Incremental prognostic value of multiparametric echocardiographic assessment for severe aortic stenosis

HEART
and Education in Heart

Incremental Prognostic Value of Multiparametric Echocardiographic Assessment for Severe Aortic Stenosis

Journal:	*Heart*
Manuscript ID:	Draft
Article Type:	Original article
Date Submitted by the Author:	n/a
Complete List of Authors:	Nistri, Stefano; CMSR Veneto Medica, Cardiology Sevice Olivotto, Iacopo Faggiano, Pompilio Antonini Canterin, Francesco; Ospedale Civile, A.R.C, Cardiology Locantore, Elisa Papesso, Barbara Brigido, Silvana; Ospedale Civile, A.R.C, Cardiology Cioffi, Giovanni Rossi, Andrea
Keywords:	AORTIC VALVE DISEASE < VALVULAR DISEASE, TRANSTHORACIC < ECHOCARDIOGRAPHY < IMAGING AND DIAGNOSTICS

Incremental Prognostic Value of Multiparametric Echocardiographic Assessment for Severe Aortic Stenosis

Stefano Nistri[1], Iacopo Olivotto[2], Pompilio Faggiano[3], Francesco Antonini-Canterin[4], Elisa Locantore[3], Barbara Papesso[1], Silvana Brigido[4] Giovanni Cioffi[5], Andrea Rossi[6], Catherine M Otto[7]

1- Cardiology Service, CMSR-Veneto Medica. Altavilla Vicentina (VI) Italy
2-Referral Center for Myocardial Diseases, Careggi University Hospital, Florence, Italy
3-Section of Cardiovascular Diseases, University of Brescia, Brescia, Italy.
4-Cardiology, ARC, Azienda Ospedaliera S. Maria degli Angeli, Via Montereale, 24, 33170 Pordenone, Italy.
5-Department of Cardiology, Villa Bianca Hospital, Trento, Italy.
6- Section of Cardiology, Department of Medicine, University of Verona, Italy.
7-University of Washington School of Medicine, Seattle, WA USA

Short Title: Multiparametric Assessment for Severe Aortic Stenosis

Word count: 2,586 excluding title page, abstract, references, figures and tables.

Key words: Aortic stenosis, Echocardiography, Outcome

Address for Correspondence:
Stefano Nistri, MD, PhD
Cardiology Service, CMSR Veneto Medica
Via Vicenza, 204. 36077 Altavilla Vicentina (VI) Italy
Phone:+390444225111
FAX: +390444225199
E-mail: snistr@tin.it

Objective. To establish whether different criteria to assess severity of aortic stenosis (AS) may have additive prognostic relevance in asymptomatic patients with normal left ventricular function.

Design. Retrospective study.

Setting. Outpatient echocardiographic laboratories.

Patients. One-hundred forty-nine AS patients (74.5±9.4 years, 52% males), with at least one of the following 4 criteria: peak aortic flow velocity (V_{max}) >4m/sec; mean transvalvular gradient (MG)>40 mm Hg; aortic valve area (AVA) <1 cm^2; AVA indexed for body surface area (AVAI) <0.6 cm^2/m^2. Mean follow-up duration was 25.9±22.3 months.

Main outcome measures. Combination of all-cause death or aortic valve replacement (AVR).

Results. Outcome was better in the 69 patients (46%) with ≤2 criteria, than in the 80 patients with ≥3 criteria (p<0.001); and in patients with neither MG>40 mm Hg nor V_{max} >4 m/sec compared with those having at least one of these 2 criteria (p<0.001). At univariate Cox survival analysis, MG>40 mmHg and/or V_{max} >4m/sec were the best predictors for the combined end-point. At multivariate analysis, predictors of outcome were male gender (HR 1.751 CI 95% 1.111-2.758, p=0.016), higher MG (HR per 10 mmHg increase 2.626, CI95% 1.663-4.146), p<0.001) and active smoking (HR 3.84 CI 95% 1.15-12.8, p=0.028). In patients with MG≤40 mmHg, an AVAI <0.4 cm2/m2 provided further risk stratification (4-year event-free survival 33%, vs. 58% in patients >0.4 cm2/m2 (p=0.001).

