AS and Paradoxical LFLG AS (Figure 4).

Indications for intervention in aortic stenosis and recommendations for the choice of intervention mode

A) Symptomatic aortic stenosis	Class^a	Level^b
Intervention is indicated in symptomatic patients with severe, high-gradient aortic stenosis (mean gradient ≥ 40 mmHg or peak velocity >4.0 m/s). ⁹¹⁻⁹³	I	B
Intervention is indicated in symptomatic patients with severe low-flow, low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction and evidence of flow (contractile) reserve excluding pseudosevere aortic stenosis.	I	C
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) aortic stenosis with normal ejection fraction after careful confirmation of severe aortic stenosis ^c (see Figure 2 and Table 6).	IIa	C
Intervention should be considered in symptomatic patients with low-flow, low-gradient aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CT calcium scoring confirms severe aortic stenosis.	IIa	C
Intervention should not be performed in patients with severe comorbidities when the intervention is unlikely to improve quality of life or survival.	III	C
B) Choice of intervention in symptomatic aortic stenosis		
Aortic valve interventions should only be performed in centres with both departments of cardiology and cardiac surgery on site and with structured collaboration between the two, including a Heart Team (heart valve centres).	I	C
The choice for intervention must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each modality (aspects to be considered are listed in Table 7). In addition, the local expertise and outcomes data for the given intervention must be taken into account.	I	C
SAVR is recommended in patients at low surgical risk (STS or EuroSCORE II $<4\%$ or logistic EuroSCORE I $<10\%$ ^d and no other risk factors not included in these scores, such as frailty, porcelain aorta, sequelae of chest radiation). ⁹³	I	B
TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team. ^{91,94}	I	B
In patients who are at increased surgical risk (STS or EuroSCORE II $\geq 4\%$ or logistic EuroSCORE I $\geq 10\%$ ^d or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics (see Table 7), with TAVI being favoured in elderly patients suitable for transfemoral access. ^{91,94-102}	I	B
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients or in patients with symptomatic severe aortic stenosis who require urgent major non-cardiac surgery.	IIb	C
Balloon aortic valvotomy may be considered as a diagnostic means in patients with severe aortic stenosis or other potential causes for symptoms (i.e. lung disease) and in patients with severe myocardial dysfunction, pre-renal insufficiency or other organ dysfunction that may be reversible with balloon aortic valvotomy when performed in centres that can escalate to TAVI.	IIb	C
C) Asymptomatic patients with severe aortic stenosis (refers only to patients eligible for surgical valve replacement)		
SAVR is indicated in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF $<50\%$) not due to another cause.	I	C
SAVR is indicated in asymptomatic patients with severe aortic stenosis and an abnormal exercise test showing symptoms on exercise clearly related to aortic stenosis.	I	C
SAVR should be considered in asymptomatic patients with severe aortic stenosis and an abnormal exercise test showing a decrease in blood pressure below baseline.	IIa	C
SAVR should be considered in asymptomatic patients with normal ejection fraction and none of the above-mentioned exercise test abnormalities if the surgical risk is low and one of the following findings is present: <ul style="list-style-type: none"> ● Very severe aortic stenosis defined by a $V_{max} >5.5$ m/s ● Severe valve calcification and a rate of V_{max} progression ≥ 0.3 m/s/year ● Markedly elevated BNP levels ($>$threefold age- and sex-corrected normal range) confirmed by repeated measurements without other explanations ● Severe pulmonary hypertension (systolic pulmonary artery pressure at rest >60 mmHg confirmed by invasive measurement) without other explanation. 	IIa	C

D) Concomitant aortic valve surgery at the time of other cardiac/ascending aorta surgery		
SAVR is indicated in patients with severe aortic stenosis undergoing CABG or surgery of the ascending aorta or of another valve.	I	C
SAVR should be considered in patients with moderate aortic stenosis ⁶ undergoing CABG or surgery of the ascending aorta or of another valve after Heart Team decision.	IIa	C

BNP = B-type natriuretic peptide; CABG, coronary artery bypass grafting; CT = computed tomography; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LV = left ventricular; LVEF = left ventricular ejection fraction; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVI = transcatheter aortic valve implantation; V_{max} = peak transvalvular velocity.

^aClass of recommendation.

^bLevel of evidence.

^cIn patients with a small valve area but low gradient despite preserved LVEF, explanations for this finding other than the presence of severe aortic stenosis are frequent and must be carefully excluded. See *Figure 2* and *Table 6*.

^dSTS score (calculator: <http://riskcalc.sts.org/stswebriskcalc/#/calculate>); EuroSCORE II (calculator: <http://www.euroscore.org/calc.html>); logistic EuroSCORE I (calculator: <http://www.euroscore.org/calce.html>); scores have major limitations for practical use in this setting by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation, etc.¹⁰³ EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better-performing EuroSCORE II with this regard; it is nevertheless provided here for comparison, as it has been used in many TAVI studies/registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality.

^eModerate aortic stenosis is defined as a valve area of 1.0–1.5 cm² or a mean aortic gradient of 25–40 mmHg in the presence of normal flow conditions. However, clinical judgement is required.

Fig 3. Indications for intervention in aortic stenosis and recommendations for the choice of intervention mode. © 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739-91.

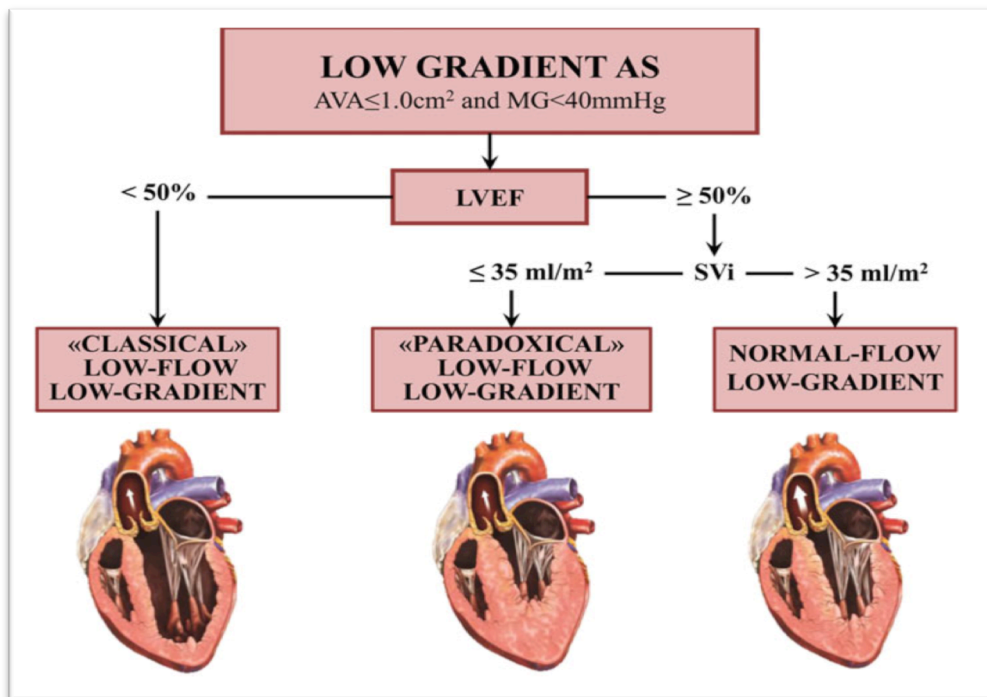


Fig 4. Subtypes of LFLG AS. AVA: aortic valve area, LVEF: left ventricular ejection fraction, MG: mean gradient, SVi: stroke volume index. © Clavel MA, Magne J, Pibarot P. Eur Heart J 2016;2645-2657.

1.2. True low-flow low-gradient AS, TLFLG AS (also called Classical or CLFLG AS).

The classical LFLG pattern is seen in patients with dilated left ventricles and decreased LVEF (< 50%). The low flow state is predominantly due to the combination of the depressed LV systolic dysfunction and the severe AS.

This entity has to be differentiated from the Pseudo-severe AS form; these patients have moderate AS and non-related myocardial dysfunction as the primary

pathology, most frequently due to ischemic cardiomyopathy. In this setting, the aortic valve might appear stenotic as a result of the flow-dependent nature of the valve area calculation and the inability of the ventricle to generate adequate force to fully open the valve.

Distinguishing between these two entities has important implications, as the treatment and prognosis differs considerably. To differentiate between the two dobutamine stress echocardiogram (DSE) is recommended. In patients with severe AS, the inotropic effect of dobutamine improves contractility of the LV, hence the ejection fraction which increases the flow through a fixed valve orifice, resulting in increased peak velocity and hence the gradient. In pseudo-severe AS, the increased flow is not associated with an increased gradient and the valve area increases by $> 0.2 \text{ cm}^2$ (Figure 5). In this setting AVR is not recommended; they should be managed conservatively with optimized heart failure medication and coronary revascularization if indicated.

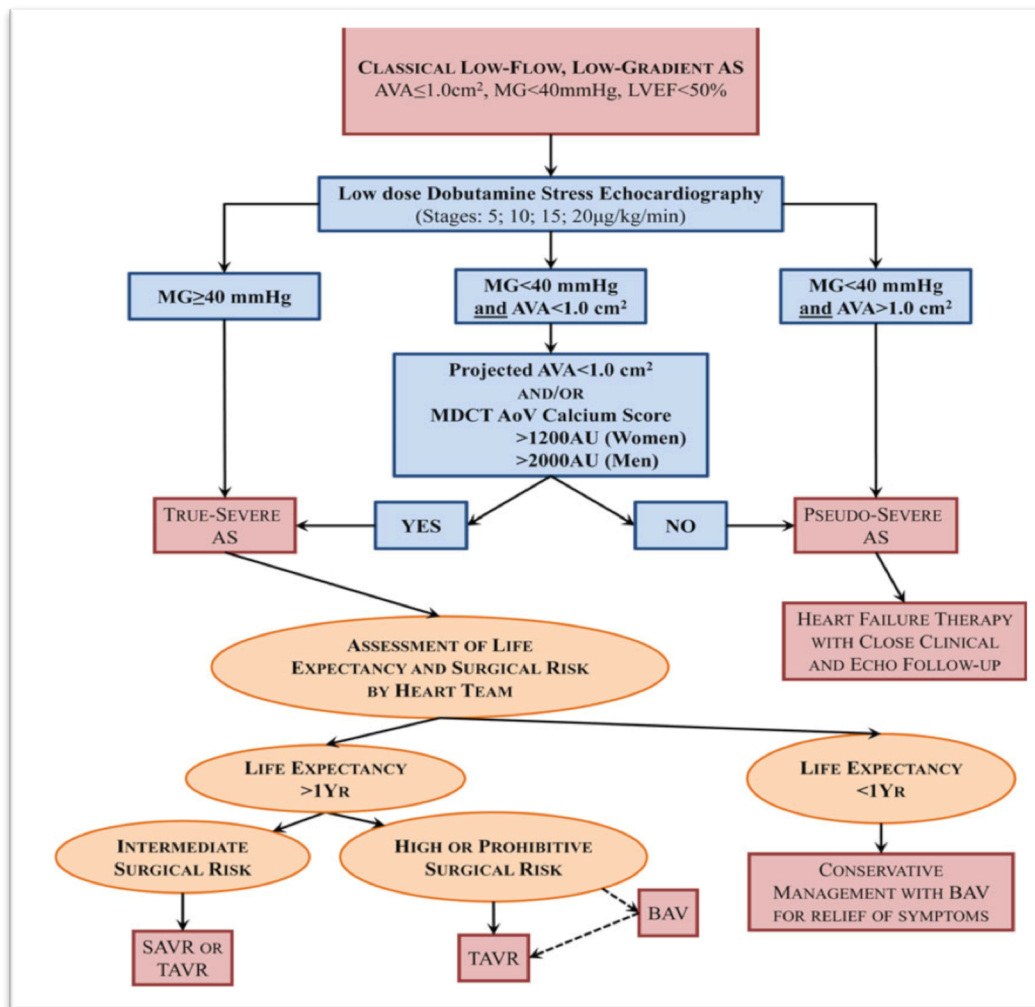


Fig 5. Algorithm for the management of TLFLG AS. The differential diagnosis between TLFLG AS and Pseudo-severe AS is achieved with Dobutamine Stress Echocardiography (DSE) and/or Multi-detector Computed CT (MDCT). AoV: aortic valve, SAVR: surgical aortic valve replacement, TAVR: transcatheter aortic valve replacement. . © Clavel MA, Magne J, Pibarot P. Eur Heart J 2016;2645-2657.

DSE is also useful to determine the ventricular flow reserve, which has important prognostic value. About one-third of the patients with TLFLG AS have no flow reserve, defined as < 20% increase in SV during DSE. This clinical picture increases the risk of surgery for AVR [27].

A multi-detector computed tomography (MDCT) might be also required to differentiate between TLFLG and Pseudo-severe AS if the DSE does not generate a significant increase in flow (< 15%). The valve calcium score measured by the MDCT predicts the severity of the AS as well as the rate of progression and occurrence of adverse events. Values of >2000 Agatston units (AU) in men and > 1200 AU in women likely represent LFLG AS (Figure 5) [27].

Patients with TLFLG AS have the highest risk of mortality and adverse events. Survival with conservative treatment is 40 - 50 % at 2 years, similar to any form of severe AS with the rest of the 50% having very poor quality of life. While AVR in this group is also associated with high 30-day mortality (8-33%), however it confers a considerable survival benefit compared with medical therapy and a much better quality of life [27].

The ESC/EACTS guidelines on the management of valvular heart disease published in 2012 and their American counterpart published by the AHA/ACC in 2014, did only recommend surgical intervention for patients with symptomatic LFLG AS with a Class IIa, Level C evidence [21, 22]. The recently updated ESC/EACTS guidelines have taken into account the new evidence gathered from single institutional series of patients with LFLG treated medically or surgically. Current recommendations include surgical intervention for symptomatic TLFLG AS with flow reserve (Class I, Level C evidence) or without flow reserve (Class IIa, Level C). The lack of flow reserve associates a higher surgical mortality, which is still lower than the mortality with medical therapy; besides, those who survive the operation, experience a similar LV recovery and long-term survival compared to those with flow reserve [23, 24] (Figure 4).

As for the NFHG AS, guidelines recommend a thorough and careful preoperative assessment of surgical risks to evaluate the choice between surgical AVR vs. TAVI (Figures 4 and 5) [23, 24]. Recent studies suggest that TAVI might be associated with better recovery of the LV function, less patient-prosthesis mismatch and higher long-term survival, especially for those with no flow reserve, but additional studies comparing the two techniques in this cohort of patients are necessary [27].

1.3. Paradoxical low-flow low-gradient AS (PLFLG AS).

The paradoxical LFLG pattern (PLFLG AS) is seen in patients with severe AS ($AVA < 1.0$ cm) and preserved LVEF who have paradoxically low peak and mean transaortic gradients (Figure 3). These patients have reduced SV_i through a combination of mechanisms that include concentric remodeling, impaired diastolic filling and abnormal longitudinal LV function. It is important to confirm carefully the severity of the AS in this subgroup of patients, to exclude measurement errors (i.e. a moderate AS in a patient with small body size, underestimation of AVA/LVOT/velocity measurements) and also to try to identify any underlying cause for the reduced SV (i.e. atrial fibrillation, associated mitral/tricuspid pathology, right ventricular dysfunction) (Figure 6) [27].

