AORTIC VALVE STENOSIS: FROM FORMULA TO GUIDELINE

MAARTEN VAN CAENEGERM

Promotor: Prof. dr. F. Timmermans

Masterproef voorgedragen in de master in de specialistische geneeskunde Cardiologie
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References
MDG  Mean Doppler Gradient
DI   Dimensionless Index
AU   Agatston units
CMR  Cardiac magnetic resonance
AVA  Aortic valve area
AVAi Indexed aortic valve area
LVOT LV outflow tract
MPG  Mean pressure gradient
MR   Mitral regurgitation
TR   Tricuspid regurgitation
Aortic valve stenosis is one of the most common valvular diseases and is the third most common cardiovascular disease in developed countries. The understanding of calcific AS has changed significantly, from a concept of a "mechanical" process of aging limited with the valve, to a modern concept of a progressive systemic disease. Because of a possible fatal course when AS left untreated, valve replacement is the recommended treatment for symptomatic patients with severe AS. The precise diagnosis and knowledge of the disease hemodynamic impact are for that reason essential in clinical decision-making.

Until recently, the AS spectrum was classically divided into mild, moderate and severe AS, based on different echocardiographic parameters such as transvalvular peak flow velocity and an indexed aortic valve area by body surface area. However, assumed that gradients appear to be a squared function of flow, even a slight decrease in flow can lead to a significant reduction in gradient and hence, underestimating gradients.

LF-LG AS may occur with depressed or preserved LVEF, and both situations are challenging in patients with valvular heart disease. In both cases will a reduction in transvalvular flow result in a decrease in gradient relative to AS severity. The main challenge in patients with depressed LVEF is to distinguish between true severe (LAS) versus pseudosevere AS (PAS). In contrary, PLFAS is a recently described entity with a normal LVEF and characterized by a pronounced LV concentric remodeling, a restrictive physiology and small LV cavity size. This entity is often misdiagnosed and could result in underestimation of AS severity and delay in referral for surgery.

The present paper reviews the diagnostic aspects of LF-LG AS, regarding the controversy and pitfalls in the current guidelines of the ESC–EACTS and the AHA–ACC, respectively of 2012 (1) and 2014 (2).
METHODS

For this manuscript, a PubMed search of the literature was performed using the terms “aortic stenosis” and “low flow or low gradient” The search was limited to the title and abstract of full-length articles written in English and published from 2000 to the present. The last update of the search was in March 2016.
RESULTS

The Pubmed search resulted in 103 articles, 52 of which were excluded because they were not related to the topic. Among the remaining 68 articles, 54 were original articles and 14 were review articles, editorials, letters, or case reports. The reference lists from these articles were also checked to ensure that no important studies were missed. We focused primarily on original studies and multicenter prospective trials to provide the most robust evidence with regard to diagnosis and treatment.

1. Aortic stenosis severity

For clinical purpose, ‘severe AS’ must be derived from an accurate haemodynamic assessment with a combination of flow-dependent and flow-independent measurements which are proven to be associated with adverse clinical outcome and can be used for interval follow-up or interventions. The criteria proposed by current guidelines to identify patients with severe AS are a peak velocity >4 m/s, a mean gradient >40 mmHg, and a valve effective orifice area <1.0 cm² or an indexed (to body surface area) EOA <0.6 cm²/m². These values are based on several studies on the natural history of aortic stenosis with characteristic morphology, functionality, clinical presentation and outcome of each severity-level.

According to the peak velocity > 4 m/s, Otto et al. described as first in a small prospective trial in adults with asymptomatic AS the rate of hemodynamic progression and clinical outcome and identified a jet velocity > 4.0 m/s at entry as a strong significant predictor for poor event-free survival without valve replacement at 2 years (21±18%) in comparison to a jet velocity below 4 m/s (3). This cut-off was confirmed by Pellikka et al. (4) in 2005 after multivariate analysis and was an independent predictor of all-cause mortality (5).

Secondly, the presence of an AVA < 1 cm² is based on theoretical considerations showing that the aortic valve area must be reduced to one-fourth of its natural size before significant changes in circulation occur. As a result, since the triangular orifice area of the normal (adult) aortic valve is approximately 3.0-4.0 cm², an area exceeding 1 cm² would not be defined as critical. The clinical relevance of this cut-off was first illustrated by a prospective trial of Kennedy et al. (6) with an estimated probability of 59% for remaining free of any complication of aortic stenosis after 4 years. These findings were confirmed by Amato et al. (7) and Das et al. (8) with a significant increase in overall cardiac complications and death if AVA < 1 cm².

Thirdly, the mean gradient > 40 mmHg cut-off is also important. However, there is a lack of outcome studies at present to strongly support this measurement, but shows a close correlation with peak aortic jet velocity, reflecting the same phenomenon (9,10).
Although AVA and peak gradient are highly influenced by the flow across the aortic valve, the calculation of AVA by the continuity equation relies on the accurate measure of the LVOT, frequently underestimated by echocardiography, and can raise doubts over whether AVA is the best parameter for AS quantification (11).

Furthermore, a recent study of Minners et al. (12) suggested that the recommended mean gradient and peak aortic jet velocity cut-offs do not correspond to an AVA of 1 cm². Moreover, when measurement of LV outflow tract diameter is problematic, the ratio of outflow tract velocity to aortic jet velocity can be substituted for valve area, because this ratio is indexed for body size with a ratio less than 0.25 indicating severe stenosis. This parameter is refined as dimensionless index (DI) and is based on the fact that an acceleration of flow velocity of more than 4 times through the valve (i.e. DI < 0.25) indicates significant AS based on a prospective Doppler-catheterization correlation in 100 patients by Oh et al. (13). In clinical setting it is more often used in patients with prosthetic valves. This relation of DI to long-term outcome in aortic stenosis with preserved LVEF was illustrated by Rusinaru et al. (14) with a significant excess risk of cardiac events and mortality if DI < 0.25. According to this parameter, they suggested to adapt the definition of severe AS into a combination of these 4 mentioned measurements (peak aortic jet velocity ≥4m/s, MDG ≥40mmHg, AVA <1cm² or < 0.6cm²/m² and DI <0.25).

Next to the transvalvular pressure gradients and EOA as parameters used for the hemodynamic evaluation, the presence of the pressure recovery phenomenon that occurs downstream from the aortic valve has also to be taken into account. There is a fundamental difference between the gradient measured by Doppler echocardiography and that measured by catheterization. The pressure recovery phenomenon is the difference between the maximum transvalvular pressure gradient and the net pressure drop, i.e. the gradient of pressure between the LVOT and the ascending aorta. It is due to the conversion of a certain amount of kinetic energy to potential energy downstream the aortic valve. To correct AVA for the pressure recovery phenomenon, the “energy-loss index” was created. Garcia et al. (15) illustrated a significant correlation between ELI and outcome after multivariate analysis with a cut-off of ≤ 0.52cm²/m² as predictor of adverse outcomes (positive predictive value of 67%) with a normal value of > 1.35 cm²/m².

Also a calcium score by computed tomography provides the reliable assessment of calcification on the valve leaflets and annulus among all imaging modalities. It is measured by multiplying the measured area by an attenuation coefficient based on the peak attenuation in the region, and is expressed in Agatston Units (AU). A recent study of Cueff et al. (16) in patients with reduced LVEF (<
showed that a calcium score <700 AU excluded severe AS with a high negative predictive value, whereas a score >2000 AU suggested severe AS. A threshold of 1651 AU provided the best combination of sensitivity (80%) and specificity (87%), particularly for patients with depressed EF. These results were confirmed by Clavel et al. (17) in 2013. Nevertheless, outcome studies of this parameter are absent at present (table 1).