Conclusions. Hierarchical prognostic assessment of AS severity favors MG>40 mmHg as the most potent predictors of outcome. However, the convergence of multiple criteria adds predictive accuracy , supporting the need for multiparametric assessment of hemodynamics in asymptomatic patients with severe AS.

Word count: 250

Doppler echocardiography plays a pivotal role in non-invasive hemodynamic assessment of aortic stenosis (AS). Among multiple available measures, peak aortic flow velocity (V_{max}), mean transvalvular gradient (MG) and effective aortic valve area, either simple (AVA) or indexed for body surface area (AVAI), are recommended for the assessment of the severity of AS. In particular, V_{max} >4m/sec, MG>40 mm Hg, AVA <1 cm^2 and AVAI<0.6 cm^2/m^2 have all been suggested as cutoffs indicating severe AS. [1-3] However, it has been recently shown that these parameters are not interchangeable, resulting into inconsistent estimates of the prevalence of severe AS, with potential implication for clinical follow-up and decision making.[4-6] Furthermore, while each of these criteria has been utilized for defining AS severity, their relative accuracy in predicting outcome is unresolved.

The apparent discrepancies in AS severity measures might be clinically relevant both in symptomatic and asymptomatic individuals. In symptomatic patients, inconsistencies among different echocardiographic parameters may lead to misinterpretation of symptoms and subsequent inappropriate delay of aortic valve replacement (AVR). In asymptomatic patients, such discrepancies can result in inappropriate follow-up strategies and hinder appropriate management. This is particularly relevant in elderly individuals, in whom interpretation of symptoms and management decisions are complicated further by multiple, age-related problems associated with AS.[7-9]

In order to resolve these challenging issues, we therefore chose to assess outcome in asymptomatic AS patients with normal left ventricular (LV) ejection fraction and at least one echocardiographic criterion for severe AS. The aim of the study was to evaluate whether different criteria have variable prognostic relevance in these patients, and whether the presence of multiple criteria might hold incremental value in predicting outcome.

METHODS

Patient Population. We enrolled subjects with a diagnosis of AS aged ≥21 years, consecutively studied at outpatient echocardiographic laboratories, having at least one of the following 4 criteria: V_{max} >4m/sec; MG>40 mm Hg; AVA <1 cm^2; AVAI<0.6 cm^2/m^2. Exclusion criteria were: any symptom attributable to AS; left ventricular (LV) ejection fraction <50%; the presence of additional valvular disease more than mild in severity; the presence of congenital heart disease except bicuspid aortic valve; previous valvular or aortic surgery, primary hypertrophic or restrictive cardiomyopathy; neoplastic disease or significant co-morbidity of potential prognostic impact.

Echocardiographic and Doppler Measurements. Echocardiography was performed with commercially available ultrasound systems. All patients underwent a comprehensive examination including M-mode and two-dimensional echocardiography, with continuous wave, pulsed and color Doppler, by experienced operators. For each measurement, three cardiac cycles were averaged. In all patients the LV end-diastolic and end-systolic volumes (indexed for body surface area) were measured using the biplane Simpson's rule method, from which the LV ejection fraction was calculated.[10] The LV mass (in grams) was calculated using the Devereux formula and then indexed for body surface area. Relative wall thickness was computed as 2x posterior wall thickness/LV radius at end-diastole.[10]

