SYDNEY HEART TEAM | SPRING 2024 NEWSLETTER

SYDNEY HEART TEAM VALVULAR HEART DISEASE UPDATE:
Key Insights into Low-Gradient Aortic Stenosis

Despite the serious clinical implications of severe aortic stenosis (AS), large gaps in our knowledge remain regarding the diagnosis and management of significant AS, particularly with respect to low-gradient AS. We are familiar with the diagnosis of high-gradient (HG) severe AS and its indications for intervention[1,2]. However, a large proportion of patients with severe AS do not meet the conventional criteria for high-gradient AS and have low-gradient haemodynamics. Until recently, the prevalence and clinical significance of low-gradient AS, along with its indications for intervention, were poorly appreciated and understood.

Using the National Echo Database of Australia (NEDA), we recently undertook the largest ever study of the prevalence and outcomes of severe AS, involving over 12000 patients[3]. Significantly, we found that approximately half of those patients with severe AS in routine clinical practice have low-gradient hemodynamics. Furthermore, low-gradient severe AS is associated with long-term mortality comparable with or worse than high-gradient severe AS. Not surprisingly, we found that the rates of aortic valve replacement in low-gradient AS are less than half of those with high-gradient AS. These insights have significant implications in terms of improving our diagnosis, recognition and management of low-gradient severe AS.

In this newsletter, we will provide an update on contemporary definitions of low-gradient severe AS, a summary on our seminal study of the prevalence and outcomes of severe AS and provide a succinct approach to adjudication of disease severity in patients with low-gradient AS.

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What is Low-Gradient Aortic Stenosis?

A significant proportion of aortic stenosis patients have 'low-gradient' AS that is characterised by a small aortic valve area (AVA ≤1.0 cm^2) consistent with severe AS but a low mean transaortic gradient (<40 mmHg) that is not consistent with severe AS. The 3 types of low-gradient AS, shown in Figure 1, are as follows:

01. Classical Low-Flow Low-Gradient (LFLG) AS

The most frequent cause of low-gradient AS is the presence of a low-flow state, defined as a stroke volume index ≤35 mL/m^2 across a stenotic aortic valve. When the low-flow state occurs because of reduced left ventricular ejection fraction (LV EF <50%), this is termed "Classical" LFLG AS. Aortic valve replacement, either by transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (AVR), is recommended by current guidelines in patients with true severe Classical LFLG AS who are symptomatic[1,2].