Some studies recommend the use of DSE to differentiate the diagnosis of PLFLG AS from Pseudo-severe AS; however, DSE should not be performed in patients with restrictive LV physiology, often found in these patients. Hence, the preferred approach to confirm the diagnosis is to assess the morphology of the valve

and the degree of calcification by echocardiography and/or MDCT (Figure 6) [27].

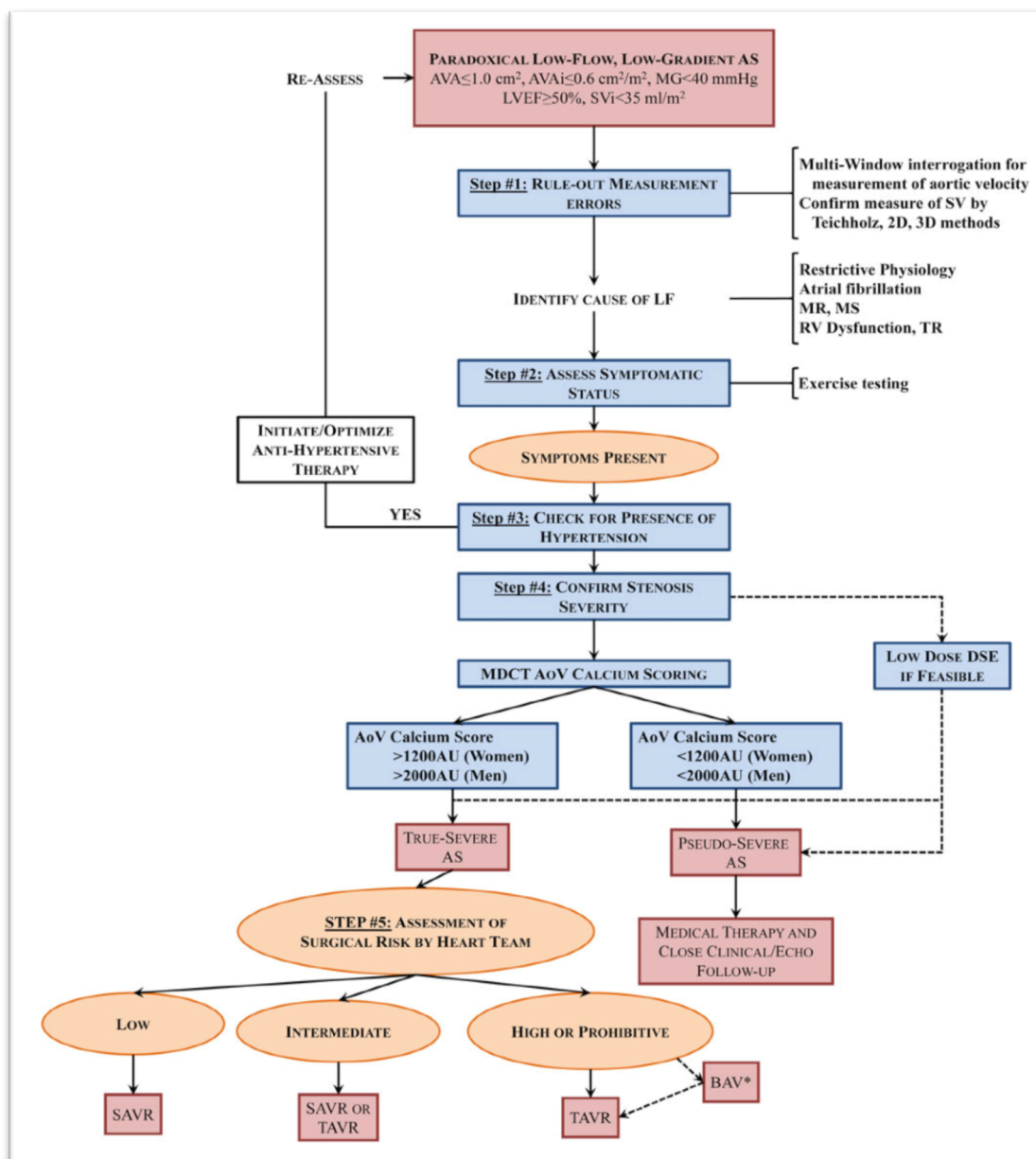


Fig 6. Algorithm for the management of PLFLG AS. AVA: aortic valve area, AVAi: indexed aortic valve area, MG: mean gradient, LVEF: left ventricular ejection fraction, SVi: stroke volume index, LF: low flow, AoV: aortic valve, DSE: dobutamine stress echocardiography, MDCT: multi-detector computed tomography, SAVR: surgical aortic valve replacement, TAVR: trans-catheter aortic valve replacement, BAV: balloon valvuloplasty.. © Clavel MA, Magne J, Pibarot P. Eur Heart J 2016;2645-57.

Patients with PLFLG AS have worse prognosis than patients with moderate AS or NFHG severe AS, but better prognosis than patients with TLFLG AS. Survival is markedly improved with AVR versus medical treatment, but AVR carries higher risk than in patients with NFHG AS, possibly due to the intrinsic restrictive physiology of the LV [27].

Based on recent clinical evidence, the recently updated ESC/EACTS guidelines recommend AVR for patients with symptomatic PLFLG AS confirmed with echocardiography, DSE and/or MDCT (Class IIa C) [23, 24].

1. 4. Normal-flow low-gradient aortic stenosis (NFLG AS)

This is another group of patients with low gradient (< 40 mmHg) but normal flow ($SV_i > 35$ ml/m²) (Figure 3). This entity is relatively frequent (15-40%) and it can be explained by reduced aortic compliance due to systolic hypertension that may lead to a substantial decrease in gradient [27].

2. HYPOTHESIS

2. HYPOTHESIS

The primary hypothesis of our research project was that AVR could be performed in patients with LFLG AS with low in-hospital mortality.

The secondary hypothesis was that AVR in patients with LFLG AS could also provide excellent mid-term symptomatic relief among survivors, which would be translated in an improvement of their functional status class.

3. OBJECTIVES

3. OBJECTIVES

The primary objective of our research project was to determine the operative and mid-term outcomes of surgical intervention in patients with LFLG AS compared to NFHG AS.

As secondary objective, we also aimed to determine if survival with surgical intervention was superior to survival with medical management, comparing our surgical results with the medical results available in the literature.

Therefore, we analysed operative outcomes and mid-term results (clinical status and mortality) following isolated AVR in patients with LFLG AS compared to NFHG AS. For further stratification of risk between the two different categories of LFLG AS, we also compared the outcomes post AVR in the two subgroups (CLFLG and PLFLG AS).

Our primary end points were in-hospital mortality and mid-term mortality (at one and five years). Secondary end points included immediate postoperative complications and clinical status of survivors and late complications during the follow-up period.

4. MATERIALS AND METHODS

4. MATERIALS AND METHODS

4.1. Patient selection and data collection

A retrospective analysis of prospectively collected data was performed including all patients with severe AS who underwent isolated AVR at Morriston Regional Cardiac Centre from October 1997 to April 2014 (although patients in the LFLG AS groups were only recruited from January 2001 onwards).

Preoperative characteristics, cardiovascular risk factors, postoperative complications and in-hospital mortality were prospectively recorded in our database (Patients Administration and Tracking System, PATS).

All patients had a complete preoperative echocardiography in our centre to assess the severity of the AS (AVA and mean gradients) and to classify it into the different categories according to the LVEF. Not all the patients in the LFLG AS had a DSE as part of the diagnosis; it was only conducted in 25% of the patients with TLFLG AS to confirm the diagnosis or to assess the myocardial reserve according to the referring cardiologist criteria.

For those who had a DSE, the low-dose protocol with an increasing infusion of dobutamine starting with a 5 µg/kg/min to a final dose of 20 µg/kg/min was used. Atropine was required in some of the cases to reach the targeted heart rate. All DSEs performed were considered optimal and all demonstrated myocardial reserved before surgery. We did not use MDCT in our center for routine assessment of these patients.

Indications for AVR were established by the operating surgeon and the referring cardiologist in the preoperative clinic visits and were made on the basis of a

combination of the symptomatic status of the patient and degree of AS according the current guidelines.

Mid-term follow-up consisted of routine clinical visits annually from 6 weeks of discharge or clinical letters from the cardiologist on those patients who were not seen by any specialist in the previous year to determine survival and functional class. The follow-up results described in the study were obtained from January to July 2015 by 1 of the 2 methods described previously.

Postoperative echocardiograms were performed at the clinic visits at 6 weeks after discharge for all patients and then annually for those who remained on our follow-up system. For this analysis we have used the last postoperative echocardiogram available for each patient (a generalized linear mixed model was used to compare them with the preoperative echocardiograms). LVEF, AVA, and gradients were recorded.

The data used in this study were approved by the institutional review board, which deemed an individual consent form was not needed because no patient-identifiable information was used.

For this study, we identified two groups, one with further subdivision into two subgroups:

A) Group I: Patients with LFLG AS (198 patients, 23%), further subdivided into:

- True or Classical LFLG AS, patients with reduced LVEF (66 patients, 33%)
- Paradoxical LFLG AS, patients with normal LVEF (132 patients, 67%)

B) Group II: patients with NFHG AS (648 patients, 77%).

4.2. Statistical methods

Continuous variables were expressed as mean \pm standard deviation or median \pm interquartile range (depending on distribution of data), and comparison between groups was performed with the t test/Mann-Whitney U test. Categorical variables were expressed as percentages and compared by the use of Fisher exact test as appropriate.

A multiple logistic regression model was used to identify the predictors of early mortality and Cox regression was applied to identify the best predictors of late mortality including all the significant variables listed in annexed tables (cut-off at $p < 0.05$). The results were expressed as odds ratios (ORs) and hazard ratios with corresponding 95% confidence intervals (CIs).

Because the 2 LFLG AS subgroups were significantly different with respect to their baseline characteristics, propensity score matching (with a match tolerance of 0.05) was performed (including the preoperative characteristic except echocardiographic parameters) using SPSS 22.0 (IBM Corp, Armonk, NY). The matched groups were analyzed via the methods described previously.

A Kaplan-Meier survival analysis was done, building curves for the groups, which were compared by the log-rank statistic.

Follow-up results (New York Heart Association [NYHA] class and LVEF) were compared with their respective preoperative values and to assess the patterns of the repeated measures a generalized mixed model was fitted with LFLG, follow-up

time (months for LVEF and years for NHYA class changes), and LFLG-by-time interaction as covariates. A coefficient estimated was considered statistically significant if its p value (2-sided) was < 0.05 . SPSS 22.0, STATA 12 (StataCorp, College Station, Tex), and Prism 7 (GraphPad Software, Inc, La Jolla, Calif) were used to analyze the data.

4.3. Definitions

- NFHG AS: $AVA < 1.0 \text{ cm}^2$, mean transvalvular gradient $> 40 \text{ mmHg}$, Stroke Volume Index (SVi) $> 35 \text{ ml/m}^2$, variable LVEF.
- LFLG AS: $AVA < 1.0 \text{ cm}^2$, mean transvalvular gradient $< 40 \text{ mmHg}$, SVi $< 35 \text{ ml/m}^2$, variable LVEF. After DSE, AVA remains $< 1.0 \text{ cm}^2$, mean gradient increases $> 40 \text{ mmHg}$.
- TLFLG AS or CLFLG AS: $AVA < 1.0 \text{ cm}^2$, mean transvalvular gradient $< 40 \text{ mmHg}$, SVi $< 35 \text{ ml/m}^2$, impaired LVEF.
- PLFLG AS: $AVA < 1.0 \text{ cm}^2$, mean transvalvular gradient $< 40 \text{ mmHg}$, SVi $< 35 \text{ ml/m}^2$, preserved LVEF.
- Pseudo-severe AS: $AVA < 1.0 \text{ cm}^2$, mean transvalvular gradient $< 40 \text{ mmHg}$, SVi $< 35 \text{ ml/m}^2$, impaired LVEF. After DSE, AVA $> 1.0 \text{ cm}^2$, mean gradient remains $< 40 \text{ mmHg}$.
- Pulmonary hypertension: pulmonary artery pressure $> 50 \text{ mm Hg}$ measured by echocardiography.

- Poor LVEF / Severe ventricular dysfunction: < 30%.
- Fair LVEF / Moderate ventricular dysfunction: 30 – 50%.
- Good LVEF / Normal ventricular function: > 50%.
- Previous neurological disease: Cerebrovascular accident (CVA) or transient ischaemic attack (TIA) diagnosed before the operation, with or without residual deficits.
- Postoperative neurological events: new focal deficit after surgery, either TIA or CVA.
- Long-term ventilation: postoperative ventilation for more than 7 days, including reintubation or tracheostomy.
- Respiratory complications: acute distress respiratory syndrome or pneumonia during the postoperative period.
- Gastrointestinal (GI) complications: bowel ischaemia, GI bleeding or laparotomy for any cause during the postoperative period.

5. RESULTS

5. RESULTS

5.1. FIRST ARTICLE



Eur J Cardiothorac Surg 2016;49:1685-90.

5.1.1. ABSTRACT

OBJECTIVES: To analyse operative outcomes and mid-term results following isolated aortic valve replacement (AVR) in patients with low-flow low-gradient severe aortic stenosis (LFLG AS) compared with normal flow high-gradient aortic stenosis (NFHG AS).

METHODS: A retrospective analysis of data for all isolated AVRs performed for AS at our centre in the last 17 years (n = 846). Two groups were identified: LFLG AS (n = 198, 23%) [Subdivided into: True LFLG AS (n = 66, 33%) and Paradoxical LFLG AS (n = 132, 67%)] and NFHG AS (n = 648, 77%). Follow-up was done by clinical visits and telephone interviews. The mean follow-up was 5.8 ± 4.2 years.

RESULTS: The mean age was 71.5 ± 9.7 years in the LFLG AS group and $68.7 \pm$

10.8 years in the NFHG group ($P = 0.01$). The LFLG AS group had a mean gradient 31.2 ± 7.4 mmHg compared with 59.1 ± 16.6 mmHg in the NFHG group ($P = 0.001$). Diabetes, chronic obstructive pulmonary disease, previous coronary disease, peripheral vascular disease, atrial fibrillation and pulmonary hypertension were significantly more frequent in the LFLG AS patients ($P < 0.01$). The in-hospital mortality rate was 2% in the LFLG and 1% in the NFHG group, $P = 0.13$. One- and 5-year mortality rates were significantly higher in the LFLG group (13 and 28 vs. 4 and 16% in the NFHG, respectively, $P = 0.001$). Patients with true LFLG AS also had a significantly higher long-term mortality than those with paradoxical LFLG AS (27 vs. 6% at 1 year and 42 vs. 20% at 5 years, $P < 0.05$).

