Clinical Efficacy of Doppler-Echocardiographic Indices of Aortic Valve Stenosis: A Comparative Test-Based Analysis of Outcome

Javier Bermejo, MD, Rodolfo Odreman, MD, Josefina Feijoo, MD, M. Mar Moreno, MD, Paz Gómez-Moreno, RDCS, Miguel A. García-Fernández, MD

Madrid, Spain

**OBJECTIVES**

This study was designed to assess which hemodynamic index best accounts for clinical severity of aortic stenosis (AS) and to analyze the value of low-dose dobutamine testing.

**BACKGROUND**

Pressure gradient and valve area are suboptimal because they depend on flow rate, correlate poorly with symptoms, and provide limited prognostic information. Recently, new indices and low-dose inotropic stimulation have been introduced, but their clinical value remains uncertain.

**METHODS**

A total of 307 consecutive patients with AS were included in an ambispective study design (71 ± 12 years old; peak jet velocity: 3.7 ± 1.1 m/s). Clinical and Doppler-echocardiographic data were obtained, as well as results of low-dose dobutamine infusion (47 patients). Using receiver-operator-characteristic curve analysis, we evaluated jet velocity, pressure gradient, valve area, resistance, stroke-work loss (SWL), and dobutamine-induced increase in area for predicting 1) symptomatic status at entry, 2) early (≤3 months) cardiovascular death or aortic valve replacement, and 3) long-term outcome. Logistic regression and Cox models were designed multivariate and adjusted by bootstrapping.

**RESULTS**

Only 28% of patients were alive without valve replacement at the end of the follow-up period (22 ± 4 months). The decision for valve replacement was made by the referring physician, blinded to the SWL, valve resistance, and dobutamine results. Non-flow-corrected indices performed better than valve area and valve resistance. Among them, SWL best predicted the defined end points. Odds/hazard ratios associated with a SWL Δ = 17% were 5.14 for presenting AS symptoms, 4.68 for early events, and 2.31 for late outcome. A cutoff value of SWL >25% best discriminated clinical end points. Other independent predictors of prognosis were symptomatic status and left ventricular ejection fraction. Dobutamine testing added no value to baseline models.

**CONCLUSIONS**

Non-flow-corrected indices show the highest clinical efficacy in aortic stenosis. Among these, SWL best predicts symptomatic status and outcome and therefore should be incorporated to aid patient management in unclear situations.

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Therapeutic decisions in adult aortic stenosis (AS) are based on the definition of symptomatic status and of hemodynamic severity (1). Accurate evaluation of these two issues is mandatory, because prognosis of asymptomatic patients is not improved by surgery (2) and because poor outcome follows replacement of nonseverely stenotic valves (3,4). However, establishing symptomatic status and severity of AS is not always straightforward. Assessment of subjective symptoms and functional capacity is frequently ambiguous, particularly in the elderly (5). Also, establishing disease significance can be challenging because a gold standard of valve obstruction is unavailable (6). Current hemodynamic assessment of severity relies on indices such as transvalvular pressure gradient (ΔP) and aortic valve area (AVA) that are obtained by cardiac catheterization or, more frequently today, by Doppler echocardiography (1). It is recognized that these indices are suboptimal because they correlate poorly with patients’ symptoms (7), provide little prognostic information (8), and depend on flow rate (9–11). Furthermore, the appropriate cutoff values of AVA and ΔP for establishing severity are unclear (12). On the basis of different fluid-dynamic assumptions, aortic valve resistance (AVR) and left ventricular (LV) stroke-work loss (SWL) have been proposed as alternative indices of AS (13–15), but their clinical value remains to be ascertained. Also, it has been suggested that stress echocardiography may play a prognostic role in AS (16); by unmasking the reserve of valve orifice enlargement available when cardiac output increases, stress echocardiography may predict patients’ symptoms and anticipate valve replacement (16).

Evaluation of diagnostic tests should be performed with a hierarchical framework in which clinical outcome efficacy represents the final objective of diagnostic imaging (17–19). Clinical outcome efficacy summarizes correlation with symptom severity, functional outcome, patient utility assessment, quality of life, morbidity avoided, and mortality rate (17,19). Previous longitudinal studies have aimed to identify...
natural-history predictors among classic indices of AS and have focused on selected patient groups such as asymptom-
atic (2,20–25) or moderate disease (26). Hence, a test-based comparative evaluation including conventional and alternative indices is lacking. The present study was designed to compare the clinical outcome efficacy of severity indices and of low-dose inotropic stress testing, in terms of 1) symptom correlation, 2) identification of critical disease, and 3) prediction of long-term prognosis.