02. Paradoxical Low-Flow Low-Gradient AS

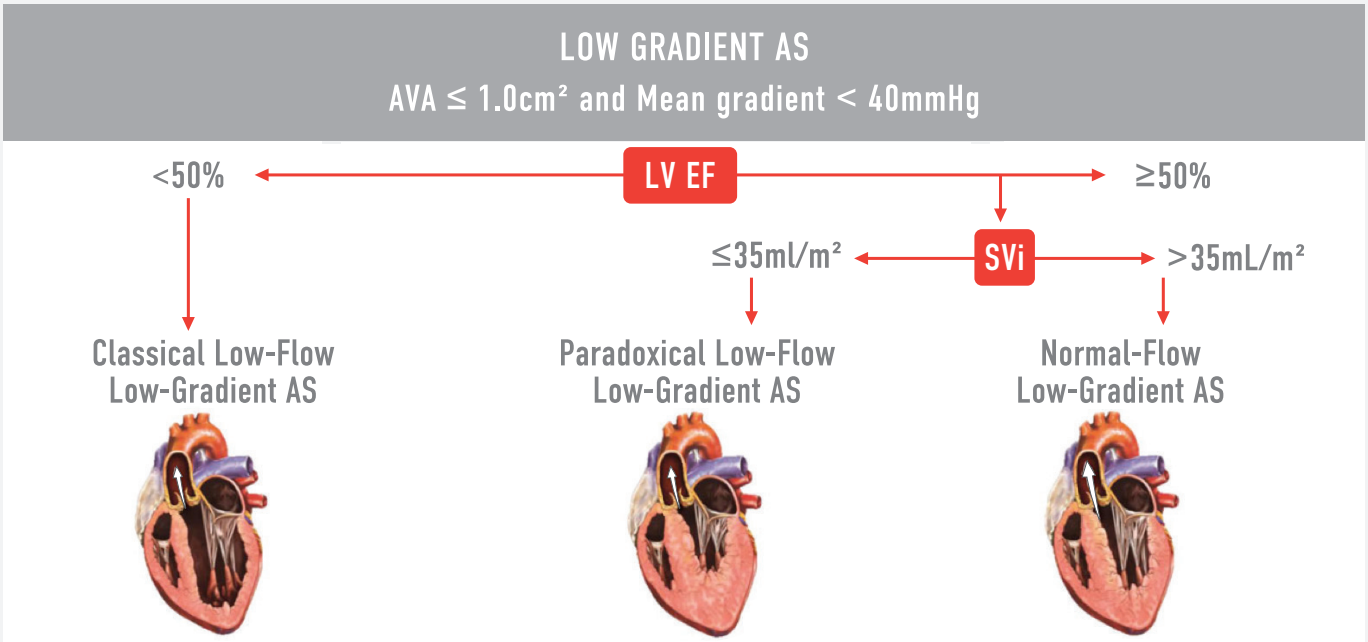
This refers to severe AS in the context of a low-flow state (stroke volume index ≤35 mL/m^2) where the left ventricular ejection fraction is preserved (LV EF ≥50%). The term "paradoxical" refers to the presence of unexpectedly low stroke volume despite a normal LV EF. The reduced stroke volume is generally related to LV concentric remodelling with small LV cavity, impaired LV diastolic filling and reduced LV systolic longitudinal filling. Atrial fibrillation also contributes to a low-flow state. Aortic valve replacement (either by TAVI or SAVR) is guideline-recommended in patients with symptomatic Paradoxical LFLG AS who are symptomatic[1,2].

03. Normal-Flow Low-Gradient (NFLG) AS

This refers to a type of AS associated with a small aortic valve area (AVA ≤1.0 cm^2) and low mean transaortic gradient (<40 mmHg) where the LV stroke volume is in the normal range (stroke volume index >35 mL/m^2). The significance of NFLG AS is debated, with the European Guidelines of the view that NFLG AS is more consistent with moderate AS[1]. There are no guideline recommendations for aortic valve replacement in NFLG AS.

The diagnostic criteria for all types of severe aortic stenosis are summarised in Table 1.

Figure 1. Types of Low-Gradient Aortic Stenosis



Adapted from Clavel MA et al. Eur Heart J 2016;37:2645.

Table 1. Diagnostic Criteria for Severe Aortic Stenosis

TYPE OF SEVERE AORTIC STENOSIS	AORTIC VALVE AREA	MEAN GRADIENT	AV PEAK VELOCITY	LV EF	STROKE VOLUME INDEX
High-Gradient AS	≤1cm²	≥40mmHg	≥4m/s	N/A	N/A
Classical LFLG AS	≤1cm²	<40mmHg	<4m/s	<50%	≤35mL/m²
Paradoxical LFLG AS	≤1cm²	<40mmHg	<4m/s	≥50%	≤35mL/m²
Normal-flow low-gradient AS	≤1cm²	<40mmHg	<4m/s	≥50%	>35mL/m²

AS: aortic stenosis; AV: aortic valve; AVA: aortic valve area; LVEF: left ventricular ejection fraction; SVi: stroke volume index.