The LV outflow tract diameter was measured in mid-systole from the parasternal long-axis view below the aortic valve. Pulsed-wave Doppler sampling of the LV outflow tract was performed below the aortic valve at the point where the flow velocity dropped when moving the sample volume from the aortic valve level into the outflow tract, matching the location of LV outflow tract diameter measurement. Maximum velocity and velocity time integral were measured by tracing the modal velocity (middle of the dense signal) for use in the continuity equation and calculation

of stroke volume using an optimal signal . Transvalvular velocities were interrogated by continuous-wave Doppler (including a non-imaging transducer) from multiple windows to obtain V_{max}. Maximal instantaneous gradient across the aortic valve was calculated using a modified Bernoulli equation; MG was measured by tracing of the velocity curve. AVA was calculated by the continuity equation [3] and indexed for body surface area (AVAI). Calcification of the aortic valve was qualitatively assessed and classified as previously suggested.[3] Arterial blood pressure was measured at the right arm by a trained nurse, using a properly sized cuff sphygmomanometer.

Follow-up and Endpoints. Follow-up information was obtained from office visits or direct interviews with the patients, their relatives or their general practitioner. The endpoint was a composite of all-cause mortality and AVR. Mean follow-up duration was 26±22 months (range 4-122 months) and was completed in all study patients.

Particular attention was given to the information regarding indications for AVR and cause of death, so that the reports from in-hospital stay and death certifications were obtained in all patients and carefully examined. The primary indications for AVR were classified as (a) development of AS-related symptoms, (b) patients with severe AS who developed LV ejection fraction <50%; (c) patients with severe AS undergoing coronary artery bypass graft surgery; and (d) patients with severe AS undergoing surgery on the aorta. Causes of death was ascertained by the review of reports from in-hospital stay and death certifications.

Statistical methods. Continuous variables are expressed as mean±SD unless otherwise specified. Unpaired Student's t-test or one-way analysis of variance were employed for comparison of normally distributed data. Chi-square or Fisher's exact test, as appropriate, were utilized to compare noncontinuous variables expressed as proportions. Survival curves were constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. Hazard ratios and 95% confidence intervals were calculated using univariate and

multivariate Cox proportional hazard regression models. Multivariate analyses were performed with a stepwise forward regression model, by which only variables with a p-value of ≤0.05 (based on univariate analysis) were entered into the model; variables included age, gender, hypercholesterolemia, diabetes mellitus, arterial hypertension, coronary artery disease (defined as previous acute coronary syndrome and/or revascularization procedures, or positive stress tests of inducible ischemia, or any coronary artery stenosis >70% at coronary angiography), LV ejection fraction, LV mass index, V_{max}, MG, AVA, AVAI. All P-values are two-sided and considered significant when <0.05. Calculations were performed using a SPSS 12.0 software (Chicago, IL).

RESULTS

Baseline patient features. The study group consisted of 149 patients whose main clinical and echocardiographic characteristics are shown in Table 1 .

Table 1: Baseline characteristics of study patients. Data are reported as mean ± SD (range) unless otherwise specified.

Variable	Patients (n=149)
CLINICAL DATA	
Age (Years)	74.5±9.4 (40-94)
Male (n;%)	78 (52%)
Height (m)	1.66±0.1 (1.45-1.9)
Weight (kg)	74±13 (46-110)
Body surface area (m^2)	1.80±0.2 (1.2-2.28)
Body mass index (kg/m^2)	26.7±4.1 (16.5-40.4)
Systolic Blood Pressure (mmHg)	142±16 (105-185)
Diastolic Blood pressure (mmHg)	79.5±9.5 (50-110)
Arterial hypertension (n;%)	115 (77%)
Diabetes (n;%)	25 (16.8%)
Hypercholesterolemia (n;%)	57 (38%)