CONCLUSIONS: AVR in patients with LFLG AS is associated with similar surgical mortality but increased mid-term mortality compared with NFHG AS. Patients with true LFLG AS have the worst outcomes. Surgery should still be offered for LFLG AS on prognostic grounds and for symptomatic benefit among survivors.

5.2.2. FULL ORIGINAL TEXT

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Low-flow low-gradient aortic stenosis: surgical outcomes and mid-term results after isolated aortic valve replacement[†]

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Abstract

OBJECTIVES: To analyse operative outcomes and mid-term results following isolated aortic valve replacement (AVR) in patients with low-flow low-gradient severe aortic stenosis (LFLG AS) compared with normal flow high-gradient aortic stenosis (NFHG AS).

METHODS: A retrospective analysis of data for all isolated AVRs performed for AS at our centre in the last 17 years ($n = 846$). Two groups were identified: LFLG AS ($n = 198$, 23%) [subdivided into: True LFLG AS ($n = 66$, 33%) and paradoxical LFLG AS ($n = 132$, 67%)] and NFHG AS ($n = 648$, 77%). Follow-up was done by clinical visits and telephone interviews. The mean follow-up was 5.8 ± 4.2 years.

RESULTS: The mean age was 71.5 ± 9.7 years in the LFLG AS group and 68.7 ± 10.8 years in the NFHG group ($P = 0.01$). The LFLG AS group had a mean gradient 31.2 ± 7.4 mmHg compared with 59.1 ± 16.6 mmHg in the NFHG group ($P = 0.001$). Diabetes, chronic obstructive pulmonary disease, previous coronary disease, peripheral vascular disease, atrial fibrillation and pulmonary hypertension were significantly more frequent in the LFLG AS patients ($P < 0.01$). The in-hospital mortality rate was 2% in the LFLG and 1% in the NFHG group, $P = 0.13$. One- and 5-year mortality rates were significantly higher in the LFLG group (13 and 28 vs 4 and 16% in the NFHG, respectively, $P = 0.001$). Patients with true LFLG AS also had a significantly higher long-term mortality than those with paradoxical LFLG AS (27 vs 6% at 1 year and 42 vs 20% at 5 years, $P < 0.05$).

CONCLUSIONS: AVR in patients with LFLG AS is associated with similar surgical mortality but increased mid-term mortality compared with NFHG AS. Patients with true LFLG AS have the worst outcomes. Surgery should still be offered for LFLG AS on prognostic grounds and for symptomatic benefit among survivors.

Keywords: Aortic stenosis • Aortic valve replacement • Adult cardiac

INTRODUCTION

Aortic stenosis (AS) is the most common valve disorder and the most frequent indication for aortic valve replacement (AVR) in adults.

Severe AS has been defined with aortic valve area (AVA) < 1.0 cm², mean transvalvular gradient > 40 mmHg and peak flow velocity > 4.0 m/s. The natural history of the disease, its prognosis and therapeutic options have been broadly studied over the last decades and are well documented in the guidelines [1, 2].

It is estimated that 30% of patients in whom the AVA meet the criteria of severe AS have transvalvular gradients in the range of moderate AS (< 40 mmHg) due to a reduced transvalvular flow. This entity is known as LFLG AS and can be subdivided into two

categories depending on the left ventricular ejection function (LVEF) [3, 4].

The classical LFLG pattern is seen in patients with dilated left ventricles and decreased LVEF. Only ~10% of these patients might have truly severe AS with resultant myocardial failure (True LFLG AS) while the rest will just have moderate AS and non-related myocardial dysfunction as the primary pathology (pseudo-severe AS). In this setting, the aortic valve might appear stenotic as a result of the flow-dependent nature of the valve area calculation and the inability of the ventricle to generate adequate force to fully open the valve.

Distinguishing between these two entities has important implications.

Dobutamine stress echocardiogram (DSE) is useful in differentiating between the two. In patients with severe AS, the inotropic effect of dobutamine increases the flow through a fixed valve orifice, resulting in increased gradients and peak velocities. In

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pseudo-severe AS, the increased flow is not associated with an increased gradient and the valve area increases by $>0.2 \text{ cm}^2$ [3, 4].

Another 10–25% of patients with severe AS ($\text{AVA} < 1.0 \text{ cm}^2$) and preserved LVEF have paradoxically low peak and mean transaortic gradients (paradoxical LFLG AS). These patients have reduced indexed stroke volume, through a combination of mechanisms that include concentric remodelling, abnormal ventriculo-aortic impedance and abnormal longitudinal LV function [3–5].

Although the surgical mortality for patients with true LFLG AS has decreased in the last decades, these patients continue to have a higher morbidity and mortality independently of the management of their disease [6–9].

Patients with paradoxical LFLG AS have worse prognosis than those with moderate or severe NFHG AS although they seem to have better prognosis than the true LFLG AS patients [3, 4].

The natural history of LFLG AS treated medically has been reported as poor by Pibarot and co-workers [4], with less than 50% survival at 3 years. The objective of our study aim to find the outcome of surgical intervention in LFLG AS in our unit and whether that would be better than the medical management published in the literature [3–5]. Therefore, we analysed operative outcomes and mid-term results (clinical status and mortality) following isolated AVR in patients with LFLG AS compared with NFHG AS.

MATERIALS AND METHODS

Patient selection and data collection

A retrospective analysis was performed including all patients with AS who underwent isolated AVR at Morriston Regional Cardiac Centre from October 1997 to April 2014. Preoperative characteristics, cardiovascular risk factors, postoperative complications and in-hospital mortality were prospectively recorded in our database (Patients Administration and Tracking System).

All the patients had a complete preoperative echocardiography at our centre to assess the severity of the AS and to classify it into the different categories. Not all the patients in the LFLG AS had a DSE as part of the diagnosis; it was only conducted in some patients with TLFLG AS to confirm the diagnosis or to assess the myocardial reserve. For those who had a DSE, the protocol used was the low-dose protocol with an increasing infusion of dobutamine starting with a $5 \mu\text{g}/\text{kg}/\text{min}$ to a final dose of $20 \mu\text{g}/\text{kg}/\text{min}$. Atropine was required in some of the cases to reach the targeted heart rate. All DSEs performed were considered optimal.

Mid-term follow-up consisted of routine clinical visits annually from 6 weeks of discharge, with clinical letters from the cardiologist on those who were discharged from our surgical follow-up. We performed also telephone interviews of those in the LFLG AS group to determine survival and functional class.

For this study, we identified two groups, one with further subdivision into two subgroups:

- Group I: patients with low-flow low-gradient aortic stenosis (LFLG AS, 198 patients, 23%), further subdivided into:
 - True LFLG AS, patients with reduced LVEF (TLFLG AS, 66 patients, 33%)
 - Paradoxical LFLG AS, patients with normal LVEF (PLFLG AS, 132 patients, 67%)
- Group II: patients with normal flow high-gradient aortic stenosis (NFHG AS, 648 patients, 77%).

Statistical methods

Continuous variables are expressed as mean/median \pm standard deviation (depending on distribution of data) and comparison between groups was performed with the Mann-Whitney *U*-test/*t*-test (depending on distribution of data). Categorical variables are expressed as percentages and compared using the Pearson χ^2 or the Fisher's exact test as appropriate.

A multiple logistic regression model was used to identify the predictors of early mortality and a Cox regression was applied to identify the predictors of late mortality including all the variables listed in annexed tables. The results are expressed by odds ratios and hazard ratios reported with 95% confidence intervals (CIs). A Kaplan–Meier survival analysis was done, building curves for the groups which were compared by the log-rank statistic.

SPSS 22.0 was used to analyse the data.

Definitions

NFHG AS: $\text{AVA} < 1.0 \text{ cm}^2$, mean transvalvular gradient $>40 \text{ mmHg}$, Stroke Volume Index (SVI) $>35 \text{ ml}/\text{m}^2$, variable LVEF.

LFLG AS: $\text{AVA} < 1.0 \text{ cm}^2$, mean transvalvular gradient $<40 \text{ mmHg}$, SVI $< 35 \text{ ml}/\text{m}^2$, variable LVEF. After DSE, AVA remains $<1.0 \text{ cm}^2$, mean gradient increases $>40 \text{ mmHg}$.

TLFLG AS: $\text{AVA} < 1.0 \text{ cm}^2$, mean transvalvular gradient $<40 \text{ mmHg}$, SVI $< 35 \text{ ml}/\text{m}^2$, impaired LVEF.

PLFLG AS: $\text{AVA} < 1.0 \text{ cm}^2$, mean transvalvular gradient $<40 \text{ mmHg}$, SVI $< 35 \text{ ml}/\text{m}^2$, preserved LVEF.

Pseudo-severe AS: $\text{AVA} < 1.0 \text{ cm}^2$, mean transvalvular gradient $<40 \text{ mmHg}$, SVI $< 35 \text{ ml}/\text{m}^2$, impaired LVEF. After DSE, AVA $> 1.0 \text{ cm}^2$, mean gradient remains $<40 \text{ mmHg}$.

Poor LVEF: $<30\%$.

Fair LVEF: $30\text{--}50\%$.

Good LVEF: $>50\%$.

Previous neurological disease: Cerebrovascular accident (CVA) or transient ischaemic attack (TIA) diagnosed before the operation, with or without residual deficits.

Postoperative neurological events: new focal deficit after surgery, either TIA or CVA.

Long-term ventilation: postoperative ventilation for more than 7 days, including reintubation or tracheostomy.

Respiratory complications: acute distress respiratory syndrome or pneumonia during the postoperative period.

Gastrointestinal (GI) complications: bowel ischaemia, GI bleeding or laparotomy for any cause during the postoperative period.

RESULTS

We identified 846 patients who fulfilled the inclusion criteria, 648 of them in the NFHG AS group and 198 patients in the LFLG AS group.

Patients with LFLG AS were significantly older than those with NFHG AS (71.5 ± 9.7 vs 68.7 ± 10.8 years, $P = 0.01$).

More patients with LFLG AS were with CCS class III–IV angina (40 vs 23% , $P = 0.001$), as well as having higher risk factors for coronary artery disease such as hypertension (65 vs 54% , $P = 0.008$) and diabetes (22 vs 9% , $P = 0.001$). Other comorbidities such as chronic obstructive pulmonary disease (COPD), previous neurological disease, chronic renal failure on haemodialysis, peripheral vascular disease and permanent atrial fibrillation were also significantly more frequent in the LFLG AS group (Table 1).

Table 1: Preoperative characteristics in patients undergoing isolated AVR for severe AS in the different groups

	Total	NFHG	LFLG	P
n	846	648	198	
Age	69.4 ± 10.6	68.7 ± 10.8	71.5 ± 9.7	0.01
Female	395 (47%)	304 (47%)	91 (46%)	0.81
Angina CCS III-IV	222 (26%)	149 (23%)	73 (37%)	0.001
NYHA III-IV	480 (57%)	373 (58%)	107 (54%)	0.38
DM	98 (12%)	55 (9%)	43 (22%)	0.001
HT	478 (56%)	350 (54%)	128 (65%)	0.008
Dialysis	4 (0.5%)	1 (0.2%)	3 (1%)	0.02
COPD	106 (12%)	68 (10%)	38 (19%)	0.001
CVA	8 (1%)	3 (0.5%)	5 (2%)	0.009
PVD	38 (4%)	23 (3%)	15 (8%)	0.02
AF	81 (10%)	53 (8%)	28 (14%)	0.01
Logistic EuroSCORE	8.4 ± 8.2	7.3 ± 6.5	10.3 ± 10.4	0.14

NFHG: normal flow high-gradient; LFLG: low-flow low-gradient; CCS: Canadian Cardiovascular Society Class; NYHA: New York Heart Association Class; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; PVD: peripheral vascular disease; AF: atrial fibrillation; AS: aortic stenosis; AVR: aortic valve replacement.

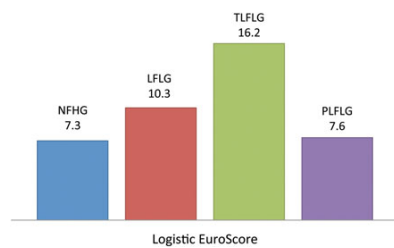


Figure 1: Expected operative mortality according to logistic EuroSCORE (%)/Flow groups. NFHG AS: normal flow severe high-gradient; LFLG: low-flow low-gradient; TLFLG: true low-flow low-gradient; PLFLG AS: paradoxical low-flow low-gradient aortic stenosis.

The mean logistic EuroSCORE was 10.3 ± 10.4 in the LFLG AS group and 7.3 ± 6.5 in the NFHG AS group (P = 0.14) (Table 1 and Fig. 1).

Echocardiographic analysis confirmed higher severity of the AS in the NFHG AS group based on mean gradients (59.1 ± 16.6 vs 31.2 ± 7.4 mmHg, P = 0.001) and AVA (0.6 ± 0.2 vs 0.8 ± 0.2 cm², P = 0.001). There were more patients with poor left ventricular function and pulmonary hypertension in the LFLG AS group (13 vs 6% and 4 vs 1%, respectively, P = 0.001) (Table 2 and Fig. 2).

The choice of prosthesis used for the AVR was based mainly on patients' and surgeons' preferences. In some patients, the choice of the prosthesis was governed by existence of clinical conditions preventing them from being on Warfarin safely. A total of 614 patients (73%) had a bioprosthesis (67% pericardial and 6% porcine) and 232 patients (27%) received a bileaflet mechanical prosthesis; 1% of the prostheses used were stentless.

The sizes varied from 18 to 32 mm, with 90% of them between 21 and 27 mm. In our series, we did not find any relation between the size of the valve and late mortality, not even for sizes below 21 mm (Table 3).

The global in-hospital mortality rate for all patients who underwent isolated AVR was 1% (12 deaths), categorized as follows: 5

Table 2: Preoperative echocardiographic characteristics in patients undergoing AVR for severe AS in the different groups

	Total	NFHG	LFLG	P
Mean gradient (mmHg)	46.6 ± 19.1	59.1 ± 16.6	31.2 ± 7.4	0.001
AVA (cm ²)	0.7 ± 0.2	0.6 ± 0.2	0.8 ± 0.2	0.001
Poor LVEF	62 (7%)	36 (6%)	26 (13%)	0.001
Fair LVEF	174 (21%)	134 (21%)	40 (20%)	0.88
Good LVEF	610 (72%)	478 (74%)	132 (67%)	0.05
SVI (ml/m ²)	-	-	29.5 ± 5.1	-
Pulmonary HT	17 (2%)	8 (1%)	9 (4%)	0.004

AS: aortic stenosis; AVR: aortic valve replacement; NFHG: normal flow high-gradient; LFLG: low-flow low-gradient; AVA: aortic valve area (cm²); LVEF: left ventricular ejection fraction; SVI: stroke volume index; pulmonary HT: pulmonary hypertension (PAP > 55 mmHg).