Large-Scale Real-world Insights into Severe Aortic Stenosis

Using data from the National Echocardiography Database of Australia (NEDA), we recently undertook the largest prevalence and outcomes study of aortic stenosis ever undertaken, with 12013 patients followed up for a median period of 6.2 years[3]. This editorialised seminal study provides a number of important insights into low-gradient aortic stenosis, including the following findings:

01. Low-Gradient Severe AS is Common, Accounting for Approximately 50% of the Burden of Severe AS

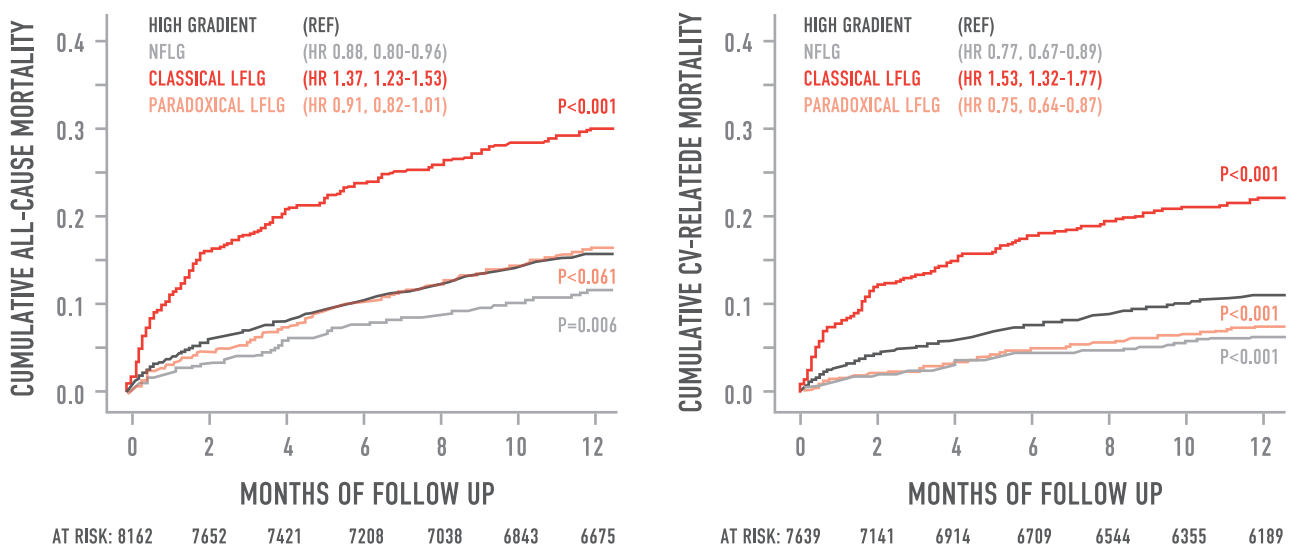
Of 12013 patients with severe AS, 53.4% (n=6412) had low-gradient severe AS and 46.6% (n=5601) had high-gradient AS[3]. The prevalence of different low-gradient subgroups were: 13.3% classical LFLG, 20.8% paradoxical LFLG and 19.2% NFLG severe AS ,respectively. These large-scale real world data show that the relative prevalence of LFLG severe AS in routine clinical practice is higher than previously estimated, representing approximately half of all patients with severe AS.

02. Low-gradient AS is Associated with Long-Term Mortality Similar or Worse than High-Gradient AS

Patients with classical LFLG severe AS had significant worse 1- and 5-year all-cause and cardiovascular mortality than those with high-gradient severe AS (e.g. HR 1.65 [95% CI, 1.48-1.84] for all-cause mortality at 5 years compared to patients with high-gradient severe AS) (Figures 2 and 3)[3]. Those with paradoxical LFLG AS had similar all-cause mortality at 1- and 5-years to those with high-gradient severe AS. However, a higher proportion of deaths in those with paradoxical LFLG AS were non-cardiovascular related compared with high-gradient AS. In patients with NFLG AS, all-cause mortality was lower at 1-year but at 5-years was similar to high-gradient AS. Cardiovascular mortality in NGLG AS was lower at 1-year and 5-years than for high-gradient AS (e.g. HR 0.82 [95% CI, 0.71-0.94] for cardiovascular mortality at 5 years compared to patients with high-gradient AS).