Coronary artery disease	24 (16%)
Current Smoking (n;%)	7 (4.6%)
ECHOCARDIOGRAPHIC DATA	
Left Ventricular end-diastolic diameter (mm)	50.1±5(37-64)
Inter-ventricular septal thickness (mm)	12.9±1.6 (8-18)
Posterior wall thickness (mm)	11.9±1.4 (8-17)
Left ventricular mass (g)	252.9±61 (135-458)
Left ventricular mass index (g/m^2)	141.1±35.3 (80-238)
Relative wall thickness	0.51±0.39 (0.3-0.76)
Left ventricular end-diastolic volume index (ml/m^2)	66±12 (40-90)
Left-ventricular ejection fraction(%)	61.2±5 (50-78)
Stroke volume index (ml/m^2)	44.1±9.6 (26,6-70
Peak aortic velocity (m/sec)	4.08±0.64 (2.6-6.8)
Mean aortic gradient (mmHg)	41.6±15.5 (13-115)
Aortic valve area (cm^2)	0.88±0.20 (0.45-1.5)
Indexed aortic valve area (cm^2/m^2)	0.45±0.62 (0.16-0.8)

Aortic valve calcification was severe in all subjects. Most patients (111; 74%) were >70 years. AVAI was <0.6 cm^2/m^2 in 142 (95%); 104 patients (70%) had AVA<1 cm^2, 82 (55%) V_{max} >4m/sec, and 77 (52%) MG>40 mmHg. MG was directly related to V_{max} (R^2=0.79, beta 0.89, p<0.001) and inversely to AVA (R^2=0.29, beta -0.54, p<0.001). AVAI was only moderately related to AVA (R^2=0.28, beta 0.53, p<0.001), V_{max} (R^2=0.18, beta -0.43, p<0.001) and MG (R^2=0.12, beta -0.35, p<0.001). LV stroke volume indexed for body surface area was higher in patients with MG>40 mmHg (46.7±9.2 ml/m^2) than in patients with MG<40 mm Hg (40.9±9 ml/m^2 ; p<0.001) and was below normal limits (<35 ml/m^2) in 22 patients (14.7%).

Outcome. During follow-up (26±22 months, range 4-122 months), a total of 86 patients (58%) either died (n=31;20%) or had AVR (n=55;37%). Survival was 95% at 1 year, 84% at 2 years, 76% at 3 years, 70% at 4 years; survival free of the combined end-point of all-cause mortality and

AVR was 84% at 1 year, 61% at 2 years, 46% at 3 years and 36% at 4 years. AVR was advised due to progression of symptoms in 48 patients or decline of LV ejection fraction (<50%) in 2, rapid progression of AS in 3 patients, and triggered by need for coronary artery revascularization in 2. The cause of death was of definite cardiovascular origin in 24 patients (including 2 ischemic strokes), of non-cardiac origin in 5 (including 1 with perioperative mortality at noncardiac surgery), and could not be determined in the remaining 2. Event-free survival at 4 years was not different in patients with stroke volume index < or ≥35 ml/m^2 (32% vs 37%, respectively, p=0.78) .

Relevance of multiparametric evaluation of AS to outcome. Event- free survival was significantly better in the 69 patients (46%) with ≤2 positive criteria for severe AS, compared with the remaining 80 patients who had ≥3 criteria (p<0.001) (Figure 1). There was a clear, additive trend towards a worse prognosis based on the number of positive criteria. In particular, survival was better for AS patients who had neither MG>40 mmHg nor V_{max} >4 m/sec compared with those who had at least one of these 2 criteria [58% (SE 8%) vs 19% (SE 11%) at 4 years]. Moreover, in 73 patients (49%) with MG≤40 mmHg, an AVAI <0.4 cm^2/m^2 (i.e.: the median value for AVAI) was associated with a 4 year event-free survival of 33% compared to 58% (P=0.001) (Figure 2).

At univariate Cox survival analysis, MG>40 mm Hg, V_{max} >4m/sec or their combination showed the best predictive capability for the combined end-point (Figure 3). At multivariate Cox survival analysis, the three independent predictors of outcome were male gender (HR 1.75, CI 95% 1.11-2.76; p=0.016), increased MG (HR per 10 mmHg increase 2.62, CI95% 1.66-4.15; p<0.001) and active smoking (HR 3.84, CI 95% 1.15-12.8; p=0.028). Predictors did not change after excluding the 5 patients without primary indication to AVR (data not shown). Of note, patients with ≥3 variables, compared to those with ≤2, had an almost 3-fold increase in likelihood for the combined end-point (HR 2.88, CI 95% 1.68-4,94; p<0.001).