Table 1
Clinical outcomes in prospective studies of asymptomatic aortic stenosis in adults

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study</th>
<th># pts</th>
<th>Severity</th>
<th>Mean FU</th>
<th>Event-free survival without symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak velocity</td>
<td>Otto et al.</td>
<td>123</td>
<td>Vmax &gt; 4m/s</td>
<td>2.5±1.4y</td>
<td>26±10% at 5y</td>
</tr>
<tr>
<td></td>
<td>Pellikka et al. 1990</td>
<td>113</td>
<td>Vmax &gt; 4m/s</td>
<td>20 mo</td>
<td>62% at 2y</td>
</tr>
<tr>
<td></td>
<td>Pellikka et al. 2005</td>
<td>662</td>
<td>Vmax &gt; 4m/s</td>
<td>5.4±4.0y</td>
<td>33% at 5y</td>
</tr>
<tr>
<td></td>
<td>Rosenhek et al. 2000 (18)</td>
<td>128</td>
<td>Vmax &gt; 4m/s</td>
<td>22±18 mo</td>
<td>33±5% at 4y</td>
</tr>
<tr>
<td>AVA</td>
<td>Kennedy et al.</td>
<td>66</td>
<td>AVA 0.7-1.2cm²</td>
<td>35 mo</td>
<td>59% at 4y</td>
</tr>
<tr>
<td></td>
<td>Pai et al.</td>
<td>740</td>
<td>AVA &lt; 0.8cm²</td>
<td>40 mo</td>
<td>38% at 5y</td>
</tr>
<tr>
<td></td>
<td>Amato et al.</td>
<td>66</td>
<td>AVA ≤ 1cm²</td>
<td>15±12 mo</td>
<td>38% at 2y</td>
</tr>
<tr>
<td></td>
<td>Das et al.</td>
<td>125</td>
<td>AVA &lt; 1.4 cm²</td>
<td>12 mo</td>
<td>71% at 1y</td>
</tr>
<tr>
<td></td>
<td>Rosenhek et al. 2010</td>
<td>116</td>
<td>AVA &lt; 0.6 cm²</td>
<td>41 mo</td>
<td>2.1% at 5 y</td>
</tr>
<tr>
<td>MPG</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DI</td>
<td>Rusinaru et al.</td>
<td>448</td>
<td>DI &gt; 0.25, 0.25-0.2 and &lt; 0.20</td>
<td>32 mo</td>
<td>56±3% vs 41±6% vs 22±5% at 5y</td>
</tr>
<tr>
<td>ELI</td>
<td>Garcia et al. a</td>
<td>138</td>
<td>≤ 0.52 cm²/m² vs &gt; 0.52 cm²/m²</td>
<td>8 mo</td>
<td>65% T or AVR vs 31%</td>
</tr>
<tr>
<td>AU</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a: retrospective trial. #:number, FU: follow-up, y: year, mo: months
2. High gradient severe aortic stenosis with normal flow, previous ‘classical’ severe aortic stenosis

Aortic valve stenosis is one of the most common valvular diseases and is the third most common cardiovascular disease in developed countries with an exponential age-dependent increase in prevalence. Severe AS occurs in about 2.8% of patients ≥75 years of age and can arise because of degenerative calcification, rheumatic disease or congenital valvular defects such as bicuspid aortic valve. (19)

Increased life expectancy has led to a higher prevalence of calcific aortic valve disease. Both ends of the disease spectrum-sclerosis of the aortic valve without hemodynamic obstruction and the late stage of AS - have been associated with increased morbidity and mortality. Without intervention, patient mortality typically occurs within 5 years of the onset of symptoms. (20)

According to the Current ACC/AHA and ESC-EACTS guidelines, the definition of severe AS is well-known and based on natural history studies of patients with AS, which show that the prognosis is poor once there is a peak aortic valve velocity of >4.0 m/s, “corresponding” to a mean aortic valve gradient >40 mm Hg and a AVA <1.0 cm² or a valve area indexed by body surface area is <0.6 cm²/m². (2)(Table 2)

The management of these patients with severe valvular AS by interventional approaches regarding to AVR are exhaustively described in the current ESC-EACTS and AHA-ACC guidelines, particularly class I and IIa recommendations. Nevertheless, there is a challenging group of patients, in whom a mean pressure gradient < 40 mm Hg, corresponding to “moderate AS”, is associated with an AVA of < 1.0cm², indicating severe stenosis. It is well known that this echocardiographic “discordance” between AVA (small) and MG (low) can occur in patients with severe AS and reduced left ventricular ejection fraction (LVEF) and the reason of this “discordance” will be discussed later. (Table 2)

As transvalvular pressure gradients are flow-dependent, measurement of valve area represents therefore the best way to quantify AS from a theoretical point of view. In clinical practice, possible operator-dependency of valve area measurements must be considered. For that reason valve area alone, with absolute cut-off values, cannot be relied upon for clinical decision-making and should be considered in a multiparametric assessment with a combination of flow rate, pressure gradients, size and wall thickness, ventricular function, degree of valve calcification and blood pressure, as well as functional status. (1).

In order to improve the assessment of AS severity and the determination of the optimal treatment strategy, a new flow-gradient classification has been proposed based on the recognition of flow dependence of pressure gradients (21-24) according to the Gorlin equation as described later on (21-
Dumesnil et al. and Lancelotti et al. suggested that the clinical spectrum of severe AS is more complex than previously believed and includes 3 main entities based on differences in terms of transvalvular flow and LVEF in the presence of a small AVA (<1.0 cm² and/or indexed AVA of <0.6 cm²/m²). (Table 3)

Regarding this consideration, patients with AS and a low transaortic volume flow rate due to either a small hypertrophied left ventricle with a low stroke volume (PLFAS) or due to LV systolic dysfunction with a low LVEF (LAS versus PAS), pose a diagnostic and management challenge markedly different from the majority of patients with AS who have a high gradient and velocity when AS is severe.

**Table 2**
Classical definition of aortic valve stenosis according to current European / American guidelines (a ESC/EACTS & b AHA/ACC guidelines)

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic jet velocity (m/s)</td>
<td>&lt; 3.0 (2.0-2.9)</td>
<td>3.0-4.0</td>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&lt; 30 (&lt; 20)</td>
<td>30-50 (20-40)</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>&gt; 1.5</td>
<td>1.5-1.0</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>AVA index (cm²/m²)</td>
<td>&gt; 0.85</td>
<td>0.60-0.85</td>
<td>&lt; 0.6</td>
</tr>
</tbody>
</table>

**Table 3**
Typical characteristics of the 3 main entities of severe aortic stenosis proposed by Pivarot and Dumesnil (21)

<table>
<thead>
<tr>
<th></th>
<th>Normal Flow High Gradient</th>
<th>Preserved LVEF (paradoxical) with Low Flow, Low Gradient</th>
<th>Reduced LVEF, Low Flow, Low Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&gt;40</td>
<td>&lt; 40</td>
<td>&lt; 40</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>AVA index (cm²/m²)</td>
<td>&lt; 0.6</td>
<td>&lt; 0.6</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>ZVA mm Hg/ml/m²</td>
<td>&gt; 4.5</td>
<td>&gt; 4.5</td>
<td>&gt; 4.5</td>
</tr>
<tr>
<td>LV enddiastolic diameter mm</td>
<td>45-55</td>
<td>&lt; 47</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>&gt; 0.43</td>
<td>&gt; 0.5</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>LVEF %</td>
<td>&gt; 50</td>
<td>&gt; 50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Global longitudinal strain %</td>
<td>14-20</td>
<td>&lt; 14</td>
<td>&lt; 14</td>
</tr>
<tr>
<td>Stroke volume index ml/m²</td>
<td>&gt; 35</td>
<td>&lt; 35</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Myocardial fibrosis</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>CT valve calcium score AU</td>
<td>&gt; 1650</td>
<td>&gt; 1650</td>
<td>&gt; 1650</td>
</tr>
</tbody>
</table>
3. Low flow versus normal flow.

As mentioned before, a new clinical spectrum of severe AS is based on the differences of transvalvular flow, LVEF and AVA < 1cm² and/or indexed AVA of <0.6 cm²/m². Until recently, it was assumed that normal LVEF implied normal LV systolic function and normal transvalvular flow. Nevertheless, common belief has been changed with 20-50% of the patients have reduced SVi and thus a low cardiac output and a lower transvalvular flow rate. In order to understand its clinical importance, we evaluate the origin of this cut-off and its rationale.

Traditionally, calculation of valve area has been considered as a flow-independent measure of aortic stenosis severity. However, since Gorlin valve areas vary with changes in transvalvular flow rate by using fixed orifice areas in in vitro models, a growing awareness of flow-dependency was established. A lot of scientist suggested already in the eighties that errors may be as great as 100% in patients with low valvular flow and pressure gradients, because the frequently used Gorlin equation was based on several assumptions, like the presence of laminar flow and a constant coefficient of velocity, as will be discussed later on. The relationship between transaortic pressure difference and flow during dobutamine stress echocardiography in patients with AS by Takeda et al. illustrated that a pressure drop can be related directly to flow in all grades of AS (25).

The commonly used SVI cut-off of < 35ml/m² is based on several preliminary studies that have arbitrarily used this cut-off to define low flow and its relation to outcome was recently described by Eleid et al. (26). They illustrated that lower SVI < 35ml/min is incrementally associated with mortality in PLFAS. Moreover, Kamperidis et al. (27) suggested also a higher mortality rate at 3-years follow-up after AVR compared with those with a normal flow (33 versus 4.6%).