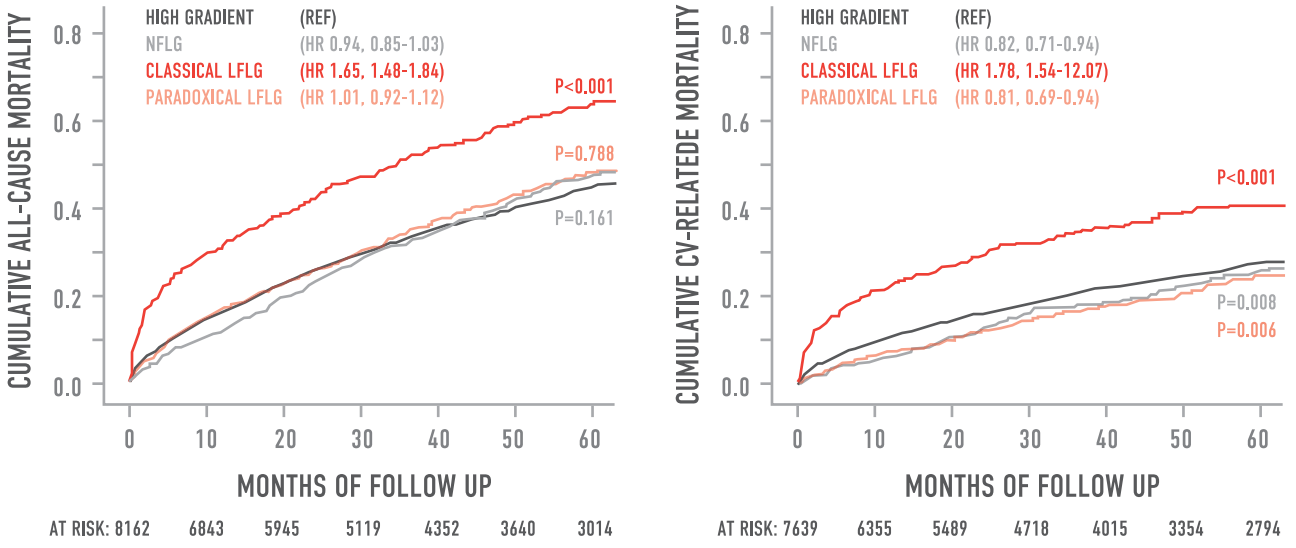
Overall, our study shows that the long-term outcomes for the low-gradient severe AS sub-populations are at least as serious and often worse than for patients with high-gradient severe AS. The lowest survival rates were seen in patients with LFLG and underlying LV systolic impairment (i.e. classical LFLG severe AS).

Figure 2. One-Year All-Cause and Cardiovascular Mortality According to AS Subtype



Adapted from Snir AD, Ng MK, Strange G, et al. J Am Heart Assoc 2021;10:e021126.

Figure 3. Five-Year All-Cause and Cardiovascular Mortality According to AS Subtype



Adapted from Snir AD, Ng MK, Strange G, et al. J Am Heart Assoc 2021;10:e021126.

LFLG: Low-Flow Low-Gradient; NFLG: Normal-Flow Low-Gradient

03. Rates of Aortic Valve Replacement are Lower for Patients with Low-Gradient Severe AS

The highest rate of aortic valve replacement (AVR) was observed in patients with high-gradient severe AS (41%) followed by patients with NFLG severe AS (27.5%) and classical LFLG severe AS (19.5%), with the lowest rate of AVR being observed in patients with paradoxical LFLG severe AS (13%). Per mean follow-up years, the rate of AVR was 5.2% for patients with high-gradient severe AS, 4.0% for patients with NFLG severe AS, 3.1% for patients with classical LFLG severe AS, and 2.4% for patients with paradoxical LFLG severe AS ($P<0.001$)[3].