DISCUSSION

Management of severe AS in the absence of symptoms is controversial and challenging [1-3, 5, 11-13]. Because of the natural history of severe asymptomatic AS, accurate echocardiographic grading is crucial for clinical decision making. Nevertheless, echocardiographic methods employed to this purpose have shown limitations in predicting symptom onset and outcome. Specifically, the relative predictive accuracy of the most commonly used parameters used to define severe AS (i.e.: V_{max} >4m/sec, or MG>40 mm Hg, or AVA <1 cm^2, or AVAI<0.6 cm^2/m^2) is unresolved. As a novel contribution we thus planned to assess the value of multiparametric echocardiographic evaluation in asymptomatic AS patients with ≥1 criterion for severe AS and normal LV ejection fraction. Our findings show that (i) V_{max} >4 m/sec and MG>40 mm Hg predicted the combined end-point of death or AVR more effectively than the area-related criteria, with MG>40 mm Hg resulting as the only independent echocardiographic predictor at multivariable analysis; (ii) the positivity for multiple criteria had a significant additive effect compared to any single criterion alone, in predicting worse event-free survival; and that (iii) in patients with MG≤40 mm Hg , an extreme narrowing of AVAI< 0.4 cm^2/m^2 provided increasing predictive value.

Increasing V_{max} has been related to the natural history of AS in multiple studies, over a broad range of values ranging from mild to very severe increase in aortic peak velocity. [12-16] Consistently, rate of progression of AS severity in terms of yearly changes in V_{max}, is prognostically relevant in asymptomatic patients with any grade of AS severity, both from referral centers and outpatient facilities.[3,5,9] Due to the strict relation between V_{max} and MG, the prognostic superiority over area-related parameters is similar for V_{max} and MG in the present study. However, because obstruction related to AS persists throughout the systolic ejection period, the relationship between V_{max} and mean gradient depends on the shape of the velocity curve, which varies with

stenosis severity and flow rate. [3] Thus, since MG is assessed from multiple mean instantaneous calculations around the whole continuous-wave Doppler envelope, it retains informations of the waveform shape, and it is likely more representative of the severity of AS than V_{max}. [17, 18] Thus, MG constitutes the optimal indicator of severity of obstruction by retaining all these information, and is more reliably related to invasive hemodynamics than peak aortic gradient [3,6, 17-20].

Conversely, conflicting results have been reported regarding the prognostic significance of AVA. Some recent studies, in fact, have demonstrated that AVA is not necessarily related to mortality [11, 15,16]. These results, however, could have been at least partially biased by referral criteria segmenting a priori subsets of AS patients enrolled in tertiary center studies. Indeed, a recent community study including AS patients without life-threatening comorbid conditions, with any degree of AS severity, and a wide range of clinical presentations, demonstrated AVA<1 cm^2 to be the only measure of AS severity independently predictive of survival on medical treatment. [21] Since AVA is related to cardiac output and therefore to body size [22], the correction for body surface area has been proposed in the early 1960's, with the advantage that indexing AVA for body surface area provides a measure of severity of aortic valve narrowing which also incorporates stroke volume index. A value of AVAI<0.7 cm^2/m^2 is generally proposed as a cut-off for severe AS .[23] Intriguingly, a similar AVAI value of ≤0.6 cm^2/m^2 has been shown to correlate with a LV stroke work loss of ≥30%.[24] Recently, in 103 consecutive, asymptomatic patients with AVA <1 cm^2 and a small average body surface area (1.50±0.15 m^2), AVAI <0.6 cm^2/m^2 was shown to be a significant predictor of outcome.[25]

For each value of AVA, different situations can be detected in terms of transaortic flow rates and pressure gradients, giving rise to a discordance between gradients and AVA. While such discrepancies might represent an inherent inconsistency of the criteria present in most guidelines, or reflect small body size or measurement errors [4,6] an increasing body of evidence now

supports the entity of low gradient severe AS with paradoxical low-flow (i.e.: reduced stroke volume index with normal ejection fraction) whose natural history seems to be comparable to severe narrowing of the AVA coexisting with high flow and high gradient.[11,26-29] Indeed, we observed no differences in outcome in our patients with low or normal stroke volume index.