In addition, patients with low flow versus normal flow have distinct clinical and echocardiographic characteristics. The low flow group are more frequently female and older and have higher systemic vascular resistance, lower systemic compliance, and higher LV global afterload than patients with normal flow. They also show smaller LVOT and LV cavity dimensions, increased concentric remodeling, a restrictive physiology and lower LVEF compared with normal-flow patients (28). These different characteristics can be illustrated by the ASKLEPIOS study figure 1, 29), which shows the prevalence of a low flow state in a healthy population and interestingly correlate with predominant demographic findings, as discussed later on. According to the ASKLEPIOS study, 30.7% of healthy individuals have a SVI less than 35 ml/m² (35.4% in female and 25.7% in male population). Differences in heart rate and LVOT size were the only significant predictors for SVI after multivariate analysis in both sexes.
Figure 1
Distribution of stroke volume index in a healthy population by the Asklepios study (29).
3.1. Low flow, low gradient severe aortic stenosis with preserved EF

3.1.1 Paradoxical low flow, low gradient aortic stenosis (PLFAS)

3.1.1.1 Definition

PLFAS despite a normal LVEF is a recently described entity that is characterized by prominent LV concentric remodeling, a restrictive physiology leading to impaired LV filling, small LV cavity size with altered myocardial function and poor prognosis. It is a common belief that patients with severe AS and preserved LVEF have a high transvalvular gradient. However, Hachicha et al. (30) reported that an extensive proportion of patients with severe AS on the basis of EOA <1.0 cm$^2$ and/or indexed EOA <0.6 cm$^2$/m$^2$ might develop a restrictive physiology, resulting in a low stroke volume (i.e., SVI <35 ml/m$^2$) and lower than expected transvalvular gradients (i.e., <40 mm Hg) despite the presence of a preserved LVEF (i.e., ≥50%). This clinical entity was labeled PLFAS. (31)

The most recent ESC–EACTS (1) and AHA–ACC guidelines (2) have recognized PLFAS as an important entity that deserves particular attention and recommend surgery as class Ila indication for surgery if the severity and the relationship with symptoms are confirmed.

3.1.1.2 Epidemiology

The prevalence of PLFAS reported in the literature varies between 17 and 38%. According to the simvastatine and ezetimibe in aortic stenosis trial (SEAS), approximately 29% of the patients with apparently mild or moderate AS, presented with a constellation of low gradient severe aortic stenosis, defined as a mean gradient of < 40 mm Hg, corresponding to moderate AS and an AVA of < 1cm$^2$, indicating severe AS, all with an ejection fraction ≥ 55% (32). Minners et al. (23) reported a similar ratio of 30% of 3483 consecutive patients from an echocardiographic database, including patients with normal LV function and a calculated AVA < 1cm$^2$. PLFAS is more frequent in women and elderly people as they are more prone to develop concentric remodeling.

3.1.1.3 Pathophysiology

PLFAS shares many clinical and pathophysiological similarities with HF-PEF. (33). The prevalence of both entities increases with female gender, older age and concomitant presence of systemic arterial hypertension. Typically, a reduced stroke volume despite a preserved LVEF due to restrictive physiology with compromised LV pump function is present.

Firstly the LV size, compliance and LV filling are reduced due to prominent LV concentric remodeling,
decreased longitudinal function and myocardial fibrosis (34). Both impaired myocardial relaxation and increased stiffness are contributing to impaired LV diastolic filling.

Secondly a reduction in intrinsic LV systolic function is noticed, not illustrated by LVEF, but rather by other more sensitive parameters directly measuring LV mid-wall or longitudinal axis shortening (33).

Subsequent studies reported that other factors prevalent in the AS population, such as atrial fibrillation (AF), reduced arterial compliance, mitral regurgitation or tricuspid regurgitation, may also reduce SVi in the context of ‘normal’ LVEF. Also hypertension, atherosclerosis and metabolic syndrome are other well-known co-morbidities and can cause direct variations of LV mechanics and changes to vascular stiffness and increased afterload.

Briand et al. (35) suggested that increased afterload should be taken into account when assessing AS severity by demonstrating that valvuloarterial impedance (Zva) is increased in this population and can be calculated by dividing the total systolic pressure (systolic blood pressure plus mean transvalvular gradient) by the SVI. It represents the cost in mmHg for each systemic millimeter of blood indexed for the body size and was able to demonstrates that increased afterload is strongly associated with LV systolic and diastolic dysfunction in AS patients.

Similar findings were demonstrated by Hachica et al. (30) with increased Zva (>3.5 mmHg/mL/m²) as predictor for poor outcome in asymptomatic severe AS patients due to afterload associated LV systolic and diastolic dysfunction.

In a SEAS substudy, Zva was found as the main determinant of LV dysfunction in asymptomatic patients in the setting of PLFAS(36).

These data suggest that measures of afterload, including an increased Zva can guide risk stratification and follow up decisions and are incremental to measures of LVEF.

3.1.1.4 Natural history

To identify the possibility of PLFAS as a true pathophysiological entity, the literature is rather controversial at present. Because PLFAS is frequently associated with concentric LV remodelling, low transvalvular flow, reduced long-axis LV function, increased interstitial fibrosis (31) and restricted prognosis, this entity has been considered to represent a more advanced stage of “severe AS”.

However, a recent retrospective study of Dahl et al. (37) illustrated that only 5% of the patients in the LFLG-sAS group were found to have ever had a mean gradient ≥40 mm Hg, indicating high gradient severe stenosis.

During the 5 years before the diagnosis of paradoxical LFLG, AVA decreased more rapidly in these patients than in classical severe AS group, which may suggest worsening of AS severity.
Nevertheless, the mean gradient increased more slowly in paradoxical than in classical severe AS group. This difference in the evolution of AVA and gradient in PLFAS versus classical severe AS is probably related to the more rapid deterioration in SVi, which is paralleled by more rapid decrease in LVEF and by significant increase in relative wall thickness and decrease in LV end-diastolic diameter (figure 2).

Jander et al. (38) also found that PLFAS is a heterogeneous subgroup of patients with aortic valve calcification (based on CT), echocardiographic and cardiovascular magnetic resonance features between those observed in concordant moderate and severe disease.

On the other hand, Maes et al. (39) illustrated that more than 80% of patients with PLFAS experienced progression of their mean transvalvular gradients, with almost half of them to high-gradient severe disease at the end of follow-up. Most patients with HG-SAS also increased their mean transvalvular gradient over time, but a minority of them displays reduced gradients at follow-up. Remarkably, in all patients with a decrease of transvalvular gradients over time, this was associated with a concomitant decrease in LVEF. Instead of becoming PLFAS, these patients developed the classical form of low-flow low-gradient AS due to depressed LV output and ejection fraction. So instead of an advanced stage of severe disease, these studies have suggested that PLFAS is a distinct entity of AS, rather than a stage preceding or following high-gradient AS in the natural history of the disease. In addition, this is probably much more than a valve disease and probably a more advanced stage of ventricular disease The ability to accurately stage paradoxical LF-LG AS is limited because of the lack of longitudinal data, both in terms of LV and aortic valve function in these patients.
Figure 2

3.1.1.5 Prognosis

Hachicha et al. (30) and Melis et al. (40) have demonstrated that the prognosis of patients with PLFAS was markedly improved by AVR compared with medical treatment, but were associated with reduced survival compared to patients with moderate AS or patients with normal flow and high gradient AS.

The study by Hachicha et al. (30), including 512 patients with severe AS and preserved LVEF (> 50%), 35% of them with low gradient, showed that patients who underwent surgical AVR had better survival than patients treated medically (medical versus surgical: 2 years, 65±7% versus 93±3%; 3 years, 58±8% versus 93±3%; P=0.001, and P value adjusted for age and gender=0.002).

However, compared with normal flow patients, low flow patients had a lower overall 3-year survival (76% versus 86%, p < 0.006).
In contrast, Jander et al. (38) demonstrated that patients with asymptomatic severe AS, low gradient, and preserved LVEF had comparable outcomes with those of patients with moderate AS (major cardiovascular events 14.8±1.0% vs 14.1±1.5%, respectively, p = 0.59). Accordingly, the investigators considered that patients with low gradient, severe AS with preserved LVEF do not represent a true severe AS group and the progression of the disease was similar to moderate AS. These seemingly conflicting results could be explained by differences within the group of patients with low gradient, severe AS with preserved LVEFs. Based on LV stroke volume, patients with low-gradient, severe AS with preserved LVEF can be further divided into those with low flow (<35 ml/m2) or normal flow (>35 ml/m2), which each subgroups of patients have distinct clinical and characteristics.

Clavel et al. (33) illustrated that surgical AVR was associated with a two-fold decrease in mortality compared to medical therapy after adjusting for differences in baseline characteristics (figure 3). Also the use of TAVR compared to medical therapy in the inoperable patients with PLFAS had much better survival compared to medical therapy, according the PARTNER-I trial. There was also a reduced mortality at 12 months in this group compared to surgical AVR (66% versus 35%; hazard ratio, 0.38; P=0.02). The potential superiority of TAVR over SAVR in these patients could be explained by the lower procedural mortality and the lower incidence of prosthesis-patient mismatch.