These data demonstrate that, despite guideline recommendations for AVR for classical LFLG AS and for paradoxical LFLG AS[1,2], rates for AVR in low-gradient AS are substantially lower than for high-gradient AS. They indicate a widespread lack of recognition with respect to the clinical significance of LG AS, despite conditions such as classical LFLG AS having the poorest prognosis of all the AS subtypes.

Adjudication of Low-Flow Low-Gradient Aortic Stenosis Severity

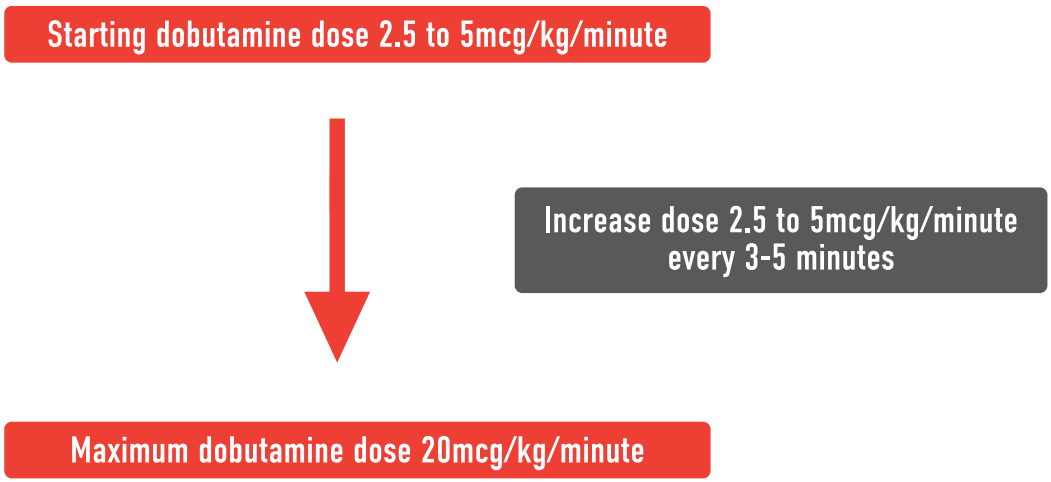
The adjudication of severity in low-gradient aortic stenosis is a key aspect of AS management as valve replacement (either by TAVI or SAVR) is indicated only in patients with confirmed severe AS. As aortic valve replacement is recommended in classical LFLG severe AS and in paradoxical LFLG severe AS, adjudication of the severity of these 2 conditions is discussed below.

Determining AS Severity in Classical Low-Flow Low-Gradient AS

In patients with low-flow, low-gradient AS with reduced ejection fraction (LV EF <50%), it is necessary to distinguish between true-severe AS due to valve stenosis from pseudo-severe AS from primary myocardial dysfunction with only moderate AS[2]. Low-dose dobutamine stress echocardiography (DSE) is recommended to distinguish between true-severe and pseudo-severe AS[1,4]. A protocol for DSE in AS is shown in Table 2. DSE findings are consistent with true-severe AS when peak stress achieves a maximum aortic velocity ≥4m/s or mean transaortic gradient ≥40mmHg but with the aortic valve area remaining ≤1.0cm^2 [2]. On the other hand, a finding of an increase of the aortic valve area to >1.0cm^2 with increased flow at peak stress is consistent with a diagnosis of pseudo-severe AS. Patients with true-severe AS should undergo aortic valve replacement while patients with pseudo-severe AS do not have an indication for AVR.