The findings of the present study may have several implications for the hierarchical use of primary hemodynamic parameters recommended for assessment of risk associated with severe AS. The independent accuracy of MG>40 mm Hg underscores the need for accurate velocity recording from multiple acoustic windows, in order to optimize the assessment of aortic velocities, which remains the more robust and reproducible measurement in daily practice. Moreover, convergence of more measures should be interpreted as a further increase in predictive capability, with practical influences on follow-up and decision making. In patients with MG≤40 mmHg, who were characterized by lower stroke volume index, the same hierarchical approach can be proposed to identify those at greater risk. Indeed, further stratification of these patients based on an AVAI threshold of 0.4cm^2/m^2 provided a clinically meaningful predictor of the combined end-point, consistent with a recently proposed classification of severe asymptomatic AS. [11]

Irrespective of the parameter utilized for its assessment, our findings confirm that the prognosis of severe, asymptomatic AS is dismal.[15,16,30] Thus, it is important not to underestimate the hemodynamic severity of AS in patients with less than expected MG or V_{max} . [25-30] Maximal care should be paid in assessing each of the components of the continuity equation, particularly as regards consistency of LV stroke volume as assessed by Doppler with that assessed by evaluation of LV ejection fraction, but also to optimize hemodynamic systemic conditions know to potentially affect AVA (i.e.: systemic arterial hypertension). Furthermore, in selected patients, additional diagnostic tools (such as magnetic resonance, computed tomography

or cardiac catheterization) should be taken in consideration for proper assessment of severity. [28,30]

This study has several limitations. Although the baseline data were prospectively collected in consecutive patients with AS referred to the echocardiographic laboratory, the outcome data were retrospectively obtained. Moreover, we did not assess the rate of hemodynamic progression of AS in our patients, which have been shown to be an independent determinant of outcome in multiple clinical setting. Similarly, symptomatic status was not objectively assessed.. Future prospective studies are warranted to assess the value of multiparametric assessment in AS in the light of disease progression and n objective evaluation of functional capacity.

Conflict of interest. None

FIGURE LEGENDS

Figure 1: Kaplan-Meier event-free (overall-mortality and AVR) survival for patients with one or two criteria (n=69) and patients with three or four criteria (n=80).

Figure 2: Kaplan-Meier event-free (overall-mortality and AVR) survival for patients with MG > 40 mmHg and ≤40 mmHg with AVAI < or ≥0.4cm^2/m^2.

Figure 3: Univariate Cox regression analysis for the combined end-point (overall mortality and AVR) for each parameter and their combination (Hazard Ratio ± 95% confidence interval).

REFERENCE LIST

1. Vahanian A, Alfieri O, Andreotti F et al Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;**33**:2451-96
2. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol.* 2006;**48**:e1–e148.
3. Baumgartner H, Hung J, Bermejo j et al, Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *European Journal of Echocardiography* 2009; **10**: 1–25
4. Minners J, Allgeier M, Gohlke-Baerwolf C, et al Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. *Heart* 2010;**96**:1463– 8.
5. Dal-Bianco JP, Khanderia BK, Mookadam F et al. Management of asymptomatic severe aortic stenosis. *J Am Coll Cardiol*; 2008:**52:**1279-92
6. Flachskampf FA. Severe aortic stenosis with low gradient and apparently preserved left ventricular systolic function-under-recognized or overdiagnosed? *Eur Heart J*;2008:**29**:966-8
7. Bach DS, Siao D, Girard SE, Duvernoy C, McCallister BD, Gualano SK. Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement. The

potential role of subjectively overestimated operative risk. *Circ Cardiovasc Qual Outcomes* 2009;**2**:533-539

