HEART
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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

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Incremental Prognostic Value of Multiparametric Echocardiographic Assessment for Severe Aortic Stenosis

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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

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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

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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%)

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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

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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

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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).

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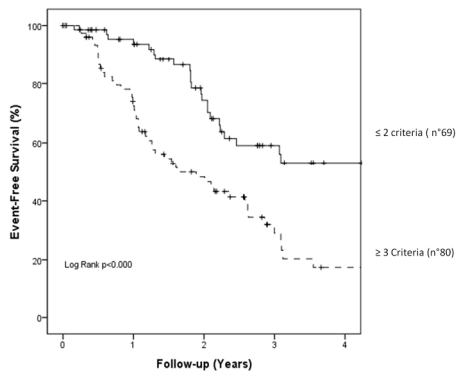
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| ≥3 criteria | 74 | 48 | 24 | 10 | 5 |

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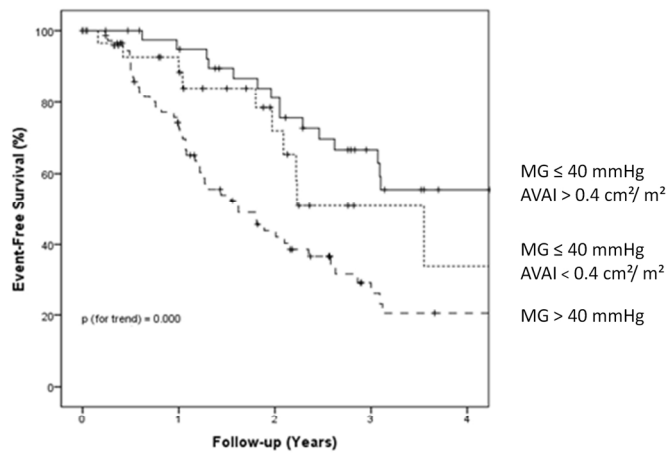48
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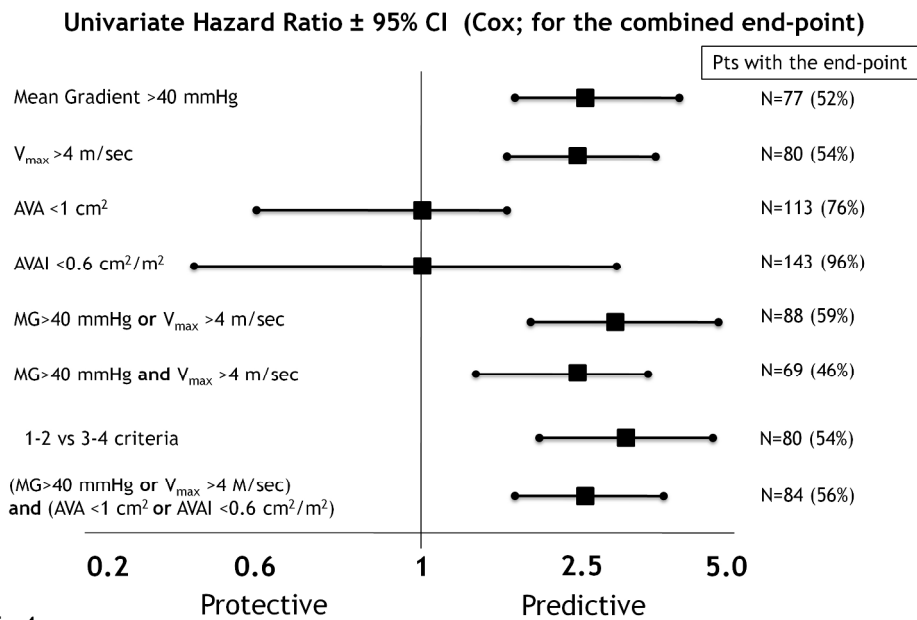52
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190x142mm (300 x 300 DPI)

Fig 4

254x190mm (300 x 300 DPI)