In some cases, DSE may be inconclusive due to a lack of contractile reserve i.e. failure to achieve an increase in stroke volume ≥20% with dobutamine. In this scenario, aortic valve calcium score, measured by non-contrast ECG-gated multislice CT, is helpful in adjudicating AS severity. The degree of aortic valve calcification is a strong predictor of clinical outcome in AS. Sex-specific aortic valve calcium scores of ≥1200 Agatson Units (AU) in women and ≥2000 AU in men are consistent with a likely diagnosis of severe AS[4].

Table 2. Low dose dobutamine stress echocardiography protocol



DOBUTAMINE INFUSION SHOULD BE STOPPED WHEN:

01. Maximum dobutamine dose is reached (20mcg/kg/minute)
02. Positive result is obtained
03. Heart rate rises 10-20bpm over baseline or exceeds 100bpm
04. Symptoms, hypotension or significant arrhythmias develop

INTERPRETATION:

01. An increase in effective AVA to final valve area >1.0cm² indicates AS is not severe
02. Severe stenosis is diagnosed by AS jet velocity ≥ 4.0 m/s or a mean gradient ≥ 40mmHg provided that aortic valve are remains ≤ 1.0cm² at any flow rate
03. Test may be inclusive if there is a lack of contractile reserve, defined as a failure to increase stroke volume by ≥20%

AS: aortic stenosis; AVA: aortic valve area

Determining AS Severity of Paradoxical Low-Flow Low-Gradient Aortic Stenosis

Severe paradoxical LFLG AS is characterized by a small aortic valve area (≤1.0cm^2) and a low mean gradient (≤40mmHg) in the context of low-flow (stroke volume index ≤35mL/m^2) despite a normal LV EF (> 50%). The confirmation of AS severity in this scenario requires considering the following key points:

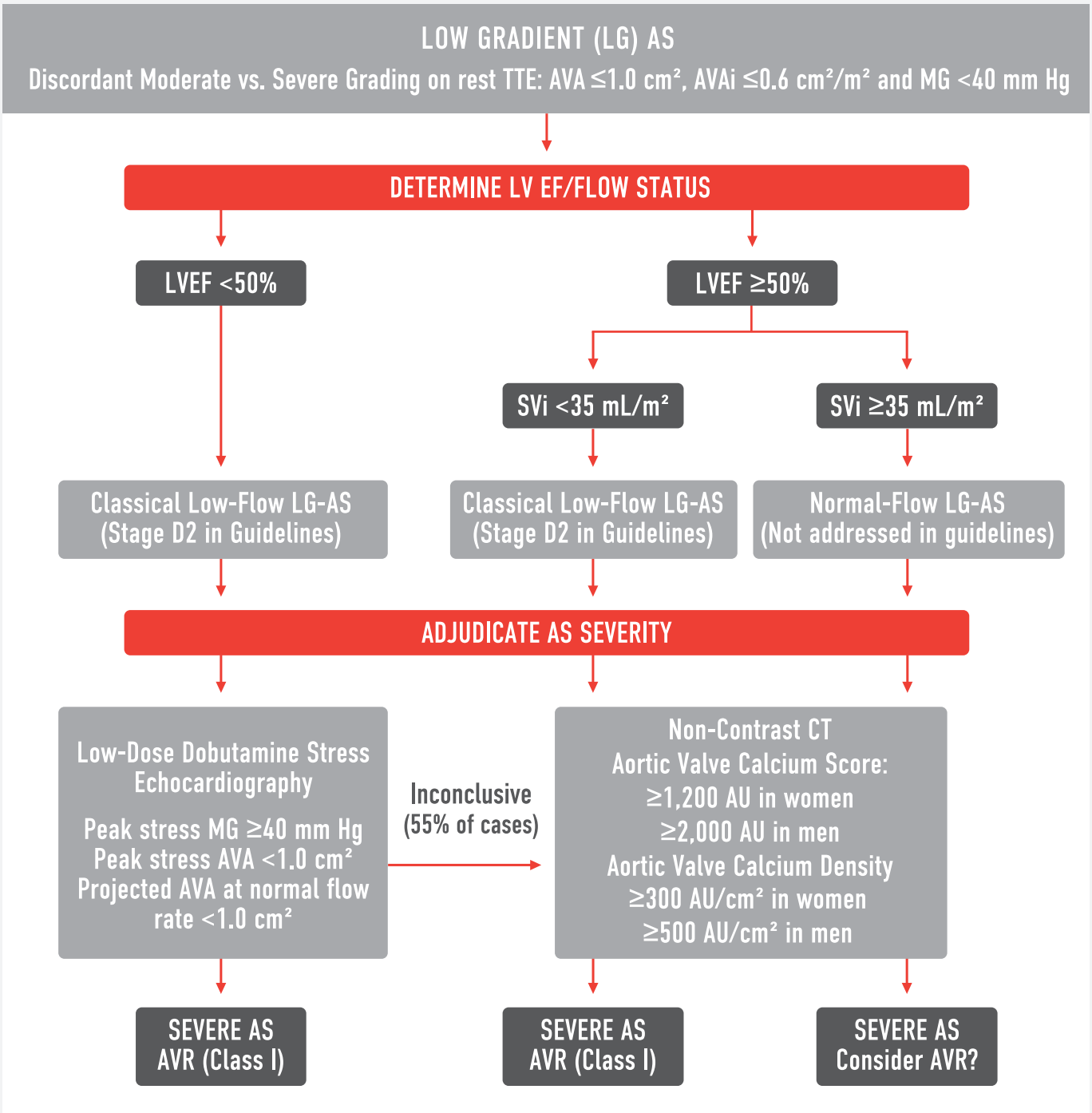
a) Echo measurement errors must be excluded (most importantly underestimation of left ventricular outflow tract area and thus flow) in moderate AS (true valve area >1.0cm^2)