8. Schueler R, Hammerstingl C, Sinning JM, Nickenig G, Omran H. Prognosis of octogenarians with sever aortic valve stenosis at high risk for cardiovascular surgery. *Heart* 2010;**96**:1831-1836
9. Nistri S, Faggiano P, Olivotto I et al. Hemodynamic progression and outcome of asymptomatic aortic stenosis in primary care. *Am J Cardiol* 2012;**109**:718-23
10. Lang RM, Bierig M, Devereux RB, et al; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Eur J Echocardiogr* 2006;**7:**79-108.
11. Lancellotti P, Magne J, Donal E et al Clinical outcome in asymptomatic severe aortic stenosis. Insights from the new proposed grading classification. *J Am Coll Cardiol* 2012;**59**:224-32
12. Kitai T, Honda S, Okada Y et al Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis. *Heart* 2011;**97**:2029-32
13. Monin JL, Lancellotti P, Monchi M, et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. *Circulation* 2009;**120**:69 –75.

14. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–70

15. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation* 2010;**121**:151-6.

16. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005;**111**:3290-3295

17. Chamber JB. Aortic Stenosis. *Eur J Echocardiogr* 2009;**10**:111-9

18. Rajani R, Hancock J, Chambers JB. The art of assessing aortic stenosis. *Heart* 2012;**98**:iv14–iv22

19. Nishimura RA, Carabello BA, Hemodynamics in the cardiac catheterization laboratory of the 21st Century. *Circulation*. 2012;**125**:2138-2150

20. Geske JB, Cullen MW, Sorajja P, MD, et al , Assessment of left ventricular outflow gradients. Hypertrophic cardiomyopathy versus aortic valvular stenosis. *J Am Coll Cardiol Intv* 2012;**5**:675– 81

21. Malouf J, Le Tourneau T, Pellikka P et al. Aortic valve stenosis in community medical practice: determinants of outcome and implications for aortic valve replacement. *J Thorac Cardiovasc Surg* 2012;**144:**1421-7

22. Rahimtoola SH. Determining that aortic valve stenosis is severe: back-to-the-future. *J Am Coll Cardiol Img* 2010;**3**:563-6

23. Braunwald E, Roberts WC, Goldblatt A, et al. Clinical staff conference; aortic stenosis: Physiological, pathological and clinical concepts. *Ann Int Med* 1963;**58**:494-522

24. Tobin JR, Rahimtoola SH, Blundell PE et al Percentage of left ventricular stroke work loss: a simple hemodynamic concenpt for estimation of severity in valvular aortic stenosis. *Circulation* 1967;**35**:868-79

25. Saito T, Muro T, Takeda H et al. Prognostic value of aortic valve area index in asymptomatic patients with severe aortic stenosis. *Am J Cardiol* 2012;110:93-7

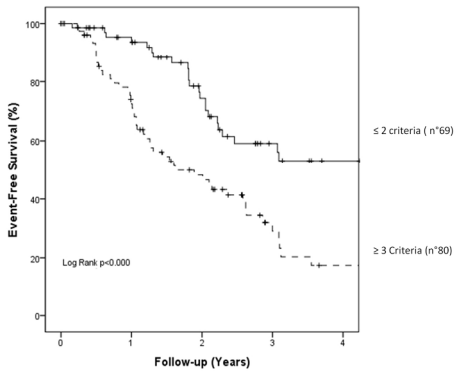
26. Clavel M-A, Dumesnil JG, Capoulade R et al Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2012;**60**:1259-67

27. Barasch E, Fan D, Chukwu EO, et al. Severe isolated aortic stenosis with normal left ventricular systolic function and low transvalvular gradients: pathophysiologic and prognostic insights. *J Heart Valve Dis* 2008;**17**:81– 8.