As opposed to the studies mentioned above, a substudy of the SEAS trial (36), which included 435 patients with asymptomatic low gradient severe AS with preserved LVEF, reported similar prognosis in patients with low flow versus those with normal flow. However, outcomes after AVR were not evaluated. Nevertheless, by study design, patients with severe AS were excluded from this trial thus introducing a selection bias and some concerns have been raised about the validity of the measurements of the stroke volume measured in the LV outflow tract by Doppler.

As mentioned by several studies, there was the aim to provide further evidence to the association between flow and survival in patients with low gradient AS. The study of Kamperidis et al. (27) and Mohty et al. (41) demonstrated that flow status, low flow (<35 ml/m²) versus normal flow (>35 ml/m²), is independently associated with long-term outcomes in patients with PLFAS treated with AVR.

The PARTNER-I trial (42) also illustrated that low flow but not low LVEF or low gradient is an independent predictor of early and late mortality following TAVR in high-risk patients with severe AS. Two-year mortality was significantly higher in patients with LF compared with those with normal stroke volume index (47% versus 34%; hazard ratio, 1.5; 95% confidence interval, 1.25–1.89; P=0.006).
These findings suggesting that SVi should be integrated in the risk stratification process of these patients. Though, further studies are necessary to determine the optimal type of therapy in patients with PLFAS.

**Figure 3**
Kaplan-Meier curves of overall survival according the group of patients and type of treatment: AVR versus conservative (cons). HG-SAS: high gradient severe AS PLG-SAS: paradoxical low gradient severe AS MAS: moderate AS. Clavel et al. (43)
<table>
<thead>
<tr>
<th>First author</th>
<th>Mean follow-up months</th>
<th>No PLFAS</th>
<th>Cutoff values used PLFAS</th>
<th>Age</th>
<th>AVA cm²</th>
<th>Peak velocity m/s</th>
<th>Mean gradient mmHg</th>
<th>LVOT mm</th>
<th>SVI ml/m²</th>
<th>EF %</th>
<th>Outcome Mx %</th>
<th>AVR %</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hachicha et al.</td>
<td>25±9</td>
<td>123/518</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>73±13</td>
<td>0.76±0.23</td>
<td>3.5±0.9</td>
<td>17±1</td>
<td>34±2</td>
<td>62±8</td>
<td>58±8</td>
<td>93±3</td>
<td></td>
<td>0.05 Overall survival 3 year</td>
</tr>
<tr>
<td>Mels et al.</td>
<td>25,3 (14.8-33.2)</td>
<td>42/363</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>78±6</td>
<td>0.77</td>
<td>3.3 (3.2-3.5)</td>
<td>26 (24-29)</td>
<td>20 (19-20)</td>
<td>31 (30-32)</td>
<td>64 (62-67)</td>
<td>57</td>
<td>83,3</td>
<td></td>
</tr>
<tr>
<td>Jander et al.</td>
<td>46</td>
<td>435/610</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>69±8±9,2</td>
<td>0.82±0.13</td>
<td>3.3±0.5</td>
<td>26.2±7,3</td>
<td>20.2±2</td>
<td>35.1±2</td>
<td>56.9±5,7</td>
<td>7.8</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Maes et al.</td>
<td>28 (3-140)</td>
<td>115/349</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>79±10</td>
<td>0.44±0.1</td>
<td>3.39±0.49</td>
<td>27±7</td>
<td>/</td>
<td>28±5</td>
<td>72±6</td>
<td>22</td>
<td>31</td>
<td>&lt;0.001 Overall survival</td>
</tr>
<tr>
<td>Clavel et al.</td>
<td>42±24</td>
<td>409/805</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>74±12</td>
<td>0.82±0.10</td>
<td>3.0±0.05</td>
<td>22±8</td>
<td>/</td>
<td>30±4</td>
<td>62±8</td>
<td>24±4</td>
<td>63±4</td>
<td>&lt;0.001 Overall survival 5 year</td>
</tr>
<tr>
<td>Kamperidis</td>
<td>1,8 year</td>
<td>134</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>76±10</td>
<td>0.8±0.1</td>
<td>3.6±0.4</td>
<td>32±6</td>
<td>/</td>
<td>38±10</td>
<td>61±6</td>
<td>SVI ≤ 35: 4,6 SVI &gt;35: 3,5</td>
<td>63±6</td>
<td>&lt;0.001 Overall mortality 3 year after AVR</td>
</tr>
<tr>
<td>Mohity</td>
<td>4.6±3 year</td>
<td>100/768</td>
<td>AVA ≤ 1 cm²</td>
<td>77±6</td>
<td>0.72±0.17</td>
<td>3.5±1.3</td>
<td>30±7</td>
<td>/</td>
<td>29±5</td>
<td>70±11</td>
<td>38±15</td>
<td>63±6</td>
<td>0.007 Overall survival 5 year</td>
</tr>
<tr>
<td>Ozkan</td>
<td>28±24</td>
<td>260</td>
<td>AVA ≤0.6 cm²/m²</td>
<td>78±4</td>
<td>0.76±0.14</td>
<td>3.6±0.34</td>
<td>20±5,3</td>
<td>/</td>
<td>35±9</td>
<td>60±7</td>
<td>70</td>
<td>30</td>
<td>&lt;0.001 Overall mortality</td>
</tr>
<tr>
<td>PARNTER I</td>
<td>25</td>
<td>530/970</td>
<td>SVI ≤ 35 ml/m²</td>
<td>83±5</td>
<td>0.56±0.18</td>
<td>/</td>
<td>40±3±14,3</td>
<td>/</td>
<td>26±8,5,6</td>
<td>49±14</td>
<td>76,2</td>
<td>45,9</td>
<td>&lt;0.001 Mortality 2 years Inoperable cohort</td>
</tr>
</tbody>
</table>
3.2 Low flow, low gradient severe aortic stenosis with reduced EF

3.2.1 Pseudo severe stenosis (PAS)

PAS is defined as a valve area ≤1.0 cm² with an aortic velocity <4.0 m/s or mean transvalvular pressure gradient ≤40 mmHg and will have an increase in the calculated aortic valve area and a decrease in valve resistance in response to an elevation in cardiac output induced by dobutamine infusion (up to 20 μg/kg/min). Nishimura et al. (2) suggested to define pseudo-severe AS by an AVA > 1.2 cm² or increase of AVA > 0.3 cm² with a mean transaortic gradient < 30-40 mmHg at peak dobutamine infusion.

Patients have a low transvalvular pressure gradient because of the combination of moderate AS and low cardiac output due to low EF. The low output decreases the valve opening forces, causing restricted mobility of a valve that is not severely diseased. It could be incorrectly suggest severe stenosis based on the calculated valve area, because of several limitations of valve area equation when applied to low flow rate conditions. The valve area can be underestimated by the standard Gorlin equation when cardiac output is low and therefore, the formula has limited use for differentiating pseudostenosis (a flow-dependent phenomenon) from true severe AS (44,45). This entity of low flow, low gradient severe AS occurs in the setting of a low flow rate across the valve due to LV systolic dysfunction with reduced LVEF.

Approximately 20 to 30 % of the AS population is part of this subgroup and these patients usually have a dilated LV cavity with importantly depressed myocardial systolic function, frequently due to a concomitant cardiomyopathy in relation to ischemic heart disease and/or to afterload mismatch (46). Low-dose dobutamine stress echocardiography has a crucial role in the diagnostic algorithm in these patients because of the possibility to assess the presence of myocardial contractile reserve and to differentiate a pseudosevere from a true severe stenosis.

Distinguishing between these possibilities has important clinical implications for accounting prognosis and management options, as patients with true AS will likely benefit from corrective valve surgery, whereas patients with PAS may not.

In the setting of low flow, low gradient aortic stenosis, outcomes of PAS remain poorly described. In 2012, Fougères et al. (47) reported the outcomes of PAS under conservative treatment and illustrated that mortality within 5 years was significantly lower in PAS (43 ± 11%, n = 10), when compared with the true severe AS (91 ± 6%, n = 33; P = 0.001) and comparable with that of propensity-matched patients with LV systolic dysfunction (LVEF < 40%) and no evidence of valve disease (figure 4). Monin et al. (48) also reported outcome after surgical versus medical treatment in patients with low flow, low gradient AS with low LVEF and described a dramatic improvement in
survival in patients with LV flow reserve versus medical treatment. A possible caveat is that, as in patients with low LVEF low flow, low gradient AS, the low flow state may nonetheless conceal a pseudosevere stenosis.

**Figure 4**
Kaplan-Meier survival estimates in low flow, low gradient AS under conservative treatment according to the results of dobutamine testing. Fougères et al. (47)

Due to insufficient detection of PAS, AVR in this subgroup can lead to higher mortality rates, especially in the presence of a PPM in this low flow status. To prevent PPM, the cut-off EOA of AVR can be calculated by multiplying the body surface area by 0.85, defined as PPM cut-off in cm²/m². If a severe PPM occurs, defined as < 0.65 cm²/m², a mortality risk ratio of 77.1 (p< 0.01) versus non-significant PPM was established in this subgroup with reduced LVEF (< 40%) (49).
3.2.2 True severe stenosis

Patients with severe AS and secondary LV dysfunction that leads to a low transvalvular pressure gradient are considered to have "true severe stenosis." This severe stenotic valve produces a disproportionate afterload and a reduced LVEF, resulting in a markedly decreased stroke volume and low transvalvular pressure gradient. Typically, during dobutamine infusion an increase in gradient in proportion to the relative increase in flow and little or no increase in EOA is present.