b) Severe hypertension during echo examination should be avoided. Systemic hypertension imposes a second pressure load on the left ventricle, in addition to valve stenosis, which may result in underestimation of AS severity due to a lower stroke volume and lower transaortic gradient than when the patient is normotensive. Echo assessments for AS should ideally be undertaken when the patient is normotensive (i.e. systolic blood pressure <140mmHg)

c) Aortic valve calcium scoring by multislice CT is helpful in adjudicating severity especially when the peak aortic velocity is <3.0m/s and the mean pressure gradient is <20mmHg.

d) A recently proposed multi-modality approach to adjudication of severity of low-gradient AS is shown in Figure 4.

Figure 4. A Simplified Multimodality Approach to Adjudication of Severity in Low-Gradient AS



Adapted from Clavel, MA et al. JACC Cardiovasc Imaging 2024;17:861.

AS: aortic stenosis; AVA: aortic valve area; AVAi: aortic valve area index; AVR: aortic valve repair; TTE: transthoracic echocardiogram; LV EF: left ventricular ejection fraction; MG: mean gradient; SVi: stroke volume index

CONCLUSIONS AND KEY INSIGHTS

- In the largest prevalence and outcomes study ever of aortic stenosis[3], we show that low-gradient AS is common, accounting for around half of patients with severe AS in routine clinical practice.
- Low-gradient severe AS is associated with a long-term mortality that is comparable or worse than high-gradient AS.
- The poorest survival amongst all subtypes of AS is associated with classical low-flow low-gradient severe AS where the low-flow is due to impaired left ventricular function.
- Despite guideline indications for intervention in classical LFLG severe AS and for paradoxical LFLG AS, rates of aortic valve replacement (either TAVI or surgery) in low-gradient AS are less than half of those for high-gradient AS.
- Adjudication of the severity of LG AS may require a multimodality approach. Low-dose dobutamine stress echo is recommended for adjudicating severity in classical LFLG severe AS. Aortic valve calcium scoring by multislice CT is increasingly used to adjudicate AS severity for all low-gradient AS subtypes.
- There is a clear need to enhance our knowledge and recognition of low-gradient severe AS subtypes and to refer appropriate patients for consideration of timely intervention.