28. Lancellotti P, Donal E, Magne J, et al. Impact of global left ventricular afterload on left ventricular function in asymptomatic severe aortic stenosis: a two-dimensional speckle-tracking study. *Eur J Echocardiogr* 2010;**11**:537– 43.

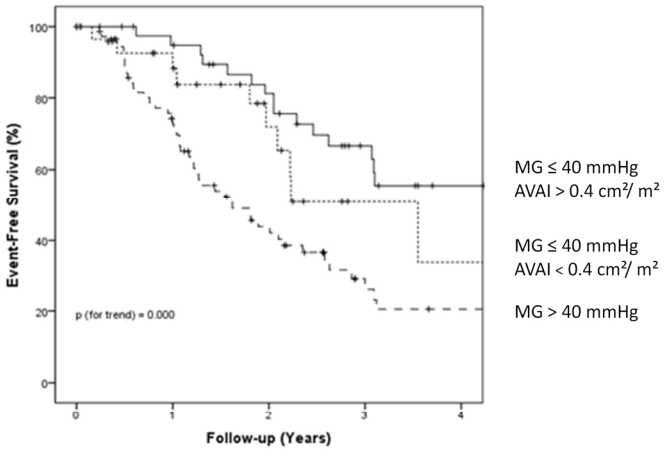
29. Rossi A, Nistri S, Cioffi G et al. Severe aortic valve stenosis with normal left ventricular function and low vs. high pressure gradient: Different hemodynamic profiles but similar clinical presentation, comorbidity and outcome. *Int J Cardiol*. 2012 [Epub ahead of print]

30. Herrmann S, Stork S, Niemann M, et al. Low-gradient aortic valve stenosis: Myocardial fibrosis and its influence on function and outcome. *J Am Coll Cardiol* 2011;**58**:402–12.



≤2 criteria	65	52	31	18	13
≥3 criteria	74	48	24	10	5

190x142mm (300 x 300 DPI)



190x142mm (300 x 300 DPI)

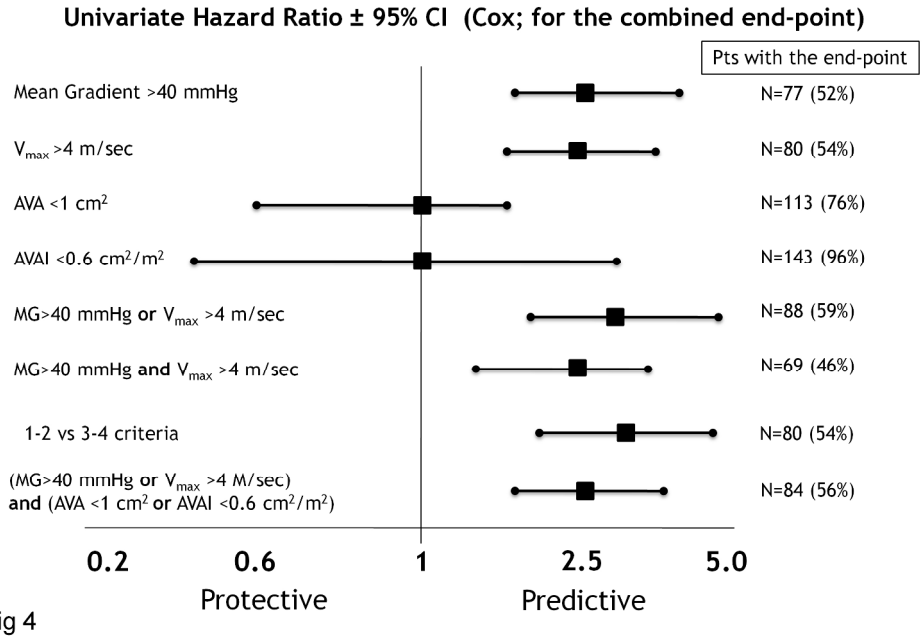


Fig 4

254x190mm (300 x 300 DPI)