As mentioned earlier, patients with true AS benefit from corrective valve surgery, whereas patients with PAS may not. Aortic valve surgery can improves myocardial performance by relief of ventricular afterload. The risk of open surgical aortic valve replacement is higher in those with left ventricular dysfunction, but is heavily dependent on small-sized aortic prosthesis, contractile reserve and patient comorbidity, according to Monin et al. (48) and Pellika et al. (4).

As cited above, Monin et al. (48) illustrated that the absence of contractile reserve, an increase in stroke volume of < 20%, was associated with a surgical mortality rate of 32 % for aortic valve replacement, in contrast to a 5–7 % incidence of perioperative death in those with contractile reserve (≥20%). Of note, patients without contractile reserve on dobutamine challenge may continue to have symptoms of heart failure after surgery. However, the improvement in left ventricular ejection fraction from aortic valve replacement can occur irrespective of contractile reserve (49).

In the PARTNER study (42), patients with left ventricular dysfunction (LVEF < 55%) were also included in both randomization studies, 26% in cohort A where TAVI was compared with conventional open AVR and 49.7% in cohort B , where TAVI was compared with best medical therapy, which included balloon aortic valvuloplasty, in non-operable patients. There was no significant interaction for left ventricular ejection fraction < 55 % and for the primary outcomes of the study for each randomization.
4. Diagnostics

To understand the hemodynamics of AS, it is important to know that flow through a stenotic AV is well approximated by flow through a convergent orifice. The GOA of the valve is formed by the free edges of the AV leaflets, whereas the EOA is the area of the flow jet at the VC.

EOA is calculated by using the continuity equation (figure 5), because the volume of blood passing through the LVOT must equal the volume of blood ejected at the EOA. The pressure difference between the LVOT and EOA is referred to as ΔP_{max}. Based on fluid mechanics theory, GOA is mostly greater than or equal to EOA (1). The contraction coefficient (Cc) is the ratio of the EOA to the GOA and depends on the 3-dimensional geometry of the valve leaflets, where Cc is significantly lower for flat valves than for doming leaflets. In addition, a pressure recovery phenomenon in the ascending aorta is also present due to some quantity of the kinetic energy of the blood that is converted back to potential energy, resulting in an increase in the local pressure.

**Figure 5**
Schematic of flow through a stenotic aortic valve. Formulas for the contraction coefficient and EOA using the continuity equation are also shown. AAo indicates ascending aorta; EOA, effective orifice area; GOA, geometric orifice area; LVOT, left ventricular outflow tract; VC, vena contracta; and VTI velocity time integral. Saikrishnan et al. (19)

The AS jet velocity can be directly measured from continuous- wave Doppler tracings through the AV. ΔP_{mean} and ΔP_{max} can be calculated by using the simplified Bernoulli equation, which assumes a proximal velocity V1 < 1 m/s. ΔP_{mean} must be computed from instantaneous ΔP after using the Bernoulli equation because of the square term in this equation.
(Aortic valve mean gradient: $4 \times V_{AVA}^2$). Both the mean aortic valve gradient and aortic valve area are used to classify the severity of stenosis. Suggested a practical algorithm for clinical diagnosis of PLFAS (figure 6).

**Figure 6**
4.1 The Gorlin equation and energy loss index

Before the use of echocardiography, invasive hemodynamic studies were essential for understanding the physiology and pathophysiology of valvular heart disease. Because of its potential complications and several pitfalls in its use and calculation methods, such as the Gorlin formula, cardiac catheterization is no longer the golden standard for diagnosis of valvular disease.

Typically, $\Delta P$ is measured between the LV and the ascending aorta preferring the use of a double-lumen fluid-filled catheters for simultaneous LV and aortic pressure measurements. However, pullback gradients are inaccurate for diagnostic purposes. Cardiac output can also be calculated using the Fick method based on arterial and mixed venous saturations, hemoglobin level, and oxygen consumption or the thermodilution method relying on injecting cold saline and measuring the change in temperature as this passes from the injection port to the thermistor on the Swan-Ganz catheter (50).

Once $\Delta P$ and CO are obtained, the Gorlin area can be calculated using the Gorlin equation (figure 7). However, this area differs from the corresponding echocardiographic measurement owing to the difficulty in precisely positioning the aortic side catheter at the vena contracta of the flow jet. Additionally, $\Delta P_{\text{mean}}$ and $\Delta P_{\text{peak}}$ may be measured, whereas only the mean CO is available for calculation.

**Figure 7**

The Gorlin equation

$$\text{Valve Area (cm}^2\text{)} = \frac{\text{Cardiac Output (ml/min)}}{\text{Heart rate (beats/min) \cdot Systolic ejection period (s) \cdot 44.3 \cdot \sqrt{\text{mean Gradient (mmHg)}}}}$$

When blood flow decelerates between the aortic valve and the ascending aorta, part of the kinetic energy is converted back to static energy because of a phenomenon called pressure recovery. Thus, the net $\Delta P$ between the LV and the mid-ascending aorta is lower than the pressure drop immediately adjacent to the valve. For that reason, the AVA obtained by use of the Gorlin formula at catheterization is derived from recovered pressures, whereas the Doppler AVA is derived by the continuity equation.

The magnitude of pressure recovery is determined by the ratio between the EOA and the cross-sectional area of the ascending aorta, which becomes predominantly important with moderate to severe AS and small aortas, in whom Doppler AVA lay lead to overestimation of severity.
Contradictory, less or no pressure recovery will be present in patients with a dilation of ascending aorta. The clinical impact of pressure recovery usually is small but can be significant with mild stenosis and a small aortic root or with a doming congenitally stenotic valve (51).

To correct AVA for the pressure recovery phenomenon, the energy-loss index was created and defined as ELI (figure 8). This index accounts for pressure recovery in the ascending aorta by including the ascending aortic size in the calculations (52).

Garcia et al. (15) illustrated in a retrospective analysis of 138 patients with moderate to severe AS that ELI was superior to the indexed AVA in predicting the composite of death or AVR during an 8-month follow-up. An energy loss index ≤0.52cm²/m² was the best predictor of adverse outcomes with a positive predictive value of 67%.

Bahlmann and colleagues (52) showed in a multicentral study that a decrease of 1 cm²/m² in ELI predicts a 6.06-fold increase in AVR, a 5.25-fold increase in aortic valve events, a 1.93-fold increase in total mortality, and a 2.28 increase in combined mortality and hospitalization for heart failure, suggesting that this may be a promising parameter to be used clinically.

In addition, a substudy of the SEAS trial suggested that approximately 20% of patients with severe AS were reclassified to moderate AS by the use of the ELI compared to AVAi (52). The relation between ELI and AVAi for the size of the ascending aorta is illustrated in figure 9. This correlation suggests that patients with a small ascending aorta can probably tolerate a more important reduction in the EOA due to a larger pressure recovery phenomenon and thus a larger ELI and a lower left ventricular pressure overload.

**Figure 8 The energy loss index**
ELI = [EOA×Aa/(Aa−EOA)])/BSA where Aa is the aortic area at the level of the sinotubular junction, BSA is the body surface area. P_LV: pressure left ventricle, P_VC: pressure at vena contracta, P_AO: pressure in aorta ascendens. Garcia D. et al. (15)
**Figure 9 Relationship between ELI and AVAi for different aorta sizes.**
The calculation of ELI becomes more relevant in patients with an ascending aorta diameter ($\Phi$) <3.0 cm and/or with an AVAi >0.5 cm²/m². *Best cut point of ELI to predict outcomes over an 8-month follow-up in the study by Garcia et al. **Cut point of ELI used for reclassification40) of stenosis severity in the SEAS substudy. ***Best cut point of ELI to predict outcomes over a 4-year follow-up in a study of Bahlmann et al. The **black dashed line** is the identity line. Pibarot et al (53).

4.2 Agatston Units
Aortic valve calcifications can be quantified using the Agatston score in CT scans in which calcific deposits are displayed as bright regions within the image. Calcified foci are defined as areas of $\geq$3 pixels with attenuation >130 Hounsfield units.

A calcium score is measured by multiplying the measured area by an attenuation coefficient based on the peak attenuation in the region, and is expressed in Agatston Units (AU). A recent study of Cueff et al. (54) showed that a calcium score <700 AU excluded severe AS with a high negative predictive value, whereas a score >2000 AU suggested severe AS. A threshold of 1651 AU provided the best combination of sensitivity (80%) and specificity (87%), particularly for patients with depressed EF. Despite other proposed methods like a calculated volumetric score, the calcium score remains the primary metric for assessing AVC.