For practitioners who are interested in more information beyond what has been presented in this update, please don't hesitate to contact us at:

referrals@sydneyheartteam.com.au

References: 1. Vahanian A, Beyersdorf F, Praz F et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. European heart journal 2022;43:561-632. **2.** Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-e227. **3.** Snir AD, Ng MK, Strange G, Playford D, Stewart S, Celermajer DS. Prevalence and Outcomes of Low-Gradient Severe Aortic Stenosis-From the National Echo Database of Australia. J Am Heart Assoc 2021;10:e021126. **4.** Clavel MA, Pibarot P. Adjudication of Low-Flow, Low-Gradient Aortic Stenosis Severity: Dobutamine Stress Echocardiography and MSCT Are Complementary, Not Competitive. JACC Cardiovasc Imaging 2024;17:861-864.

ABOUT SYDNEY HEART TEAM

Sydney Heart Team is a uniquely interdisciplinary practice of world-leading practitioners in interventional cardiology and cardiothoracic surgery working together to provide comprehensive, integrated management of structural and coronary cardiovascular problems in a single setting.

Since 2009, the we have made significant global contributions to the practice and development of many Structural Heart Disease interventions including TAVI[1], transcatheter mitral valve edge-to-edge repair (TEER)[2], transcatheter mitral valve replacement[3] and transcatheter tricuspid valve interventions[4]. The breadth and depth of our collective expertise and experience in transcatheter and surgical therapies maximises the likelihood that outstanding clinical outcomes are achieved, even in the most challenging clinical scenarios.

The multidisciplinary Heart Team, evolved to make consensus treatment decisions in patients for whom both percutaneous and surgical therapies are available, has received Class I indications in U.S. and European guidelines for clinical decision-making in Valvular Heart Disease[5] and in complex Coronary Heart Disease[6]. In Australia, these recommendations have been further reinforced by Medicare Benefits Schedule coverage for TAVI and TEER, for which Heart Team consideration has become a requirement for reimbursement. Over the last 15 years, Sydney Heart Team has led the way in forging interdisciplinary models of care[7,8] that are now enshrined as standard-of-care.

References: 1. Snir A, Wilson MK, Ju LA et al. Novel Pressure-Regulated Deployment Strategy for Improving the Safety and Efficacy of Balloon-Expandable Transcatheter Aortic Valves. JACC Cardiovascular interventions 2021;14:2503-2515. **2.** Lim DS, Kar S, Spargias K et al. Transcatheter Valve Repair for Patients With Mitral Regurgitation: 30-Day Results of the CLASP Study. JACC Cardiovascular interventions 2019;12:1369-1378. **3.** Bapat V, Rajagopal V, Meduri C et al. Early Experience With New Transcatheter Mitral Valve Replacement. Journal of the American College of Cardiology 2018;71:12-21. **4.** Khor L, Simmons LA, Von Bardeleben RS, Ng MK. Transcatheter edge-to-edge repair for tricuspid regurgitation in Barlow-type tricuspid valve prolapse. European heart journal 2020. **5.** Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-e227. **6.** Neumann FJ, Sousa-Uva M, Ahlsson A et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European heart journal 2019;40:87-165. **7.** Vallely MP, Wilson MK, Adams M, Ng MK. How to set up a successful TAVI program. Ann Cardiothorac Surg 2012;1:185-189. **8.** Martinez GJ, Seco M, Jaijee SK et al. Introduction of an interdisciplinary heart team-based transcatheter aortic valve implantation programme: short and mid-term outcomes. Intern Med J 2014;44:876-83.

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PATIENT REFERRALS

You can complete an online referral form via our website or if you wish to discuss your patient before referring, you can email details to referrals@sydneyheartteam.com.au and Dr Martin Ng will get in contact with you.

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