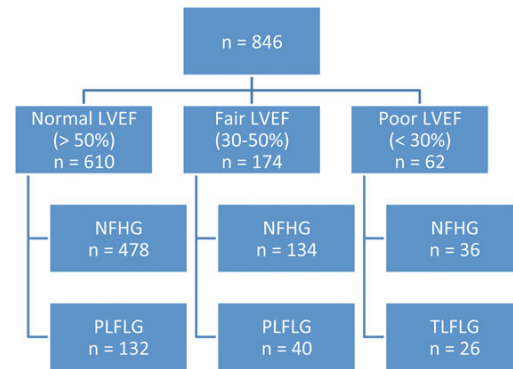


Figure 2: Number of patients for types of AS according to the LVEF. LVEF according to types of AS. LVEF: left ventricular ejection fraction; AS: aortic stenosis; NFHG AS: normal flow high-gradient aortic stenosis; TLFLG AS: true low-flow low-gradient aortic stenosis; PLFLG AS: paradoxical low-flow low-gradient aortic stenosis.

Table 3: Type of prosthesis used for the aortic valve replacement

	Total (n = 846)	NFHG (n = 648)	LFLG (n = 198)
Mechanical	232 (27%)	209 (32%)	23 (12%)
Biological	614 (73%)	439 (68%)	175 (88%)
Pericardial	566 (67%)	404 (62%)	166 (84%)
Porcine	48 (6%)	35 (6%)	9 (4%)
Stentless	8 (1%)	8 (1%)	0

NFHG: normal flow high-gradient; LFLG: low-flow low-gradient.

deaths (42%) being cardiac related, 3 deaths (25%) secondary to sepsis, 1 death (8%) due to respiratory complications, 1 to GI complications (8%) and 2 (17%) to neurological complications. The in-hospital mortality rate was 2% in the LFLG AS group compared

ADULT CARDIAC

Table 4: Postoperative outcomes in patients undergoing isolated AVR for severe AS in the different groups

	Total	NFHG	LFLG	P
<i>n</i>	846	648	198	
Postoperative IABP	3 (0.4%)	3 (0.5%)	0 (0%)	0.86
Reoperation bleeding	35 (4%)	27 (4%)	8 (4%)	0.29
Haemofiltration	21 (2%)	13 (2%)	8 (4%)	0.11
Neurological	2 (0.2%)	2 (0.3%)	0 (0%)	0.43
Prolonged ventilation	11 (1%)	7 (1%)	4 (2%)	0.31
ARDS	4 (0.5%)	2 (0.3%)	2 (1%)	0.21
GI	23 (3%)	19 (3%)	4 (2%)	0.49
In-hospital mortality	12 (1%)	7 (1%)	5 (2%)	0.13
1-year mortality	54 (6%)	28 (4%)	26 (13%)	0.003
1-year survival	750 (89%)	586 (90%)	164 (83%)	0.003
5-year mortality	159 (19%)	104 (16%)	55 (28%)	0.001
5-year survival	442 (52%)	383 (59%)	59 (30%)	0.001

AS: aortic stenosis; AVR: aortic valve replacement; NFHG: normal flow high gradient; LFLG: low-flow low gradient; IABP: intra-aortic balloon pump; ARDS: adult respiratory distress syndrome; GI: gastrointestinal.

with 1% in NFHG AS ($P = 0.13$). However, postoperative complications were similar in both groups (Tables 2 and 4).

We did not identify any preoperative characteristics as risk factors for in-hospital mortality in any of the groups.

Late outcomes

Follow-up was up to 17 years, with a median of 5.8 ± 4.2 years (range 0.5–17.2 years).

There were 126 patients in our cohort lost to follow-up (15%); majority of them were in the NFHG AS group (123 patients) with only 3 patients in the LFLG group. In the telephone interviews conducted in the LFLG AS group, only 3 patients were lost.

The 1-year mortality rate was 6% for the whole study group. It was higher in the LFLG AS group (13 vs 4% for NFHG AS, $P = 0.01$). In the subgroups, it was significantly higher in the TLFLG AS group (27 vs 6% in PLFLG AS, $P = 0.01$) (Table 4 and Fig. 3).

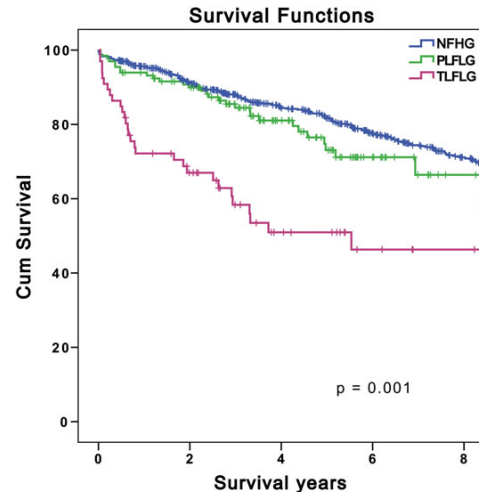
At 5 years, the overall mortality rate was 19%. It was also higher in the LFLG AS group (28 vs 16%, $P = 0.01$). In the subgroups, it was also higher in the TLFLG AS group (42 vs 20%, $P = 0.01$) (Table 4 and Fig. 3).

Mean survival calculated according to Kaplan–Meier analysis was 11.3 ± 0.3 years (95% CI 10.7–11.8) in the NFHG group and 8.6 ± 0.5 years (95% CI 7.7–9.6) in the LFLG group ($P = 0.001$) (Fig. 3).

A total of 262 patients (31%) died during the follow-up. Causes of death were categorized as follows: 59 patients (22%) being cardiac related, 35 patients (13%) due to cancer, 21 patients (8%) secondary to stroke, 21 patients (8%) due to respiratory problems, 11 patients (4%) due to renal disease, 11 patients (4%) due to sepsis and 54 patients (21%) due to other causes. We were not able to identify the cause of death in 52 patients (20%) (Table 4).

In the NFHG group, Cox regression identified the following preoperative risk factors for late mortality: age ($P = 0.001$, 95% CI 1.0–1.1), female sex ($P = 0.001$, 95% CI 0.4–0.8), diabetes ($P = 0.04$, 95% CI 1.0–3.1) and permanent atrial fibrillation ($P = 0.001$, 95% CI 1.3–2.7).

Age was identified by Cox regression as a risk factor for late mortality in the LFLG group ($P = 0.001$, 95% CI 1.0–1.1).



Years	2	4	6	8
NFHG	530	416	328	249
PLFLG	109	58	23	8
TLFLG	37	18	9	6

Figure 3: Kaplan–Meier survival curves of patients undergoing aortic valve replacement for NFHG AS, TLFLG AS or PLFLG AS. The number of patients at risk in each group at the different time frames is also provided. NFHG AS: normal flow severe high-gradient aortic stenosis; TLFLG AS: true low-flow low-gradient aortic stenosis; PLFLG AS: paradoxical low-flow low-gradient aortic stenosis.

Table 5: Mid-term follow-up status and cardiac-related events in patients who underwent aortic valve replacement according to the different flow groups

	NFHG AS (n = 435)	LFLG AS (n = 138)	P
NHYA I–II	303 (70%)	121 (88%)	0.48
NHYA III–IV	23 (5%)	14 (10%)	0.48
SR	287 (66%)	106 (77%)	0.31
PPM	10 (2%)	9 (6%)	0.31
AF	29 (7%)	20 (14%)	0.31
Stroke	11 (2%)	2 (1%)	0.17
Lost	109 (25%)	3 (2%)	

NFHG AS: normal flow high-gradient aortic stenosis; LFLG AS: low-flow low-gradient aortic stenosis; NYHA: New York Heart Association Class; SR: sinus rhythm; PPM: permanent pacemaker; AF: permanent atrial fibrillation; CVA: cerebrovascular accident.

Clinical status was excellent in those patients who survived. The follow-up interviews were completed in 98% of the LFLG AS group. Among the LFLG AS survivors at follow-up, 88% were found to be in NYHA functional class I–II and only 10% (14 patients) were in NYHA class III. Twenty patients in this group (14%) were in atrial fibrillation and 2% in paced rhythm. The incidence rate of stroke in this group was 1% (Table 5).

A few patients were readmitted to the Cardiology ward in our hospital with symptoms of heart failure in the years following their operation. We recorded a total of 27 readmissions (4%) in the NFHG group and 25 (13%) in the LFLG group ($P=0.001$). Five patients (3 in the NFHG group and 2 in the LFLG group, $P=0.31$) were treated for prosthetic endocarditis.

The analysis of postoperative echocardiograms in the TLFLG AS group demonstrated that 74% of the patients had an improvement on their LVEF, from poor to fair (36%) or poor to good (38%).

DISCUSSION

Patients with LFLG AS, and especially those with TLFLG AS, have higher mortality than those with NFHG AS [6–13]. Our cohort demonstrated remarkably low in-hospital mortality which increased in the mid-term consistent with previous reports. The fact that we did not identify any predictors of mortality was not surprising given the low in-hospital mortality rate in our cohort.

Patients who survive the operation have significant improvement in their symptoms, as previously described [3, 4]. On the other hand, it was already known from previous reports that the prognosis of LFLG AS with medical treatment is poor [3, 4, 14–17]. Therefore, our data, although purely observational, suggest that AVR is a valid option for patients with LFLG AS as it offers better prognosis and quality of life.

Patients in the LFLG AS group were significantly older than those in the NFHG group (71.5 ± 9.7 vs 68.7 ± 10.8 years, $P=0.01$). This may be due to a delay in the diagnosis by the referring cardiologists or general physicians. A better understanding of the severity of the AS, especially for those with PLFLG, and an earlier surgical referral might contribute towards a better long-term survival given the fact that, in our cohort, age was related to an increased risk of long-term mortality.

In our cohort, there was no significant difference in the logistic EuroSCORE characteristics between the two groups although the in-hospital mortality for the LFLG AS group was higher, but this did not reach statistical significance (2 vs 1%, $P=0.13$). This may be due to the small number of cases in the study group compared with the NFHG group.

We have not found any relationship between the size of the valve implanted and both in-hospital and mid-term mortality, not even for sizes of valves below 21 mm. In our unit, we started our transcatheter aortic valve implantation (TAVI) programme in 2009 but we have not used this procedure for LFLG patients as yet. We have noticed that the average sizes of valves deployed with TAVI at our centre are 23 mm for females and 26 mm for males. This is not any different from the sizes of the valves used surgically in our study group. However, it is known that TAVI valve prostheses have larger valve area and lower gradients in comparable sizes. Therefore, there is potential haemodynamic benefit if TAVI is used in this group of patients, which could make a positive impact on ventricular remodelling with potential clinical benefits. However, some of these benefits may be counterbalanced by the effect of paravalvular leak which is much higher in TAVI procedures.

Furthermore, the new technology of sutureless valves, which have similar haemodynamics to TAVI prostheses, may give similar potential benefits for this group of patients especially with the fact that paravalvular leak in sutureless valves is lower than in TAVI procedures. Future studies are needed to confirm these potential benefits.

As mentioned earlier, there was significant improvement in the ventricular function of TLFLG patients as assessed by postoperative

echocardiography (74% of the patients had an improvement on their LVEF, from poor to fair (36%) or to good (38%)), which was also reflected in clinical improvement in the patients' functional class. This gives reassurance that surgical intervention for this group of patients was significantly beneficial.

The current ACA/AHA guidelines recommend AVR for symptomatic patients with TLFLG AS (Class IIa, Level B), while the ESC/EACTS recommend AVR (Class IIa, Level C) only in patients with LV contractile reserve, but clearly there is still uncertainty regarding which subsets benefit from surgery and the exact timings and thresholds for intervention [1, 2]. For the PLFLG AS, the ACA/AHA and ESC/EACTS guidelines recommend AVR for symptomatic patients (Class IIa, Level C) only if the clinical, anatomical and haemodynamic data support valve stenosis as the most likely cause of the symptoms [1, 2].

Although it was initially debated whether PLFLG AS was a stage in between moderate to severe AS, there are data to suggest that it is actually a distinct condition and not a stage in the evolution of NFHG AS. The degree of systolic myocardial dysfunction would explain the higher mortality compared with that of NFHG AS [16–20].

Once diagnosed, progression of AS is inexorable, albeit rates of progression being highly variable between individuals as reported by Tribouilloy *et al.* [21].

Again, these patients have a better prognosis if treated surgically although they have a higher operative risk given their intrinsic myocardial dysfunction and the increasing risk of having a mismatch due to their small ventricular cavity resulting from severe hypertrophy [3, 4].

On the basis of the Kaplan–Meier survival analysis in our cohort, we have demonstrated that PLFLG AS has an intermediate survival (9.3 ± 0.6 years, 95% CI 8.0–10.6) compared with NFHG (11.3 ± 0.3 years, 95% CI 7.7–9.6) and TLFLG AS (6.4 ± 0.7 years, 95% CI 5.0–7.9). As previously mentioned, there is significant average age difference between our two groups, indicating delayed diagnosis and referral for surgery. This may be a contributing factor for worse mid-term prognosis compared with NFHG. Therefore, a better understanding of this entity of AS and an earlier referral for surgical intervention may have an impact on the long-term outcome of these patients.

Our study has the limitations of being retrospective and purely observational. On the other hand, it is one of the largest series from a single unit of LFLG AS patients (and especially PLFLG AS) undergoing isolated AVR and specifically looking at short- and mid-term clinical outcomes.

CONCLUSION

We conclude from our series that the in-hospital mortality after isolated AVR in patients with LFLG AS can be acceptable and comparable with NFHG AS. However, as previously published, our series confirm that this group of patients have a significantly higher mid-term mortality after AVR compared with NFHG AS.

We suggest that AVR is worth offering to patients with LFLG AS based on the significant symptomatic improvement in survivors and on the poor outcome of those treated conservatively.

PLFLG AS seems to have an intermediate prognosis between TLFLG AS and NFHG AS. Early diagnosis and referral for surgery might improve the surgical outcome for these patients, but definite answers will require multicentre randomized studies.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

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Dr A. de Souza (London, UK): Your in-depth analysis of low-flow, low-gradient aortic stenosis by dividing them into classical and paradoxical types and relating to their early mortality and median term outcome is interesting. The findings of your study confirm what the surgical community knows, that relief of aortic stenosis by surgical aortic valve replacement improves patients' symptoms and survival. The area of low flow, low gradient remains controversial and the best treatment for them continues to be explored.

The in-depth analysis of your group showed that the patients with low-flow, low-gradient aortic stenosis was significantly older, usually by about 3 years, which leads me to my first question, as to whether these patients were followed up longer by the cardiologist, before referral and eventual surgery, rendering the myocardium more damaged by the aortic stenosis? Was the BNP measured in these cases to determine if the myocardium had deteriorated before surgery?

Dr Lopez: To answer your first question, absolutely, there is a considerable delay of these patients by their cardiologists. I think this will be improved when the knowledge of this pathology is extended. Also, we don't know exactly how much they are delayed, because we only know the patients since they are referred. But depending also on the referring cardiologist, the delay will be longer or shorter and will be a nice thing to monitor.

Regarding the BNP, we, as surgeons, do not record that on admission or postoperatively and again, the cardiologists, I don't think that they do it routinely either. I think that only one or two cardiologists do it, so there is no data about that for our population.