Despite its capacity to suggest severe AS, it can only provide the GOA of the valve and cannot provide any hemodynamic data such as $\Delta P$ or CO in isolation. Hence, EOA cannot be calculated by using CT.
4.3 Dimensionless index

The most delicate or error-prone component of the continuity equation calculation is the LVOT radius, since its value is squared. Mostly, the LVOT can be measured using echocardiography, but when LVOT diameter is not available, the dimensionless index (DI) can be used to estimate AS severity. This parameter is based on the same duration of blood velocity in the LVOT and AS jet during ejection, resulting in a simplification of the continuity equation using a velocity ratio \( \frac{V_{\text{LVOT}}}{V_{\text{jet}}} \). The TVI is the distance that the ejected blood has travelled during the ejection phase. A calculation of cross-sectional area of flow in the LVOT can be avoided.

**Figure 10**

In the presence of a smaller LVOT diameter with the same flow, the longer the LVOT TVI will be, resulting in a smaller DI ratio when AVA and aortic TVI are constant (55).
4.4 Dobutamine stress testing and the projected AVA

When patients with a reduced stroke volume have to be assessed for aortic valve area, some difficulties can be present because the calculated valve area is proportional to stroke volume and the constant of the Gorlin equation varies with transvalvular flow. By adding dobutamine, an adrenergic agonist agent, at 5 μg/kg/min to a maximal dose of 20 μg/kg/min, an elevation in cardiac output can be expected resulting in an increase in the calculated aortic valve area and a decrease in valve resistance (36).

The response differs in patients with LAS in whom a dobutamine induce an increase in transvalvular flow and produce an increase in the mean transvalvular gradient but no change in aortic valve area. A recent multicenter study by Clavel et al. (17) illustrated the benefit of stress echocardiography, both exercise and dobutamine, in identifying PLFAS by using the projected AVA at normal flow rate to assess stenosis severity.

To overcome the limitations of DSE for assessing the severity of AS in case of poor LV contractile reserve, the TOPAS group (56) introduced the projected AVA at a normalized flow rate (Q) of 250 mL/s, assuming a linear correlation is present.

In contrast, stress EOA had a markedly lower performance than EOA_proj and indexed EOA_proj in differentiating TS and PS AS both in vitro and in vivo according to the TOPAS study. On the one hand, patients with low-flow AS often do not reach the normal range of resting flow rate under DSE, and, as a consequence, the stress EOA may remain <1.0 cm², although the valve is only mildly or moderately stenotic. This misclassification of stenosis severity may lead to the decision to operate on a patient with only a mild/moderate AS.

The projected aortic valve area at normal flow rate (AVA_proj) can be calculated using the following equation in figure 11:

\[
AVA_{PROJ} = \frac{AVA_{PEAK} - AVA_{REST} (250 - Q_{REST}) + AVA_{REST}}{Q_{PEAK} - Q_{REST}}
\]

**Figure 11**

AVA_{rest} and Q_{rest} are aortic valve area and transvalvular flow rate at rest; AVA_{peak} and Q_{peak} are AVA and Q at peak stress.
The EOA$_{proj}$ was determined with the use of a linear regression equation based on a linear relationship between flow and EOA in population of the TOPAS group (figure 12), as illustrated by previous studies of Das et al (8).

**Figure 12**
Concept of the EOA$_{proj}$ in 4 different patients (A) and calculation of the projected EOA at a flow rate of 250 mL/s (B) with the use of equation. *Peak valve EOA obtained during DSE. Blias et al. (57)

4.5 Exercise testing

The rationale of exercise testing is based on the fact that initial symptoms of AS can be subtle or insidious and patients are not always capable to recognize their symptoms. About 30% of the patients who claimed no symptoms became symptomatic during the exercise testing. In addition symptoms can also predict outcome and could be used for perioperative risk stratification.

According to Rafique et al. (58), an abnormal exercise test with symptoms, ventricular arrhythmia, ST depression above 2mm, abnormal blood pressure response, increase of mean pressure gradient above 18 or 20 mmHg or developing exercise induced pulmonary hypertension can be related to an 8 fold increase in cardiac events during follow-up and a 5,5 fold increased risk of sudden death. The review of Magne et al. (31) reported similar findings. This exercise testing can provide prognostic information next to its use in operative decision making, due to its good negative predictive value. However the problem of several exercise testing studies is the small number of included patients, the rate of feasibility and the specificity of variables.
4.6 MRI

The attractiveness of MRI lies in the avoidance of radiation exposure and in the ability to acquire both anatomic and hemodynamic measurements, full 3-dimensional information and both the GOA and the EOA can be measured, while also pressure recovery effects can be captured. Additionally, MRI does not require imaging windows to precisely identify the valve jets. On the other hand, the inherent disadvantages of MRI include the inability to accurately identify calcification, signal voids due to flow turbulence, lower spatial resolution in comparison with CT, imaging artifacts due to implanted medical devices, increased scan times and higher costs, while also the availability is sometimes a limiting factor.

4.7 Differentiating true versus pseudo severe stenosis

In patients with low flow low gradient stenosis, it is important to differentiate between true versus pseudo severe stenosis to guide therapeutic strategies (figure 13). Stress echocardiography can be helpful to confirm stenosis severity in this subgroup of patients. In a recent study of Clavel et al. (56) exercise stress echocardiography was utilized in patients with no or ambiguous symptoms and dobutamine stress in symptomatic patients. Based on the TOPAS trial (57), the projected AVA at normal flow rate was also used to assess stenosis severity. With this approach, it was possible to separate true from pseudosevere AS in 51 patients with PLF-LG with a percentage of correct classification of 94%. An indexed EOA$_{proj}$ ≤0.55 cm$^2$/m$^2$ was found to be the best criterion to discriminate TS AS from PS AS. Unfortunately, stress echocardiography may not be feasible or not conclusive, if no sufficient increase in flow rate can be established, in all patients with low flow, low gradient AS and so an alternative diagnostic test is needed to verify AS severity and guide therapeutic management in these cases. Referring to the results of Cueff et al. (16), aortic valve calcification measured by multi-detector CT correlate well with hemodynamic markers of AS severity.
Figure 13
Algorithm for use of dobutamine echocardiography. Pibarot P. et al. (46)
5. Current AHA/ACC and ESC/EASCT guidelines

The most recent European and American guidelines have recognised paradoxical LFLG AS as an important entity that deserves particular attention and recommend surgery as class IIa indication for surgery if the severity and the relationship with symptoms are confirmed (1,2). As mentioned before, recent studies reported some conflicting results with regard to the natural history and outcomes of paradoxical LFLG AS reflecting the patient heterogeneity and the complexity of this entity.

Before analysis of possible pitfalls in the current European and American valvular heart disease guidelines, it is necessary to look closely to the original studies where these guidelines are based on.

5.1 ESC/EACTS guidelines 2012

Regarding the management of low flow low gradient aortic stenosis, these guidelines mentioned already the lack of data on the natural history and outcome after surgery in patients with PLFAS. They suggested that surgery only should be preformed when symptoms are present and if comprehensive evaluation suggests significant valve obstruction. These recommendations were based on 4 studies, each one with different cut-off values.

First Monin et al. (48) reported the prognostic value of dobutamine stress in the setting of low gradient AS and enrolled 136 patients (median aortic valve area, 0.7 cm² [range, 0.6 to 0.8]; mean transaortic gradient, 29 mm Hg [range, 23 to 34 mm Hg]; cardiac index, 2.11 L/min/m² [range, 1.75 to 2.55 L/min/m²]). They concluded that in the setting of low-gradient aortic stenosis, surgery seems beneficial for most of the patients with left ventricular contractile reserve. In contrast, the postoperative outcome of patients without reserve is compromised by a high operative mortality, respectively 5 versus 32 % (p=0.0002). However, the 100% success rate of Doppler interrogation during dobutamine infusion in this study may not reflect daily practice and there was no randomization of treatment. In addition the small number of patients without contractile reserve could influence significance in the long-term survival after AVR.

Second Levy et al. (59) evaluated 217 consecutive patients with severe aortic stenosis (area <1 cm2), LVEF < 35% and and low mean gradient < 30 mm Hg who underwent AVR and concluded also that the absence of contractile reserve was a strong predictor of perioperative mortality (OR 4.4; 95% CI 1.1 to 17.5; p = 0.03). The presence of lower mean gradient (≤ 20 mmHg, OR 0.89; 95% CI 0.83 to 0.96; p = 0.02) and presence of multiple coronary vessel disease (OR 2.2; 95% CI 1.02 to 5.02; p =
0.045) were identified as independent predictors of perioperative mortality after multivariate analyse.

Jander et al. (60) the outcome in patients with low-gradient “severe” aortic stenosis (aortic valve area < 1.0 cm²; mean gradient < 40 mm Hg) with outcome in patients with moderate stenosis (aortic valve area 1.0 to 1.5 cm²; mean gradient 25 to 40 mm Hg) in 1525 asymptomatic patients with preserved ejection fraction (LVEF ≥ 55%) and concluded that there was no significant difference in aortic valve events (48.5% versus 44.6%, p=0.37), major cardiovascular events, (50.9% versus 48.5%, P=0.58), cardiovascular death (7.8% versus 4.9%, P=0.19). Contradictory to previous cited studies, there was no significant difference in aortic valve events in patients with reduced stroke volume index (<35 mL/m²) compared to those in patients with normal stroke volume index (46.2% versus 50.9%; P=0.53). Although the data were collected prospectively, the analysis was performed retrospectively with all its inherent limitations. In addition, only patients with an ejection fraction >55% were included, which in the presence of left ventricular hypertrophy may not be entirely normal.

Finally, Tribouilloy et al. (61) observed 81 consecutive patients with symptomatic calcified LF/LGAS (valve area <1 cm², LVEF ≤ 40%, mean pressure gradient < 40 mm Hg) without contractile reserve, defined as absence of increase in stroke volume of ≥ 20% compared with baseline, on DSE were enrolled. Five-year survival was higher in AVR patients compared with medically managed patients (54 ± 7% vs. 13 ± 7%, p = 0.001) despite a high operative mortality of 22% (n=12). The number of patients in this cohort was relatively small and the decision to perform AVR was left to the referring physician. Because of the small number of perioperative fatal events, the multivariable analysis on perioperative mortality could be overfitted. Also the potential inclusion of patients with moderate AS and severe left ventricular dysfunction with exhausted CR on DSE could not be ruled out. Similarly the outcome of medically managed patients if they had been treated by AVR remains unknown.
4.2 AHA/ACC guidelines 2014

The most recent American guidelines regarding to low flow low gradient AS are also based on the same studies of Monin et al. (48) and Tribouilloy et al. (61). In addition, a reference to the study of Nishimura et al. (2) was also made. They included thirty-two patients with low-output, low-gradient aortic stenosis (calculated valve area < 1 cm² and mean gradient < 40 mmHg, and LVEF <40%) and illustrated the role of dobutamine challenge in selecting those who would benefit from an aortic valve operation.

Based on the results of the dobutamine test, 21 patients underwent aortic valve replacement. All patients with a final aortic valve area <1.2 cm² at peak dobutamine infusion and a mean gradient of < 30 mm Hg were found to have severe calcific aortic stenosis at operation.
DISCUSSION

A. About AVA and gradients in classical high gradient AS

Current guidelines state that “when AS is severe and cardiac output is normal, the mean transvalvular pressure gradient is generally >40 mmHg”. However as described above, discrepancy between the valve area (<1 cm²) and transvalvular gradients (<40 mmHg) occur frequently. Many reasons exist for the discrepancy between AVA and gradient severity measures, as discussed below.

In addition, the guidelines make no distinction between catheterization data and Doppler echocardiography, which measure different parameters, values or indices, and catheterization also takes pressure recovery phenomenon into account. As echocardiographic parameters predict outcome quite accurately, invasive measurements cannot be advised on a routine base, but may be indicated in selected cases. Secondly, the severity criteria “40mmHg matches AVA < 1 cm²” is not consistent, which is highlighted by the Gorlin formula where an AVA value of 1.0 cm² is closer to 30 to 35 mm Hg rather than to the 40-mm Hg cut-off value proposed in the guidelines (62,63).

The most frequent cited validated outcome studies in these guidelines illustrate that the aortic valve area and the aortic valve velocity after multivariate analysis are predictors of development of symptoms (5) and predictors of all-cause mortality (5, 63). In addition, outcome was mostly defined as mortality or need for surgery with a lack of transparency if decision was made based on AVA and/or gradient (peak versus mean). For that reason, there has to be some note of caution with respect to the extrapolation of these outcome studies.

Regarding to mean gradient in the current definition, there is a lack of validated outcome studies.

B. The controversy on PLFAS: a need for careful work-out.

At present, there is controversy on concept of PLFAS. Most reasons for AVA versus gradient discrepancy have not been thoroughly investigated in the PLFAS studies, yielding heterogeneous populations and heterogeneous results with regard to prevalence, outcome and intervention results (figure 16). In addition, a lot of studies did not measure flow to define their population. What are potential reasons for this apparent “discrepancy” between gradient and AVA and thus misclassification of PLFAS?
B.1 Measurement issues

First, there is a discrepancy between AVA and gradient because they are different measures. An AVA of 1 cm² was found to be correlated with a mean gradient of 22.8 mmHg, whereas a mean gradient of 40 mmHg was found to be correlated with an in vivo AVA of 0.75 cm² according to Minners et al. (23) and Carabello (62), suggesting limitations of the current cut-off values. Underestimation of the velocity signal must be avoided, regarding the fact that 20% of the highest velocity is measured in the right intercostal. Doppler gradients can misclassify the severity of AS in several circumstances, such as contamination of the continuous-wave Doppler signal due to mitral regurgitation, overtracing of the spectral Doppler envelope, the presence of a high-flow state, and the pressure recovery phenomenon can be responsible for a Doppler gradient (PG_{max}) that is substantially higher than the invasively determined pressure gradient (PG_{net}).

AVA may reflect the EOA, Gorlin area or anatomic area (GOA), depending on the technique used to assess stenosis severity. The calculation of AVA based on the standard Gorlin equation for aortic valve area by cardiac catheterization has a different concept compared to AVA by Doppler echocardiography based on the continuity equation, measuring the EOA. The continuity equation states that the flow rate in the LVOT equals that in the VC, while the cross-sectional area of the jet at the level of the VC is EOA. When AVA is measured by catheterization, the Bernouilli equation is used and describes the maintenance of flow energy applied between the LVOT and the VC.

Besides the inherent inconsistency in the guidelines criteria discussed above, the other causes of AVA (<1 cm²)–gradient (<40 mm Hg) discordance are -1- measurement errors, -2- the effect of small body size, and -3- the presence of a low-flow state.

An accurate LVOT measurement plays an crucial role for several reasons, such as the calculation of AVA and stroke volume. An underestimation of AVA by approximate 17 % was illustrated by Gaspar et al (61) when LVOT measurement by conventional 2D echocardiography was compared to 3D modalities or CT scan. A possibly explanation could be the larger AVA due to a more correct assumption of LVOT shape, which is rather elliptical.
than circular by 2D, which enables measurement of larger medio-lateral diameter and LVOT and annulus area planimetry.

The consequences of suboptimal images by 2D transthoracic echocardiography was highlighted by 10%, 25%, and 25% of patients being reclassified as having moderate aortic stenosis based on calculated aortic valve areas using 3D TEE circular annular area, 3D TEE planimetered annular area, and MSCT planimetered annular area, respectively. Finally, a larger AVA calculated by CT does not improve the correlation with transvalvular gradient, the concordance gradient-AVA, or mortality prediction compared with echocardiography according to a recent report of Clavel et al. (64).

A 3D AVA planimetry allows plane position control and any change in orientation to capture smallest orifice of stenotic AV and can be useful when co-existing obstruction in LVOT, bad doppler alignment, LVOT sizing problems or discrepancy between EOA and a gradient. However, results can be biased by calcification due to reverberation and limited by temporal resolution to capture maximal systolic opening.

**AVA indexed for the body size** is also an important step in the assessment of discrepant measurement. In current guidelines, an indexed AVA cut-off value of 0.6 cm²/m² is recommended as the criterion for severe AS. If the AVA is not indexed, patients with small body surface area can be incorrectly classified as having severe AS. Conversely, overestimation of AVA in terms of disease severity could be caused by a large body size, unless it is indexed for BSA.

The presence of a low-flow state, independent of LVEF, is another frequent cause of AVA - gradient discordance. Studies have arbitrarily used a cut-off of SVI <35 mL/m² to define the low flow group (21,35,41), however, other cut-offs have not been investigated. In addition, several important outcome studies had never mentioned or measured this critical parameter, despite its hemodynamic importance. Also the high prevalence of this ‘low-flow’ state in a healthy population (30.7% in the ASKLEPIOS study) could raise questions on the rationale to use an abnormal flow cut-off of 35ml/m².

**B.2 The assessment of LV function**

The assessment of LV function is also crucial because it is well known that LVEF is a limited marker of systolic function (65). The cut-off for “normal systolic function” is unknown in the setting of AS-associated remodeling, although systolic function in the presence of normal LV geometry is regarded
as preserved when LVEF≥50% based on outcome studies (1,2). In the presence of more sensitive parameters such as global longitudinal strain of mid-wall fractional shortening, impairment of myocardial systolic function can be detected in patients with a supposed preserved LVEF≥50% (46). A recent study of Dahl et al. (37) illustrated that the traditionally accepted cut-off of LVEF<50% was associated with the highest mortality, however patients with LVEF 50% to 59% also had increased mortality compared with patients with LVEF≥60% , (hazard ratio 1.58, p=0.006) regardless of symptomatic status. Similar outcome results were showed by Pellika et al. (5) and Maes et al. (39), suggesting a reevaluation of the question “what is a normal ejection fraction in AS?”.