Dr de Souza: My second question relates to the higher mortality in the low-flow, low-gradient group at follow-up of 27.8% for low-flow group and 16% for the normal follow-up group at 5 years. And your further sub-analysis shows a further significant difference between the true low-flow mortality of 42% at 5 years compared to 20% in the paradoxical low-flow group. Do you have the causes of death for these patients, whether they were a result of arrhythmias or heart failure? Do you have any data on the size of valves inserted for these patients, leading to the question of whether a percutaneous valve replacement may render a valve with a larger effective orifice area which may in turn lead to better long-term survival? I'm obviously postulating.

Dr Lopez: Answering your first question, at the moment we only have the causes of the patients who died in the hospital, which is about 35% of the study cohort and of them, 10% died of cardiac cause related. We are still awaiting the rest of the information to be confirmed by the national statistical service, so we hope that we can implement that on the paper which will follow this presentation.

Regarding the second question, size of the valves, we have a very broad spectrum, from 18- to 32-mm valve, with the even sizes being an ATS valve, although 90% of the sizes will be in between 21 and 27 mm. We didn't find any correlation in between the size of the valve and the in-hospital or long-term mortality, not even for the lower sizes.

Dr J. Ennker (Siegburg, Germany): I have one question. Did you try to better the outcome of the low-flow, low-gradient group by employing a valve which leads to a larger effective valve orifice which leads to a laminar flow, and as also reported to have better survival in the literature, as a Medtronic Freestyle valve? What was the type of valve you employed in these patients?

Dr Lopez: The type of valve, as I said, it was variable. We used different branded valves or so, mechanical or biological. The size was variable in between 18 and 32 with 90% of them being in between 21 and 27 mm. We don't have data on the follow-up talking about remodelling of the ventricle and that will be an interesting study to follow. As I say, we haven't found any pace-makers in these patients, but we didn't look into detail into echocardiographic parameters in the long-term follow-up.

Dr Ennker: Well, I think it's interesting to have a look if a larger valve orifice leads to better survival with the stent less valve, for example.

5.2. SECOND ARTICLE

Outcome of isolated aortic valve replacement in patients with classic and paradoxical low-flow, low-gradient aortic stenosis

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5.2.1. ABSTRACT

OBJECTIVE: To analyze operative outcomes and mid-term results after isolated aortic valve replacement (AVR) in low-flow, low-gradient aortic stenosis (LFLG AS) by comparing the 2 subcategories (classic low-flow, low-gradient aortic stenosis [CLFLG] and paradoxical low-flow, low-gradient aortic stenosis [PLFLG]).

METHODS: This was a retrospective analysis of prospectively collected data for all

isolated AVR in LFLG AS performed in our center during the last 13 years (n = 198; CLFLG AS, n = 66, 33% and PLFLG AS, n = 132, 67%). Median follow-up was 3.7 ± 3.3 years.

RESULTS: Preoperative mean gradient was 30.2 ± 8.8 mm Hg in the CLFLG AS group and 31.4 ± 7.0 mmHg in the PLFLG AS group (p = 0.001). Female sex, hypertension, and neurologic and renal disease were more frequent in the PLFLG AS group (p < 0.01) whereas advanced New York Heart Association class, atrial fibrillation, and pulmonary hypertension were more frequent in the CLFLG AS group (p < 0.01). In-hospital mortality was 3% in the CLFLG AS group and 2.3% in the PLFLG AS group, p = 0.08. One- and five-year mortality rates were significantly greater in the CLFLG AS group (27% and 42% vs. 6% and 20% in the PLFLG AS group, respectively, p = 0.001). On follow-up, 90% of the total survivors were in New York Heart Association class I-II, and 51% of the patients in the CLFLG AS group had an improvement in their ventricular function.

CONCLUSIONS: AVR can be performed in LFLG AS with low in-hospital mortality. CLFLG AS carries similar in-hospital mortality to PLFLG AS but greater mid-term mortality. Surgery provided excellent functional status among survivors.

5.2.2. FULL ORIGINAL TEXT

Outcome of isolated aortic valve replacement in patients with classic and paradoxical low-flow, low-gradient aortic stenosis



Ana Lopez-Marco, MD,^a Harriet Miller, BMSc,^a Pankaj Kumar, MD,^a Saeed Ashraf, MD,^a Afzal Zaidi, MD,^a Farah Bhatti, MD,^a Adrian Ionescu, MD,^b and Aprim Youhana, MD^a

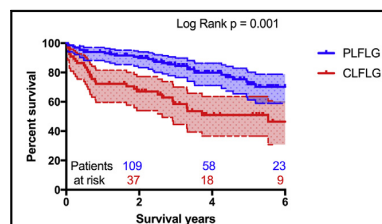
ABSTRACT

Objective: To analyze operative outcomes and mid-term results after isolated aortic valve replacement (AVR) in low-flow, low-gradient aortic stenosis (LFLG AS) by comparing the 2 subcategories (classic low-flow, low-gradient aortic stenosis [CLFLG] and paradoxical low-flow, low-gradient aortic stenosis [PLFLG]).

Methods: This was a retrospective analysis of prospectively collected data for all isolated AVR in LFLG AS performed in our center during the last 13 years (n = 198; CLFLG AS, n = 66, 33% and PLFLG AS, n = 132, 67%). Median follow-up was 3.7 ± 3.3 years.

Results: Preoperative mean gradient was 30.2 ± 8.8 mm Hg in the CLFLG AS group and 31.4 ± 7.0 mmHg in the PLFLG AS group (P = .001). Female sex, hypertension, and neurologic and renal disease were more frequent in the PLFLG AS group (P < .01) whereas advanced New York Heart Association class, atrial fibrillation, and pulmonary hypertension were more frequent in the CLFLG AS group (P < .01). In-hospital mortality was 3% in the CLFLG AS group and 2.3% in the PLFLG AS group, P = .08. One- and five-year mortality rates were significantly greater in the CLFLG AS group (27% and 42% vs 6% and 20% in the PLFLG AS group, respectively, P = .001). On follow-up, 90% of the total survivors were in New York Heart Association class I-II, and 51% of the patients in the CLFLG AS group had an improvement in their ventricular function.

Conclusions: AVR can be performed in LFLG AS with low in-hospital mortality. CLFLG AS carries similar in-hospital mortality to PLFLG AS but greater mid-term mortality. Surgery provided excellent functional status among survivors. (J Thorac Cardiovasc Surg 2017;154:435-42)



Kaplan-Meier survival curves of patients undergoing aortic valve replacement for LFLG AS or PLFLG AS performed with the log-rank test (P = .01). The number of patients at risk in each group at the different time frames also is provided. Median survival was 13.1 years (95% confidence interval 8.0-13.1) for the PLFLG group and 5.5 years (95% confidence interval 5.2-7.9) for the CLFLG group (P = .001).

Central Message

Aortic valve replacement provides good symptomatic relief and mid-term survival benefit and therefore, is worth offering to symptomatic patients with low-flow, low-gradient aortic stenosis who meet the current guidelines criteria for surgery.

Perspective

Low-flow, low-gradient aortic stenosis (LFLG AS) is becoming an increasingly complex concept. Aortic valve replacement is associated traditionally with a high mortality in patients with classic LFLG AS and is controversial in those with paradoxical LFLG AS. We report in-hospital and mid-term mortality for both LFLG AS groups and the excellent functional status among survivors. Further studies are necessary to integrate the LFLG AS into the current guidelines.

See Editorial Commentary page 443.

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Since the introduction of low-flow, low-gradient aortic stenosis (LFLG AS), the prognosis and outcomes of these patients after aortic valve replacement (AVR) have generated

Scanning this QR code will take you to a supplemental video for the article.



Abbreviations and Acronyms

AS	= aortic stenosis
AVA	= aortic valve area
AVR	= aortic valve replacement
CI	= confidence interval
CLFLG AS	= classic low-flow, low-gradient aortic stenosis
DSE	= dobutamine stress echocardiogram
LFLG AS	= low-flow, low-gradient aortic stenosis
LVEF	= left ventricular ejection fraction
NFHG AS	= normal-flow, high-gradient aortic stenosis
NYHA	= New York Heart Association
OR	= odds ratio
PLFLG AS	= paradoxical low-flow, low-gradient aortic stenosis
SVi	= stroke volume index
TAVI	= transcatheter aortic valve implantation

increasing interest in the literature. It is estimated that 30% of patients in whom the aortic valve area (AVA) meets the criteria of severe aortic stenosis (AS) have transvalvular gradients in the range of moderate aortic stenosis (<40 mm Hg) due to a reduced transvalvular flow. This entity is known as LFLG AS and can be subdivided into 2 categories depending on the left ventricular ejection fraction (LVEF, Video 1).^{1,2}

The classical or true LFLG pattern is seen in patients with dilated left ventricles and reduced LVEF. The paradoxical LFLG pattern is present in patients with preserved LVEF and paradoxically low peak and mean transaortic gradients. They have reduced stroke volume index (SVi) values (<35 mL/m²) through a combination of mechanisms that include concentric remodeling, abnormal ventriculoaortic impedance, and abnormal longitudinal left ventricular (LV) function.¹⁻³

It is important to distinguish these cases from those with just moderate AS and nonrelated myocardial dysfunction as primary pathology (pseudo-severe AS). In this entity, the valve might appear stenotic as result of the inability of the ventricle to generate adequate force to fully open it. Dobutamine stress echocardiogram (DSE) is useful in differentiating between the two. In patients with severe AS, the inotropic effect of dobutamine increases the flow through a fixed valve orifice, resulting in increased peak velocities and hence the gradient, whereas in pseudo-severe AS the dobutamine inotropic effect improves opening of the valve, hence increasing the AVA by >0.2 cm²^{1,2}; therefore, the gradient does not increase.

The surgical mortality for patients with classic low-flow, low-gradient aortic stenosis (CLFLG AS) has decreased in



VIDEO 1. Dr Adrian Ionescu, Consultant Cardiologist in Morrilton Hospital, explains the physiopathology of LFLG AS and the main findings of our paper. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30418-X/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30418-X/addons).

recent decades; however, these patients continue to have a greater morbidity and mortality after AVR compared with patients with normal-flow, high-gradient aortic stenosis (NFHG AS).⁴⁻⁷ Patients with paradoxical low-flow, low-gradient aortic stenosis (PLFLG AS) have been reported to have a worse prognosis than those with moderate AS or severe NFHG AS, although they seem to have better prognosis after AVR than the patients with CLFLG AS.^{1,2}

The objective of the study was to determine the operative and mid-term outcomes of surgical intervention in the 2 LFLG AS subgroups in our unit. Therefore, we analyzed operative outcomes and mid-term results (clinical status and mortality) after isolated AVR in patients with CLFLG AS compared with PLFLG AS (Video 1).

MATERIALS AND METHODS**Patient Selection and Data Collection**

A retrospective analysis of prospective electronically collected data of all patients with AS who underwent isolated AVR in Morrilton Regional Cardiac Centre from January 2001 to April 2014 was performed. Preoperative characteristics, cardiovascular risk factors, postoperative complications, and in-hospital mortality were recorded prospectively in our database, Patients Administration and Tracking System.

All patients had a detailed preoperative echocardiography in our center to assess the severity of the AS (AVA and gradients) and to classify it into the 2 categories according to the LVEF. DSE was performed in 25% of the patients with CLFLG AS to confirm the diagnosis or to assess the myocardial reserve according to the referring cardiologist criteria.

TABLE 1. Preoperative characteristics

	Total	CLFLG non-matched	PLFLG non-matched	P value	CLFLG matched	PLFLG matched	P value
n	198	66	132		58	58	
Age, mean ± SD	71.5 ± 9.7	72.2 ± 8.9	71.2 ± 10.1	.26	72.0 ± 8.9	71.4 ± 9.7	.50
Female	91 (46%)	22 (33%)	69 (52%)	.04	21 (36%)	21 (36%)	.99
Angina CCS 3-4	73 (37%)	20 (30%)	53 (40%)	.001	17 (29%)	16 (27%)	.84
NYHA III-IV	107 (54%)	45 (68%)	62 (47%)	.01	37 (64%)	36 (62%)	.85
DM	43 (22%)	18 (27%)	25 (19%)	.001	14 (24%)	15 (26%)	.83
HT	128 (65%)	38 (58%)	90 (68%)	.01	32 (55%)	30 (52%)	.71
Ex-smoker	87 (44%)	35 (53%)	52 (39%)	.01	31 (53%)	24 (41%)	.37
Previous MI	35 (18%)	11 (17%)	24 (18%)	.23	10 (17%)	8 (14%)	.61
Dialysis	3 (1%)	0	3 (2%)	.01	0	0	N/A
COPD	38 (19%)	16 (24%)	22 (17%)	.002	13 (22%)	10 (17%)	.48
CVA	5 (2%)	1 (1%)	4 (3%)	.02	1 (2%)	1 (2%)	.99
PVD	15 (8%)	5 (8%)	10 (8%)	.06	4 (7%)	4 (7%)	.99
AF	28 (14%)	16 (24%)	12 (9%)	.001	12 (21%)	10 (17%)	.64
Logistic EuroSCORE, median ± IQR	6.9 ± 10	13.5 ± 15	5.1 ± 6	.001	13.9 ± 15	4.6 ± 6	.18

Preoperative characteristics in patients undergoing isolated aortic valve replacement for severe aortic stenosis in different groups. CLFLG, Classic low-flow, low-gradient; PLFLG, paradoxical low-flow, low-gradient; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; DM, diabetes mellitus; HT, hypertension; MI, myocardial infarction; N/A, not available; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PVD, peripheral vascular disease; AF, atrial fibrillation; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

The low-dose protocol with an increasing infusion of dobutamine starting at 5 µg/kg/min to a final dose of 20 µg/kg/min was used. Atropine was required in some of the cases to reach the targeted heart rate. All DSEs performed were considered optimal and all demonstrated myocardial reserve before surgery. We do not use multidetector computed tomography in our center for routine assessment of these patients.

Indications for AVR were established by the operating surgeon and the referring cardiologist in the preoperative clinic visits and were made on the basis of a combination of the symptomatic status of the patient and degree of aortic stenosis (Tables 1 and 2) according to the current guidelines.

Mid-term follow-up consisted of routine clinic visits annually from 6 weeks of discharge or clinical letters from cardiologist on those who were discharged from our follow-up. We also performed telephone interviews of those patients who were not seen by any specialist in the previous year to determine survival and functional class. The follow-up results described in the study were obtained from January to July 2015 by 1 of the 2 methods described previously.

Postoperative echocardiograms were performed at the clinic visits at 6 weeks after discharge for all patients and then annually for those who remained on our follow-up system. For this analysis we have used the last postoperative echocardiogram available for each patient (a generalized linear mixed model was used to compare them with the preoperative echocardiograms). LVEF, AVA, and gradients were recorded.

The data used in this study were approved by the institutional review board, which deemed an individual consent form was not needed because no patient-identifiable information was used.

For this study, we identified 2 groups: (1) CLFLG AS: classical LFLG AS with reduced LVEF (n = 66, 33%); and (2) PLFLG AS: paradoxical LFLG AS with normal LVEF (n = 132, 67%)

Statistical Methods

Continuous variables are expressed as mean ± standard deviation or median ± interquartile range (depending on distribution of data), and comparison between groups was performed with the *t* test/Mann-Whitney *U* test. Categorical variables are expressed as percentages and compared by the use of χ^2 /Fisher exact test as appropriate.

A multiple logistic regression model was used to identify the predictors of early mortality and Cox regression was applied to identify the best predictors of late mortality including all the significant variables listed in annexed tables (cut-off at *P* < .05) (Tables 1-4). The results were expressed as odds ratios (ORs) and hazard ratios with corresponding 95% confidence intervals (CIs).

Because the 2 groups were significantly different with respect to their baseline characteristics, propensity score matching (with a match tolerance of 0.05) was performed (including the preoperative characteristic except echocardiographic parameters) using SPSS 22.0 (IBM Corp, Armonk,

TABLE 2. Preoperative echocardiographic characteristics

	Total	CLFLG non-matched	PLFLG non-matched	P value	CLFLG matched	PLFLG matched	P value
n	198	66	132		58	58	
Mean gradient	31.2 ± 7.4	30.2 ± 8.8	31.4 ± 7.0	.001	30.2 ± 7.6	31.0 ± 8.3	.43
AVA	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	.001	0.7 ± 0.2	0.8 ± 0.2	.65
Poor LVEF	26 (13)	26 (39%)	0	.001	22 (38%)	0	.001
Fair LVEF	40	40 (61%)	0	.001	36 (62%)	0	.001
Good LVEF	132 (67%)	0	132 (100%)	.001	0	58 (100%)	.001
SVi, mL/m	29.5 ± 5.1	27.2 ± 6.9	30.3 ± 3.9	.02	26.9 ± 7.2	30.1 ± 3.9	.18
Pulmonary HT	9	7	2	.001	6 (10%)	0	.001

Preoperative echocardiographic characteristics in patients undergoing aortic valve replacement for severe aortic stenosis in different groups. CLFLG, Classic low-flow, low-gradient; PAP, pulmonary artery pressure (PAP > 55 mm Hg); PLFLG, paradoxical low-flow, low-gradient; AVA, aortic valve area (cm²); LVEF, left ventricular ejection fraction; SVi, stroke volume index; Pulmonary HT, pulmonary hypertension.

TABLE 3. Type and sizes of prosthesis used for the aortic valve replacement

	Total	CLFLG	PLFLG	P value
Mechanical	23 (12%)	4 (6%)	19 (14%)	.001
Biological	175 (88%)	62 (94%)	113 (86%)	.001
Pericardial	166 (84%)	60 (91%)	106 (80%)	.001
Porcine	9 (4%)	2 (3%)	7 (6%)	.001
19 mm	5 (2%)	3 (4%)	2 (1%)	.07
21-22 mm	51 (26%)	12 (18%)	39 (29%)	.07
23-24 mm	69 (35%)	24 (36%)	45 (34%)	.11
25-26 mm	55 (28%)	19 (29%)	36% (28%)	.11
27-28 mm	16 (8%)	7 (11%)	9 (7%)	.11
29 mm	2 (1%)	1 (1%)	1 (1%)	.27

Type of prosthesis used in the aortic valve replacement are listed. CLFLG, Classic low-flow, low-gradient; PLFLG, paradoxical low-flow, low-gradient.

NY). The matched groups were analyzed via the methods described previously.

A Kaplan-Meier survival analysis was done, building curves for the groups, which were compared by the log-rank statistic.

Follow-up results (New York Heart Association [NYHA] class and LVEF) were compared with their respective preoperative values and to assess the patterns of the repeated measures a generalized mixed model was fitted with LFLG, follow-up time (months for LVEF and years for NYHA class changes), and LFLG-by-time interaction as covariates. A coefficient estimated was considered statistically significant if its *P* value (2-sided) was <.05. SPSS 22.0, STATA 12 (StataCorp, College Station, Tex), and Prism 7 (GraphPad Software, Inc, La Jolla, Calif) were used to analyze the data.

Definitions

NFHG AS was defined as AVA <1.0 cm²/indexed AVA <0.6 cm², mean transvalvular gradient >40 mm Hg, SVi >35 mL/m², variable LVEF. LFLG AS was defined as AVA <1.0 cm²/indexed AVA <0.6 cm², mean transvalvular gradient <40 mm Hg, SVi <35 mL/m², variable LVEF. After DSE, AVA remains <1.0 cm², mean gradient increases >40 mm Hg. CLFLG AS was defined as AVA <1.0 cm²/indexed AVA <0.6 cm², mean transvalvular gradient <40 mm Hg, SVi <35 mL/m², impaired LVEF. PLFLG AS was defined as AVA <1.0 cm²/indexed AVA <0.6 cm², mean transvalvular gradient <40 mm Hg, SVi <35 mL/m², preserved LVEF. Pseudo-severe AS was defined as AVA <1.0 cm², mean transvalvular gradient <40 mm Hg, SVi <35 mL/m², impaired LVEF. After DSE, AVA >1.0 cm², mean gradient remains <40 mmHg. Pulmonary hypertension was defined as pulmonary artery pressure >50 mm Hg measured by echocardiography. Severe ventricular dysfunction was defined as LVEF <30%, moderate

ventricular dysfunction was defined as LVEF 30% to 50%, and normal ventricular dysfunction was defined as LVEF >50%. Previous neurologic disease was defined as cerebrovascular accident or transient ischemic attack diagnosed before the operation, with or without residual deficits. Postoperative neurologic events was defined as new focal deficit after surgery; either transient ischemic attack or cerebrovascular accident. Long-term ventilation was defined as postoperative ventilation for more than 7 days, including reintubation or tracheostomy. Respiratory complications were defined as acute distress respiratory syndrome or pneumonia during the postoperative period. Finally, gastrointestinal complications were defined as bowel ischemia, bleeding, or laparotomy for any cause during the postoperative period.

RESULTS

We identified 198 patients who fulfilled the inclusion criteria, 66 of them in the CLFLG AS group and 132 patients in the PLFLG AS group. A propensity-matched analysis was done to compare the groups, reducing the cohort to 116 patients (58 in each group).

Patients with CLFLG AS presented with greater functional NYHA class III-IV, a greater incidence of permanent atrial fibrillation, and pulmonary hypertension (Table 1). In contrast, in the PLFLG AS group, there were more female patients, a greater incidence of systemic hypertension, previous neurologic events, and chronic

TABLE 4. Postoperative complications

	Total	CLFLG non-matched	PLFLG non-matched	P value	CLFLG matched	PLFLG matched	P value
n	198	66	132		58	58	
IABP	1 (1%)	1 (1%)	0	.42	1 (2%)	0	.31
Reoperation bleeding	8 (4%)	3 (4%)	5 (4%)	.96	3 (5%)	4 (3%)	.69
Hemofiltration	8 (4%)	2 (3%)	6 (4%)	.22	1 (2%)	2 (1%)	.56
Neurologic	0	0	0	.74	0	0	n/a
Prolonged ventilation	4 (2%)	4 (6%)	0	.001	3 (5%)	0	.08
ARDS	2 (1%)	2 (3%)	0	.01	2 (3%)	0	.15
GI complications	4 (2%)	0	4 (3%)	.37	0	3 (2%)	.08
In-hospital mortality	5 (2%)	2 (3%)	3 (2%)	.08	3 (5%)	0	.08
1-y survival	164 (86%)	44 (71%)	120 (94%)	.001	40 (71%)	54 (96%)	.002
5-y survival	59 (52%)	16 (36%)	43 (61%)	.001	13 (34%)	10 (42%)	.02

Postoperative outcomes in patients undergoing isolated aortic valve replacement for aortic stenosis in different groups. CLFLG, Classic low-flow, low-gradient; PLFLG, paradoxical low-flow, low-gradient; IABP, intra-aortic balloon pump; ARDS, adult respiratory distress syndrome; GI, gastrointestinal.

renal failure on hemodialysis. Presentation in CCS class III-IV angina also was more common in this group (Table 1).

Median logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 13.5 (Q1 5.5, Q3 20.4) in the CLFLG AS group and 5.1 (Q1 3.3, Q3 9.1) in the PLFLG AS group ($P = .001$) (Table 1). After the propensity score matching, the incidence of these preoperative characteristics was equivalent in the 2 groups (Table 1).

Echocardiographic analysis showed greater mean gradients in the PLFLG AS group but smaller AVA in the CLFLG AS group. Pulmonary hypertension was significantly more common in the CLFLG AS group. As per definition, all the patients in the PLFLG AS group had a preserved LVEF, whereas those in the CLFLG AS had an impaired LVEF (moderate 61%, severe 39%) (Table 2).

The propensity score matching did not include the LVEF category as this defines the 2 groups. Pulmonary hypertension remained more frequent in the CLFLG group after the matching (Table 2).

The choice of prosthesis used for the AVR was based on patients and surgeons' preferences. 88% had a stented bioprosthesis and 12% a bileaflet mechanical prosthesis. Choice of mechanical prosthesis was significantly greater in the PLFLG AS group (Table 3).

Prosthesis sizes varied from 18 to 32 mm (97% between 21 and 27 mm). Enlargement of the aortic root with a pericardial patch to implant a bigger valve was performed in 6% of the patients. Size 19 mm was used more frequently in the CLFLG AS group. A total of 56 patients (28%) received a valve sized <23 mm (41 patients in the PLFLG AS group and 15 patients in the CLFLG AS group). In-hospital mortality for these patients was 4% (2 patients, both in the CLFLG AS group, $P = .06$) and 23% during the follow-up (13 patients, 5 in the CLFLG AS and 8 in the PLFLG AS group, $P = .58$) (Table 4). There were no significant differences on the aortic crossclamp and cardiopulmonary bypass times between the 2 groups.

Overall in-hospital mortality for all LFLG patients who underwent isolated AVR was 2% (5 deaths), categorized as follows: 1 death (20%) was cardiac related and 4 deaths (80%) secondary to sepsis. In-hospital mortality was 3% in the CLFLG AS group compared with 2% in the PLFLG AS ($P = .08$). In the matched cohort, all in-hospital deaths (3 patients, 3%) occurred in the CLFLG group ($P = .08$) (Table 4).

Postoperative respiratory complications were greater in the CLFLG AS group. These patients had a greater rate of mortality, with 2 of them dying in the hospital. The greater incidence of respiratory complications for the CLFLG group was maintained in the matched cohort (Table 4).

We did not identify any preoperative characteristics as risk factor for in-hospital mortality in any of the groups in the univariable analysis ($P < .05$), not even in the matched

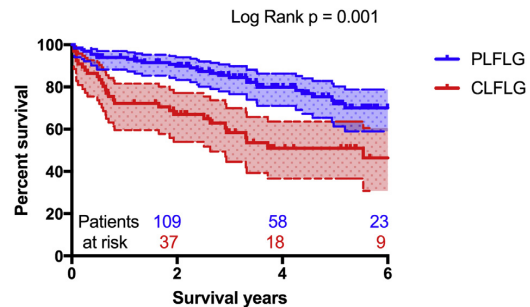


FIGURE 1. Kaplan-Meier survival curve. Kaplan-Meier survival curves of patients undergoing aortic valve replacement for CLFLG AS or PLFLG AS performed with the log-rank test ($P = .001$). Number of patients at risk in each group at the different time frames also is provided. PLFLG AS, Paradoxical low-flow, low-gradient aortic stenosis; CLFLG AS, classic low-flow, low-gradient aortic stenosis.

population, and therefore it was not possible to apply a logistic regression that included all the significant risks factors at the univariable analysis. This was explained by the insufficient events to detect predictors due to the low in-hospital mortality rate for the cohort.

Late Outcomes

Follow-up was up to 13 years, with a median of 3.7 ± 3.3 years (range 0.1-13.0 years). There were only 3 patients lost to follow-up (2%). Overall 1-year mortality was 14%. It was significantly greater in the CLFLG AS group (29% vs 6% in the PLFLG AS, $P = .01$). At 5 years, overall mortality was 48%. It also was greater in the CLFLG AS group (64% vs 39%, $P = .001$). These differences persisted in the matched cohort (Table 4, Figures 1 and 2).

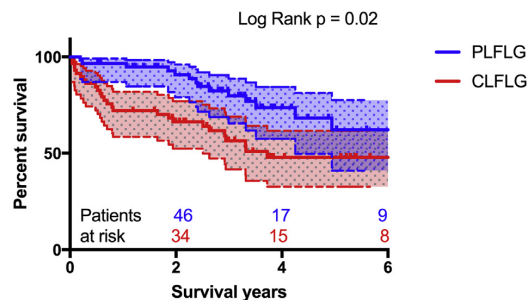


FIGURE 2. Kaplan-Meier survival curve for the matched cohort. Kaplan-Meier survival curves of patients undergoing aortic valve replacement for CLFLG AS or PLFLG AS in the matched cohort performed with the log-rank test ($P = .02$). Number of patients at risk in each group at the different time frames also is provided. PLFLG AS, Paradoxical low-flow, low-gradient aortic stenosis; CLFLG AS, classic low-flow, low-gradient aortic stenosis.

Median survival calculated according to Kaplan-Meier analysis was 13.1 years (95% confidence interval [CI], 8.0-13.1) for the PLFLG group and 5.5 years (95% CI, 5.2-7.9) for the CLFLG group ($P = .001$) (Figure 1). In the matched cohort, the median survival for the PLFLG group was 8.3 years (95% CI, 3.5-13.2) and 3.7 years (95% CI, 1.2-4.2) for the CLFLG group ($P = .02$) (Figure 2).

A total of 58 patients (29%) died during the follow-up. Causes of death were categorized as follows: 14 (24%) were cardiac related, 6 (10%) were due to cancer, 9 (15%) were secondary to stroke, 2 (4%) were due to respiratory problems, 3 (6%) were due to renal disease, 1 (2%) was due to sepsis, and 9 (15%) were due to other causes. We were not able to identify the cause of death in 14 patients (24%).

For the whole cohort, Cox regression identified as risk factors for late mortality CLFLG AS ($P = .001$, OR; 2.5, 95% CI, 1.5-4.2) and previous myocardial infarction ($P = .001$, OR, 2.6; 95% CI, 1.3-5.1). Chronic renal failure with previous hemofiltration was identified by Cox regression as a risk factor for late mortality in the PLFLG group ($P = .004$, OR, 1.2; 95% CI, 0.1-0.5). No preoperative characteristics were identified as predictors for late mortality in the CLFLG group by Cox regression despite including the preoperative characteristics that were significant in the univariable analysis (female sex, $P < .05$).

We were not able to identify any predictors of late mortality in the matched cohort, because none of the preoperative characteristics were significant in the univariable analysis.

Clinical status was excellent in those patients who survived. Among the survivors at follow-up, 90% were found to be in NYHA functional class I-II and only 10% (14 patients, 6 in the CLFLG AS group and 8 in the PLFLG AS group) were in NYHA class III. Therefore, AVR provided efficient symptomatic relief, as 68% of the patients in the CLFLG group and 47% in the PLFLG group presented in NYHA class III-IV. The generalized linear mixed model was used to assess the relationships of NYHA class with LFLG over the follow-up time (median 1.8 ± 3.2 years, range 0.1-1.7 years). The odds of the symptomatic NYHA decreased by 38% in the CLFLG group per year (OR, 0.62; 95% CI, 0.3-1.3; $P > .05$) and by 32% (OR, 0.68; 95% CI, 0.5-0.9, $P = .006$) in the PLFLG group per year.