Also measurement of afterload, including an increased Zva, can also determinate LV dysfunction and can guide risk stratification and follow up decisions (30,35,52). Nevertheless, it should be taken in account that Zva overestimates load in small aortas because pressure recovery is not considered. Subtle myocardial dysfunction and decreased longitudinal deformation could also be present and measured using different techniques such as M mode echocardiography, tissue doppler imaging and 2D speckle tracking echocardiography. A recent study of Kamperidis et al. (27) demonstrated that flow and LV global longitudinal strain (≤ -15 % versus > -15%) were independently associated with survival after AVR in patients with low gradient severe AS with preserved LF function, however the outcomes and echocardiographic data were retrospectively analyzed and a comparator group of patients who were treated medically was absent.

Also the cut-off values of EOA < 1.0 cm2 or mean gradient > 40 mm Hg found in the guidelines are discussable and were originally derived from series of patients with preserved LVEF, and it is possible that less rigorous cut-off values (e.g., EOA or EOAProj < 1.2 cm2 and mean gradient > 30 to 35 mm Hg) would be more appropriate for patients with decreased LVEF. AS severity is only one half of the equation, the other half being the degree of myocardial impairment which, for a given degree of AS severity, may vary considerably from one patient to the other.

B.3 The pressure recovery phenomenon

It is also essential to consider the pressure recovery phenomenon, because overestimation of aortic stenosis severity by echocardiography is possible in a setting of tubular aortic stenosis, patients with a small ascending aorta (<3 cm at sinotubular ridge), doming of the aortic valve and those with a narrow left ventricular outflow tract (<2 cm). Pressure recovery becomes relevant in patients with small aortas and moderate to severe AS, in whom Doppler echocardiography could overestimate the degree of severity after measurement of AVA. In contrast, less or no pressure recovery is present in
patients with a dilation of the ascending aorta and therefore a more important energy loss for a
given valve effective orifice area.
For that reason the energy-loss index was created to correct AVA for the pressure recovery
phenomenon. Despite this ELI, the physiological meaning of pressure recovery or what the real load
the ventricle faces to is unknown.
Apart from the small observation in the Garcia paper (15) and the follow-up data of the SEAS trial
(52) with reclassification of stenosis from severe to moderate in approximately 20% of patients,
outcome studies that take into account the pressure recovery are lacking.

**B.4 Dimensionless index**

*The dimensionless index* can also be used to estimate AS severity. Logically, if for a fixed AVA, the
LVOT diameter would be decreased, and the flow kept constant, aortic TVI remains stable but LVOT
tVI increases and eventually, the LVOT\textsubscript{TVI}/AO\textsubscript{TVI} increases. In other words, the DI does not appear to
be that dimensionless, as small and high LVOT diameter may increase of decrease the index,
respectively. In fact, this was recently published in a descriptive cohort with AS, showing that the DI
cut-off differs depending on the LVOT diameter (55).

**B.5 Hypertension**

Systemic hypertension may be a risk factor for AS and frequently coexists with low-gradient aortic
stenosis, which itself may cause elevated LV afterload, LV filling pressures and pulmonary artery
pressures. Eleid et al. (67) observed after treatment of hypertension a small increase in the mean
gradient and stroke volume in the majority of patients and a larger increase in the aortic valve area,
suggesting that the degree of AS was not severe. However, treatment of hypertension could also
result in an increase in the mean gradient with either no change or reduction in the valve area,
suggesting severe AS. In other words, in the presence of uncontrolled hypertension gradient could be
underestimated ("pseudonormalization"). When systemic hypertension is present, it would be
prudent to treat the hypertension with remeasurement of aortic valve hemodynamics after
normalization of blood pressure.
If all these potential reasons for suboptimal AVA or gradient measures could be taken into account, a more accurate assessment of the hemodynamic severity of AS would be possible. A recent published study of Magne and Mohty (66) redefined the concept of PLFAS and tried to summarize the potential pitfalls to create a practical algorithm for the diagnosis of PLFAS when inconsistent echocardiographic grading appears to be present. Nevertheless, this algorithm is no holy grail, because the assumption that the cut-off for low flow (defined as < 35 ml/min²) and preserved LVEF (defined as > 50%) is still considered. However, it could be an important step in further redefining the aortic valve spectrum.

Figure 16 Possible profiles of patients with “apparent” PLFAS.
C. Pseudostenosis

Distinguishing between PAS and TAS by low-dose dobutamine stress echocardiography has important clinical implications to assess prognosis and management, as patients with true AS will likely benefit from corrective valve surgery, whereas patients with PAS may not. According to the TOPAS trial, the projected AVA was suggested by assuming a linear correlation between AVA and transvalvular flow, provided a constant mean gradient. This could be a problem because both gradient and AVA often change with increasing transvalvular flow. In addition, it may be difficult or impossible to obtain a reliable estimate of the EOA_{proj} in patients having minimal or no increase in transvalvular flow rate during DSE, which makes the determination of the stenosis severity sometimes not possible. Fougères et al. (47) reported a lower mortality of PAS under conservative treatment within 5 years compared with true severe AS or those without LV contractile reserve, but a true control group with operated patients was lacking. Furthermore, the 5-year survival of PAS was properly comparable with that of propensity-matched patients with systolic HF and no evidence of valve disease. Due to insufficient detection of PAS, AVR in PAS can lead to higher mortality rates, especially in the presence of a PPM in this low flow status. Some authors (68) even suggested that PAS is comparable to moderate AS in case of severe LV systolic dysfunction with a negative prognostic impact, supported by the negative impact of moderate prosthesis patient mismatch in case of low ejection fraction.
CONCLUSION

LF-LG AS with either preserved or reduced LVEF is one of the most challenging diagnostic problem in patients with valvular heart disease. In both circumstances, a reduction of transvalvular flow will decrease the mean gradient relative to AS severity. The main challenge in patients with depressed LVEF is to distinguish between TAS versus PAS and to accurately assess the severity of myocardial impairment. PLFAS is a recently described entity with still some controversies about pathophysiology, natural history and the rationale about its current definition. Regarding to the distribution of low-flow status in a normal healthy population by the ASKLEPIOS study, is there further need for reevaluation of the current SVi-cut-off?

Recent studies have been shown that PLFAS is associated with a worse prognosis if misdiagnosed or delayed for surgery. Therefore, it must be accurately identified, and in specific, it must be differentiated from other confounding conditions, including measurement errors, small body size, and discrepancies due to the inherent inconsistencies in the guideline criteria.

In the setting of inconsistently grading AS despite preserved LV EF, symptomatic status of the patients is crucial and should be clarified next to a clearly evaluation of the possible measurement pitfalls. If the patient is symptomatic with an indexed AVA of <0.6 cm$^2$/m$^2$, AVR should be recommended. If symptoms are ambiguous, series of different measurements has to be taken into account to possibly redefine the problem. Are there characteristics of low flow status, such as restrictive filling or manifest left ventricular hypertrophy, and is the stroke volume well indexed? Has the left ventricular function been well determinated by just the LVEF, mostly based on eye-balling? The introduction of Zva made it possible to estimate total load, but it is known to overestimate the load in small aortas because pressure recovery is not considered. In addition measuring global LV strain can provide important data in terms of LV function and risk stratification.

However, it is notable that neither Zva nor global longitudinal strain can differentiate moderate and severe AS. Contractile reserve can be assessed by performing dobutamine stress echo. Other imaging modalities such as TEE, 3D TEE and MRI can better characterize LVOT measurement, but does not improve mortality prediction compared with 2D echo. Disease severity can also be evaluated by the calcium score of aortic valve. Due to the lack of prospective randomized trials about outcome of PLFAS to date, value of above-mentioned parameters is partly understood and clinical decision should be made individually.
Also further insights into natural history of PLFAS could be important to understand why some patients with AS evolve towards a classical normal-flow, high-gradient severe AS pattern, where flow and LV pump function are well preserved until late in the course of the disease, while other patients develop a PLFAS with early decrease in LF function, flow and impairment of LV structure. Some factors may contribute to the development of this pattern in patients with AS, including gender, ageing, genetics, metabolic disorders, diabetes and increased LV afterload due to concomitant hypertension.

In order to fully understand PFLAS, longitudinal studies with several imaging approaches (echocardiography, cardiac magnetic resonance and CT aortic valve calcium score) will be crucial to fully examine this complex interaction between the valve and the myocardium; and to identify exclusive features that determine evolution in the different flow-gradient patterns.
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