Twenty patients (14%) were in atrial fibrillation and 2% in paced rhythm. The incidence of stroke was 1%, all of whom were in the CLFLG AS group.

A few patients were readmitted to the cardiology ward in our hospital with symptoms of heart failure in the years after their operation. We recorded a total of 25 readmissions (13%), 18 of them (72%) in the CLFLG group ($P = .001$). Two patients were treated for prosthetic

endocarditis. We did not find any relationship between the readmissions and the size of the implanted valve.

The analysis of postoperative echocardiograms demonstrated no differences in the postoperative valve gradients or area (CLFLG AS: mean gradient 9.8 ± 3.2 mm Hg, AVA 1.6 ± 0.7 cm²; PLFLG AS: mean gradient 10.4 ± 5.5 mm Hg, AVA 1.5 ± 0.5 cm²). No cases of patient-prosthesis mismatch were seen in our cohort, not even for the 19 mm size implanted.

The ventricular function remained preserved in 81% of the PLFLG AS group, and 51% of the patients in the CLFLG AS group had an improvement in their LVEF, from severe to moderate dysfunction (13%) or to normal function (11%) and from moderate dysfunction to normal function (27%). A generalized linear mixed model was used to assess the relationships of LVEF with LFLG over the follow-up time (median 6 ± 11 months, range 1-120 months). The odds of LVEF improvement in the CLFLG group increased by 4.5% per month (OR, 1.04; 95% CI, 0.9-1.1; $P > .05$).

DISCUSSION

It is well established in previous reports that patients with LFLG AS, especially those with CLFLG AS, have poor quality of life and very high mortality (as high as 70%-80% at 3 years) with medical treatment.^{1,2,8-11} In our series we demonstrated remarkably low in-hospital postoperative mortality.^{5,7,12} However, we had high mid-term mortality, especially for the CLFLG AS, consistent with previous reports.^{4-7,12-15} The fact that we did not identify any predictors of in-hospital mortality was not surprising, given the low in-hospital mortality rate in our cohort. We confirmed a significant improvement in symptoms and quality of life among survivors.^{1,2} Therefore our data, although obtained from a purely observational and retrospective study, suggests that AVR offers both prognostic and symptomatic benefits in both subgroups of LFLG AS. We therefore suggest AVR should be offered for patients with symptomatic LFLG AS.

The significant difference in the logistic EuroSCORE between the groups was not surprising, based on the different preoperative characteristics. These differences were reflected in a greater in-hospital and mid-term mortality rate for the CLFLG AS. Despite eliminating the preoperative differences by performing a matched analysis both in-hospital and long-term differences in mortality were maintained.

We have not performed transcatheter aortic valve implantation (TAVI) for patients with LFLG AS yet (although we started the program in 2009), and therefore we cannot assess the potential benefit that these patients would obtain based on the larger AVA and lower gradients that the TAVI prosthesis offers in comparable sizes. On the other hand, we have not found any relationship between the size of the

valve implanted and both in-hospital and long-term mortality, not even for sizes of valves <21 mm. Future studies are needed to confirm the potential benefits of TAVI as well as the use of sutureless prosthesis in this cohort of patients.

There was significant improvement in the ventricular function in patients with CLFLG as assessed by postoperative echocardiography, which also was reflected in clinical improvement in patients' functional class. This gives reassurance that surgical intervention for this group of patients was significantly beneficial.

Although it initially was debated whether PLFLG AS was a stage in the progression from moderate to severe AS, current data suggest that it is actually a distinct condition and not a stage in the evolution of NFHG AS. The intrinsic myocardial dysfunction, although not translated in LVEF impairment, may explain the greater mortality compared with the NFHG AS.^{10,11,16-23} These patients have a better prognosis if treated surgically, although they have a greater operative risk, given their intrinsic myocardial dysfunction and the increasing risk of having mismatch due to their small ventricular cavity resulting from severe hypertrophy.^{1,2}

Discrepancies among previous studies on PLFLG AS highlight the importance of the correct diagnosis of this entity, because any minimal measurement error on the diagnostic echocardiography could label wrongly a different entity of AS with a complete different prognosis and outcome after AVR (ie, moderate AS with underestimated SV and AVA or severe AS with underestimated gradient).²⁰ There is a role for multidetector computed tomography and quantification of valve calcification when the echocardiography is not conclusive.^{17,20-23}

Current American College of Cardiology/American Heart Association guidelines recommend AVR for symptomatic CLFLG AS (Class IIa, Level B) whereas the European Society of Cardiology/European Association for Cardio-Thoracic Surgery recommend AVR (Class IIa, Level C) in patients with LV contractile reserve. For the PLFLG AS, the Current American College of Cardiology/American Heart Association and ESC/European Association for Cardio-Thoracic Surgery guidelines recommend AVR for symptomatic patients (Class IIa, Level C) only if the clinical, anatomic and hemodynamic data support the valve stenosis as the most likely cause of the symptoms.^{24,25} There is still uncertainty regarding which subsets benefit from surgery and the exact timings and thresholds for intervention and hopefully better indications will be further addressed in the near future guidelines.

Our study has the limitations of being retrospective and purely observational. We did not have a control nonsurgical group; hence, we cannot formulate firm conclusions on the appropriateness of surgical treatment. Because we did not perform DSE in all patients with reduced EF, AS, and low gradients, the indication for AVR was based on one of the

following criteria: lack of an alternative pathology to explain symptoms, morphologic assessment by computed tomography or transesophageal echocardiography, and/or lack of evidence of mid-wall late gadolinium enhancement by cardiac magnetic resonance to suggest a dilated cardiomyopathy. However, we provide a large number of patients with LFLG AS (especially PLFLG AS) undergoing isolated AVR and specifically look at short- and mid-term clinical outcomes.

CONCLUSIONS

Isolated AVR in LFLG AS can be performed with acceptable surgical mortality, comparable with that observed in patients with NFHG AS. However, as previously published, our series confirm that this group of patients, especially the CLFLG group, has a significantly greater mid-term mortality after AVR compared with NFHG AS. In the absence of large randomized controlled studies we surmise that, based on the good functional class of survivors and the low in-hospital mortality, AVR can be offered to patients with LFLG AS (Video 1).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: aortic stenosis, low flow low gradient, aortic valve replacement, adult cardiac surgery

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6. DISCUSSION

6. DISCUSSION

For the analysis of NFHG AS vs. LFLG AS, we identified 846 patients, 648 of them in the NFHG AS group and 198 patients in the LFLG AS group.

Demographic and preoperative characteristics differed considerably between the LFLG AS and NFHG AS groups. Patients with LFLG AS were significantly older (71.5 ± 9.7 vs. 68.7 ± 10.8 years, $p = 0.01$), presented more often in CCS class III–IV angina and had higher risk factors for coronary artery disease such as hypertension and diabetes. COPD, previous neurological disease, chronic renal failure on haemodialysis, peripheral vascular disease and permanent atrial fibrillation were also significantly more frequent in the LFLG AS group. Echocardiographic analysis confirmed more patients with poor left ventricular function and pulmonary hypertension in the LFLG AS group. These differences were reflected on a higher mean EuroSCORE for the LFLG AS group (10.3 ± 10.4 vs. 7.3 ± 6.5 for the NFHG AS group), although this difference was not statistically significant ($p = 0.14$), possibly due to the different size of the two groups.

Operative management was equivalent in the two groups, with the choice of prosthesis used based mainly on patients' and surgeons' preferences or governed by existence of clinical conditions preventing them from being on Warfarin safely. A total of 614 patients (73%) had a bioprosthesis (67% pericardial and 6% porcine) and 232 patients (27%) received a mechanical prosthesis. The sizes used varied from 18 to 32 mm, with 90% of them between 21 and 27 mm. We did not find any

relation between the size of the valve and late mortality, not even for sizes below 21 mm. Aortic cross-clamp and cardiopulmonary bypass times did not differ between groups.

Overall in-hospital mortality rate was 1% (12 deaths), 5 deaths (42%) being cardiac related, 3 deaths (25%) secondary to sepsis, 2 (17%) to neurological complications, 1 death (8%) due to respiratory complications and another 1 due to GI complications (8%). The in-hospital mortality rate was equivalent in the two groups (2% in the LFLG AS vs. 1% in NFHG AS, $p = 0.13$). Postoperative complications were also similar in both groups.

The median follow-up was 5.8 ± 4.2 years (range 0.5–17.2 years). There were 126 patients lost to follow-up (15%); majority of them were in the NFHG AS group (123 patients) with only 3 patients lost in the LFLG group.

Overall 1-year mortality rate was 6% for the whole study group. It was higher in the LFLG AS group (13 vs. 4% for NFHG AS, $p = 0.01$). At 5 years, the overall mortality rate was 19%. It was also higher in the LFLG AS group (28 vs. 16%, $p = 0.01$).

Mean survival calculated according to Kaplan–Meier analysis was 11.3 ± 0.3 years (95% CI 10.7–11.8) in the NFHG group and 8.6 ± 0.5 years (95% CI 7.7–9.6) in the LFLG group ($p = 0.001$).

A total of 262 patients (31%) died during the follow-up. Causes of death were categorized as follows: 59 patients (22%) being cardiac related, 35 patients

(13%) due to cancer, 21 patients (8%) secondary to stroke, 21 patients (8%) due to respiratory problems, 11 patients (4%) due to renal disease, 11 patients (4%) due to sepsis and 54 patients (21%) due to other causes. We were not able to identify the cause of death in 52 patients (20%).

Clinical status was excellent in those patients who survived. Among the LFLG AS survivors at follow-up, 88% were found to be in NYHA functional class I–II and only 10% (14 patients) were in NYHA class III. Twenty patients in this group (14%) were in atrial fibrillation and 2% in paced rhythm. The incidence rate of stroke during the follow-up period was 1%.

A few patients were readmitted to the Cardiology ward in our hospital with symptoms of heart failure in the years following their operation. We recorded a total of 27 readmissions (4%) in the NFHG group and 25 (13%) in the LFLG group ($p = 0.001$). Five patients (3 in the NFHG group and 2 in the LFLG group, $p = 0.31$) were treated for prosthetic endocarditis.

The analysis of follow-up postoperative echocardiograms in the TLFLG AS group demonstrated that 74% of the patients had an improvement on their LVEF, from poor to fair (36%) or poor to good (38%).

To summarize, despite the different preoperative demographic characteristics and cardiovascular risk factors that reflected in a greater Logistic EuroSCORE for the LFLG AS group, these patients had similar operative outcomes following AVR, with an equivalent in-hospital mortality and post-operative complications to the

NFHG AS group. We did not identify any predictors for in-hospital mortality, possibly due to the low in-hospital mortality found in our series. These results of equivalent in-hospital mortality after AVR for LFLG AS compared to NFHG AS differ from previous literature reports, where LFLG AS had been reported as to have higher in-hospital mortality after AVR, in some reports as high as 33%. [9]

However, as expected from previous literature reports, patients with LFLG AS, in our study, had a reduced mid-term survival compared to NFHG AS patients, but those who survived remained in an excellent functional class.

For the analysis of the LFLG AS subgroups we identified 198 patients, 66 of them in the CLFLG AS group and 132 patients in the PLFLG AS group.

In CLFLG AS group more patients presented with greater functional NYHA class III-IV, a greater incidence of permanent atrial fibrillation and pulmonary hypertension. In contrast, in the PLFLG AS group, there were more female patients, a greater incidence of systemic hypertension, previous neurologic events, chronic renal failure on hemodialysis and presentation in CCS class III-IV angina.

Echocardiographic analysis showed greater mean gradients in the PLFLG AS group but smaller AVA in the CLFLG AS group. Pulmonary hypertension was significantly more common in the CLFLG AS group. As per definition, all the patients in the PLFLG AS group had a preserved LVEF, whereas those in the CLFLG AS had an impaired LVEF (moderate 61%, severe 39%).

The difference in these preoperative demographic characteristics and other comorbidities was reflected in a significantly different median Logistic EuroSCORE (13.5 (Q1 5.5, Q3 20.4) in the CLFLG AS group and 5.1 (Q1 3.3, Q3 9.1) in the PLFLG AS group ($p = 0.001$)).

To make the two groups comparable we performed a propensity-matched analysis to compare the groups, reducing the cohort to 116 patients (58 in each group) but matching all the preoperative demographic and echocardiographic characteristics (excluding the LVEF category as this defines the LFLG AS groups). After the propensity matching, pulmonary hypertension remained more frequent in the CLFLG AS group.

Operative management was equivalent in the two groups, with the choice of prosthesis used based mainly on patients and surgeons' preferences or governed by existence of clinical conditions preventing them from being on Warfarin safely. A total of 175 patients (88%) received a stented bioprosthesis and 23 patients (12%) received a bileaflet mechanical prosthesis. Choice of mechanical prosthesis was significantly greater in the PLFLG AS group (14% vs. 6% in the CLFLG AS group, $p = 0.001$). Prosthesis sizes varied from 18 to 32 mm (97% between 21 and 27 mm). Size 19 mm was used more frequently in the CLFLG AS group.

Overall in-hospital mortality for all LFLG patients who underwent isolated AVR was 2% (5 deaths), categorized as follows: 1 death (20%) was cardiac related and 4 deaths (80%) secondary to sepsis. In-hospital mortality was 3% in the CLFLG AS group compared with 2% in the PLFLG AS ($p = 0.08$). In the matched cohort,

all in-hospital deaths (3 patients, 3%) occurred in the CLFLG group ($p = 0.08$).

Postoperative respiratory complications developed exclusively in the CLFLG AS group conferring a higher mortality in this group.

We did not identify any preoperative characteristics as predictors for in-hospital mortality in any of the groups. This was explained by the insufficient events to detect predictors due to the low in-hospital mortality rate for the cohort.

Follow-up was up to 13 years, with a median of 3.7 ± 3.3 years (range 0.1-13.0 years). There were only 3 patients lost to follow-up (2%). Overall 1-year mortality was 14%. It was significantly greater in the CLFLG AS group (29% vs. 6% in the PLFLG AS, $p = 0.01$). At 5 years, overall mortality was 48%. It also was greater in the CLFLG AS group (64% vs. 39%, $p = 0.001$). These differences persisted in the matched cohort.

Median survival calculated according to Kaplan-Meier analysis was 13.1 years (95% CI, 8.0 - 13.1) for the PLFLG group and 5.5 years (95% CI, 5.2 -7.9) for the CLFLG group ($p = 0.001$). In the matched cohort, the median survival for the PLFLG group was 8.3 years (95% CI, 3.5 - 13.2) and 3.7 years (95% CI, 1.2 - 4.2) for the CLFLG group ($p = 0.02$).

A total of 58 patients (29%) died during the follow-up. Causes of death were categorized as follows: 14 (24%) were cardiac related, 6 (10%) were due to cancer, 9 (15%) were secondary to stroke, 2 (4%) were due to respiratory problems, 3 (6%) were due to renal disease, 1 (2%) was due to sepsis, and 9 (15%) were due to other

causes. We were not able to identify the cause of death in 14 patients (24%).

For the whole cohort, Cox regression identified as risk factors for late mortality CLFLG AS ($p = 0.001$, OR; 2.5, 95% CI, 1.5-4.2) and previous myocardial infarction ($p = 0.001$, OR, 2.6; 95% CI, 1.3-5.1). Chronic renal failure with previous hemofiltration was identified by Cox regression as a risk factor for late mortality in the PLFLG group ($p = 0.004$, OR, 1.2; 95%, CI 0.1-0.5). No preoperative characteristics were identified as predictors for late mortality in the CLFLG group by Cox regression despite including the preoperative characteristics that were significant in the univariable analysis (female sex, $p < 0.05$).

We were not able to identify any predictors of late mortality in the matched cohort, because none of the preoperative characteristics were significant in the univariable analysis.

Clinical status was excellent in those patients who survived. Among the survivors at follow-up, 90% were found to be in NYHA functional class I-II and only 10% (14 patients, 6 in the CLFLG AS group and 8 in the PLFLG AS group) were in NYHA class III. Therefore, AVR provided excellent symptomatic relief, as 68% of the patients in the CLFLG group and 47% in the PLFLG group presented in NYHA class III-IV pre-operatively.

The generalized linear mixed model was used to assess the relationships of NYHA class with LFLG over the follow-up time (median 1.8 ± 3.2 years, range 0.1-1.7 years). The odds of the symptomatic NYHA decreased by 38% in the CLFLG group

per year (OR, 0.62; 95% CI, 0.3 - 1.3; $p > 0.05$) and by 32% (OR, 0.68; 95% CI, 0.5 -0.9, $p = 0.006$) in the PLFLG group per year.

Twenty patients (14%) were in atrial fibrillation and 2% in paced rhythm. The incidence of stroke during the follow-up period was 1%; all of these cases were in the CLFLG AS group.

A few patients were readmitted to the cardiology ward in our hospital with symptoms of heart failure in the years after their operation. We recorded a total of 25 readmissions (13%), 18 of them (72%) in the CLFLG group ($p = 0.001$). Two patients were treated for prosthetic endocarditis. We did not find any relationship between the readmissions and the size of the implanted valve.

The analysis of postoperative echocardiograms demonstrated no differences in the postoperative valve gradients or area (CLFLG AS: mean gradient 9.8 ± 3.2 mm Hg, AVA $1.6 \pm 0.7 \text{ cm}^2$; PLFLG AS: mean gradient 10.4 ± 5.5 mm Hg, AVA $1.5 \pm 0.5 \text{ cm}^2$). No cases of patient-prosthesis mismatch were seen in our cohort, not even for the 19 mm size implanted.

The ventricular function remained preserved in 81% of the PLFLG AS group, and 51% of the patients in the CLFLG AS group had an improvement in their LVEF, from severe to moderate dysfunction (13%) or to normal function (11%) and from moderate dysfunction to normal function (27%).

A generalized linear mixed model was used to assess the relationships of LVEF with LFLG over the follow-up time (median 6 ± 11 months, range 1- 120 months). The

odds of LVEF improvement in the CLFLG group increased by 4.5% per month (OR, 1.04; 95% CI, 0.9-1.1; $p > 0.05$).

In summary, as consistent with previous literature reports, we found that the patients with CLFLG AS had higher in-hospital mortality and postoperative morbidity after isolated AVR for AS than patients with PLFLG AS.

However, AVR provided efficient symptomatic relief, proven by the excellent functional class achieved during the mid-term follow-up in patients who survived the operation. The LVEF also improved considerably in patients with CLFLG AS and remained preserved in those with PLFLG AS years after the operation.

Natural history of AS has been broadly described and it is clearly established that AVR is the standard of treatment for severe symptomatic AS, with TAVI being currently accepted as an alternative for patients with high or prohibitive surgical risk [3-5, 21-24, 27].

Since the introduction of the definition of LFLG AS, this topic has generated a significant interest amongst clinicians dealing with this patients, especially the cardiologists, trying to understand the pathophysiology, improve the accuracy of the diagnosis and analyse the natural history of this subgroup of patients, who were initially only treated with medical therapy. This increased interest for this group of patients has resulted in many publications in the literature.

A thorough review by Pibarot and coworkers summarizes the current management of patients with LFLG AS. Low dose DSE is key for the diagnosis of these patients, not only to distinguish the entity from the Pseudo-severe AS, which has no surgical management, but also to determine the presence of flow reserve, which has important prognostic value. In cases where the DSE is not conclusive and especially for the PLFLG AS group, the MDCT has an important role for the confirmation of LFLG AS diagnosis [27].

Once the diagnosis of LFLG AS has been made and providing that the patient is symptomatic an intervention should be offered, supported by the poor prognosis of those with any other form of severe AS treated conservatively with medical management. Then, it is important to establish the life expectancy of the patient and to determine the surgical risk to decide which form of intervention is most suitable for these patients [27].

As in the high-risk NFHG AS patients, these patients should be discussed within the Heart Team in order to provide to them the best therapeutical option. If the patient has a life expectancy over a year and acceptable surgical risk, AVR should be offered, with TAVI reserved for those with high or prohibitive surgical risk. Only those with poor life expectancy (defined by the guidelines as less than a year) should be deemed for conservative management, meaning medical therapy and/or valvuloplasty [21-24, 27].

For the operative risk assessment, the classical factors to consider are: EuroSCORE II and/or STS score, general frailty, presence of other comorbidities such as poor

pulmonary function and advanced liver cirrhosis, porcelain aorta and previous cardiac operations, as it is done for the NFHG AS patients. However, patients with CLFLG AS would score more frequently as high risk due to their impaired LVEF. Other factors to consider in these patients are the presence of myocardial flow reserve, the preoperative mean gradient and the presence of marked reduced longitudinal strain, as all of them have been reported to increase considerably the surgical risk [27].

The presence or absence of flow reserve is also highlighted in the guidelines. Patients with CLFLG and flow reserve have a stronger indication (Class I Level C) than those without flow reserve (Class IIa Level C) [21-24]. However, it is well recognized that despite the higher surgical risk, these patients have better survival after AVR compared to medical treatment and also that those who survived have a similar recovery of LV and functional status similar to those with flow reserve [27].

The CLFLG AS group is the subset with the highest risk of mortality and adverse events. Survival of these patients without intervention is reported as 50% at 2 years, as per the NFHG symptomatic severe AS. Several studies of AVR for this cohort of patients reported a 30-day mortality between 8-33% [27-33], which despite being high still confers a survival benefit compared to conservative management [31, 34].

In our cohort, the in-hospital mortality post AVR for CLFLG AS patients was 3% in the non-matched group and 5% after the propensity matching. In any case, we

reported lower in-hospital mortality than expected according to the risk stratification system and those in the previous literature reports.

Preoperative NYHA III-IV, mean gradient < 20 mmHg, absence of flow reserve on the DSE, presence of coronary disease and high EuroSCORE had been reported as risks factors for in-hospital mortality after AVR for CLFLG AS [28-29, 31-32].

We did not find any preoperative characteristics as risks factors for in-hospital mortality, due to our low rate of postoperative adverse events, however we did identify the CLFLG AS category as a risk factor itself for increased mid-term mortality.

The PLFLG AS group has an intermediate prognosis between moderate NFHG AS and CLFLG AS. This entity has some similarities to preserved LVEF heart failure status, with the diastolic dysfunction being key for the worse prognosis they have compared to moderate NFHG AS. Other factors contributing to the higher surgical risk are the higher prevalence of female sex, systemic hypertension, restrictive LV physiology and small aortic annulus/root [35-40].

Despite the higher surgical risk, AVR is preferred to medical treatment as it confers better survival compared to conservative management [35, 41-46].

In our cohort, the in-hospital mortality for PLFLG AS was 2% in the non-matched group and 0% mortality after the matching, which is lower than expected as per previous literature reports and the risk stratification scores. We did not find any preoperative characteristics as risks factors for in-hospital mortality, due to our low

rate of postoperative adverse events, however we did identify chronic renal failure with haemofiltration in the PLFLG AS category as a risk factor for increased mid-term mortality.

The growing evidence regarding LFLG AS has made an impact on the valve heart disease guidelines. The ESC/EACTS guidelines on the management of valvular heart disease published on 2012 and their American counterpart published by the ACC/AHA in 2014, did only recommended surgery for symptomatic patients with CLFLG AS (Class IIa), and only if they had contractile reserve according to the ESC/EACTS guidelines [21, 22]. There was still uncertainty regarding which subsets of patients would benefit from surgery and the exact timings and thresholds for intervention.

The latest review of the ESC/EACTS guidelines done in September 2017, acknowledged this entity and the indications and benefits of AVR for these group of patients, taking into account the new evidence gathered from single institutional series. The current recommendations include surgical intervention for symptomatic TLFLG AS with flow reserve (Class I, Level C evidence) or without flow reserve (Class IIa, Level C) [23, 24].

The TOPAS (True or Pseudo-severe AS) study, was a multicenter observational study, started in 2002, that recruited patients with LFLG AS (only CLFLG AS patients as the LVEF was < 40%) to improve the assessment of the AS severity, the flow reserve and the clinical decision making in these patients [47].

They reported an 18% 30-day mortality post AVR and a 52% of deaths during the follow-up (median 15 months). Again, they demonstrated a better late survival with AVR compared to medical therapy. Also patients undergoing AVR had a significant improvement on their LVEF during the follow-up period [47].

In our cohort, in addition to very low surgical mortality we did also show a significant improvement in the LVEF in 51% of the patients in the CLFLG AS group, from severe to moderate dysfunction (13%) or to normal function (11%) and from moderate dysfunction to normal function (27%). A generalized liner mixed model identified the odds of LVEF improvement in the CLFLG AS group increased by 4.5% per month.

The potential advantages of TAVI compared to AVR for these group of patients would be a faster recovery, not only physical but also of the LV function [48, 49], as well as potentially less patient-prosthesis mismatch based on the larger AVA and lower gradients achieved with same sized TAVI prosthesis [50-56].

The PARTNER-I Cohort B, that compared TAVI vs. conservative treatment in patients deemed inoperable due to prohibitive surgical risk, included some patients with CLFLG AS and proved a survival benefit with TAVI compared to conservative management. Unfortunately, there were no patients with CLFLG AS included on the Cohort A (AVR vs. TAVI) as one of the exclusion criteria was impaired ventricular function [35].

Patients with PLFLG AS were included on the PARTNER-I Cohort A, and TAVI was associated with better one-year survival compared to AVR [35].

Another sub-cohort of the TOPAS study reported results after TAVI in patients with CLFLG AS. Mortality rate was 3.8% at 30 days, 20.1% at one year and 32.2% at two years. Low haemoglobin and moderate to severe aortic regurgitation due to paravalvular leak were identified as risk factors for re-hospitalization due to heart failure and increased mortality. The LVEF post TAVI increased by 8.3% at one-year.

They concluded that TAVI seems to be a safe alternative to AVR in this high-risk population with their reported 30-days mortality being significantly lower than the estimates from surgical scores but still higher than in our study [56].

We did not perform any TAVI in patients with LFLG AS during the period of the study, despite having had started the TAVI program in our unit in 2009, but we have proven with our series that AVR can be performed safely in this group of patients with a low in-hospital mortality, equivalent to NFHG AS patients.

Further additional studies comparing AVR vs. TAVI are necessary for this cohort of patients.

The mid-term survival results that we have reported in our study (one-year survival of 71% for CLFLG AS and 96% for PLFLG AS; five-years survival of 34% for CLFLG AS and 42% for PLFLG AS) seem to be consistent with the literature results. The excellent symptomatic relief and functional status that our patients reported at follow-up is encouraging and supports the indication for AVR in these patients despite the higher mid-term mortality compared with NFHG AS.

Our research had the limitations of being a retrospective and purely observational study. We did not have a non-surgical control group; hence we cannot formulate firm conclusions on the appropriateness of surgical treatment. However, we know from the literature the very poor prognosis and quality of life of these patients when treated medically.

From the diagnostic point of view, we did not perform DSE in all patients with suspected LFLG AS (based on AVA and low gradients) and reduced LVEF, but the indication for AVR was based on one of the following criteria: lack of alternative pathology explaining the symptoms, morphologic assessment of the valve by CT, TOE or MRI (with absence of mid-wall late gadolinium enhancement suggesting a dilated cardiomyopathy).

This study has helped us to understand better the prognosis and outcomes of LFLG AS after AVR. Based on our good results, our regional cardiologists have redefined the threshold for referring these patients for consideration of AVR.

7. CONCLUSIONS

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Based on the results of our study and the literature review, we conclude the following:

1. NFHG AS has an excellent prognosis after AVR and a long-term survival similar to the age-matched population.
2. Isolated AVR in LFLG AS can be performed with acceptable in-hospital mortality, comparable to that observed in patients with NFHG AS.
3. TLFLG AS patients have the highest in-hospital and mid-term mortality rate after AVR.
4. PLFLG AS patients have worse prognosis after AVR than NFHG AS patients but better prognosis than TLFLG AS patients.
5. AVR should be recommended for symptomatic severe LFLG AS is based on the significant symptomatic improvement and the good functional class achieved in survivors, as well as the poor outcome of those treated conservatively.
6. An earlier diagnosis and referral for AVR might improve the surgical outcome of LFLG AS patients.

7. Low-dose DSE is key for the diagnosis of TLFLG AS and has also an important prognostic value. MDCT has also an important role in the diagnosis of PLFLG AS, when DSE is not feasible.

8. The role of TAVI in LFLG AS has the potential advantages of a faster recovery (physical and of the LV function) and less patient-prosthesis mismatch. Further additional studies comparing AVR vs. TAVI in this cohort are necessary.

8. BIBLIOGRAPHY

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9 – 10. APPENDICES: ABBREVIATIONS /
FIGURES

9. APPENDIX A: ABBREVIATIONS

ACC: American College of Cardiology

AHA: American Heart Association

AS: aortic stenosis

AVA: aortic valve area

AVR: aortic valve replacement

BNP: brain natriuretic peptide

CCS: Canadian Cardiovascular Society angina class

CLFLG AS: classical low-flow low-gradient aortic stenosis

COPD: chronic obstructive pulmonary disease

CVA: cerebrovascular accident

DSE: dobutamine stress echocardiography

EF: ejection fraction

EuroSCORE: European system for cardiac operative risk evaluation

ESC: European Society of Cardiology

EACTS: European Association of Cardiothoracic Surgery

GI: gastrointestinal complications

LFLG AS: low-flow low-gradient aortic stenosis

LV: left ventricle

LVOT: left ventricular outflow tract

LVEF: left ventricular ejection fraction

MDCT: multi-detector computed tomography

NFHG AS: normal-flow high-gradient aortic stenosis

NYHA: New York Heart Association dyspnea class

PLFLG AS: paradoxical low-flow low-gradient aortic stenosis

SVi: stroke volume index

TAVI: trans catheter aortic valve implantation

TIA: transient ischemic attack

TLFLG AS: true low-flow low-gradient aortic stenosis

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