METHODS

Study population. Two patient cohorts constitute the basis for this study. Forty-seven patients (15%) were prospectively enrolled on the basis of the following criteria: a diagnosis of valvular AS, a suitable echocardiographic window, New York Heart Association functional class I to III, absence of ventricular arrhythmias, and willingness to participate. Some of these patients have been the basis of a previous report (10), and the clinical efficacy of dobutamine testing was assessed in this cohort. A total of 275 patients were retrospectively recruited among all inpatients referred for a Doppler-echocardiographic examination from 4/97 to 4/98 in whom AS was diagnosed. Patients with any >2+ valvular regurgitation or more than mild mitral stenosis were excluded. Follow-up data were unavailable for 15 patients in the retrospective group; no patient from the prospective cohort was lost. The combination of the prospective and retrospective cohorts constitutes the basis for this report (Group A, n = 307). Group B was derived as the subgroup of Group A in whom all indices of AS were available (n = 154). Group B was used for selecting the models with best predictivity among different indices of AS (model building). The performance of these models was then measured in Group A (model testing and validation).

The study was approved by the institutional review board and written informed consent was obtained from all patients in the prospective cohort; informed consent was obtained from the patients of the retrospective cohort at the time of follow-up interview. Clinical characteristics of the study population are summarized in Table 1.

Clinical data. In the prospective cohort, a full clinical interview was performed at entry. Patients were carefully screened for the presence of dyspnea, angina, or syncope using New York Heart Association functional classification. Patients manifesting angina, syncope, congestive heart failure, or exercise dyspnea class ≥2 were classified as presenting symptoms attributable to AS. Comorbidity was assessed by patient anamnesis followed by careful review of medical records, and was coded using a well-validated score (27). Identical criteria were used for collecting clinical data in the retrospective cohort. Blood pressure was measured at the time of the echocardiographic examination in the prospective cohort and taken from the patient’s clinical record.

Table 1. Clinical and Echocardiographic Data of the Study Populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 307)</th>
<th>Group B (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>71 ± 12</td>
<td>71 ± 12</td>
</tr>
<tr>
<td>Gender [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>174 (57)</td>
<td>87 (56)</td>
</tr>
<tr>
<td>Rhythm [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus</td>
<td>215 (70)</td>
<td>97 (63)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>74 (24)</td>
<td>46 (30)</td>
</tr>
<tr>
<td>Pacemaker/other</td>
<td>18 (6)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>70 ± 13</td>
<td>70 ± 15</td>
</tr>
<tr>
<td>Systolic</td>
<td>129 ± 21</td>
<td>127 ± 22</td>
</tr>
<tr>
<td>Comorbidity index [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>90 (29)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>Angina</td>
<td>101 (33)</td>
<td>44 (29)</td>
</tr>
<tr>
<td>Exertional dyspnea</td>
<td>193 (63)</td>
<td>94 (61)</td>
</tr>
<tr>
<td>CHF</td>
<td>9 (3)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>NYHA functional class [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>80 (26)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>II</td>
<td>129 (42)</td>
<td>71 (46)</td>
</tr>
<tr>
<td>III–IV</td>
<td>98 (32)</td>
<td>53 (34)</td>
</tr>
<tr>
<td>Echocardiographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.49 ± 0.23</td>
<td>0.56 ± 0.14</td>
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<tr>
<td>Aortic regurgitation [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1/4</td>
<td>177 (58)</td>
<td>97 (63)</td>
</tr>
<tr>
<td>2/4</td>
<td>128 (42)</td>
<td>55 (36)</td>
</tr>
<tr>
<td>3/4</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Diastolic mitral inflow profile [n (%)]†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>122 (57)</td>
<td>58 (60)</td>
</tr>
<tr>
<td>Delayed relaxation</td>
<td>86 (40)</td>
<td>35 (36)</td>
</tr>
<tr>
<td>Restrictive</td>
<td>7 (3)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Aortic stenosis severity</td>
<td></td>
<td></td>
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<tr>
<td>AS jet peak velocity (m/s²)</td>
<td>3.7 ± 1.1</td>
<td>4.2 ± 1.0</td>
</tr>
<tr>
<td>Mean pressure gradient (mm Hg)</td>
<td>37 ± 23</td>
<td>48 ± 20</td>
</tr>
<tr>
<td>LV stroke-work loss (%)</td>
<td>21 ± 11</td>
<td>27 ± 9</td>
</tr>
<tr>
<td>Aortic valve area (cm³)</td>
<td>0.6 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Aortic valve resistance (dynes·cm⁻³)</td>
<td>354 ± 194</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± SD. *p < 0.05 for differences between Groups A and B. † Only from patients in sinus rhythm.

AS = aortic stenosis; CHF = congestive heart failure; LV = left ventricular; NYHA = New York Heart Association.
within a <5-h interval from the index exam in the retrospective group. An ad hoc study performed in our laboratory (40 consecutive inpatients) demonstrated limits of agreement between values of systolic blood pressure (SBP) measured in the laboratory and values written in the clinical records in the hospitalization wards to be +4 to +11 mm Hg (95% confidence interval [CI]).

**Doppler-echocardiographic examination.** Examinations were performed using phase-array ultrasound devices (Acuson Sequoia [Mountain View, California] or Hewlett-Packard [Andover, Massachusetts] Sonos 1500 and 2500) with 2.5/2.0 MHz duplex and 1.9 MHz (Pedoff) transducers. All exams were either performed (prospective cohort) or reviewed by one of the investigators. Images and spectrograms were obtained from parasternal, apical, subcostal, and suprasternal views. Left ventricular volumes and ejection fraction (EF) were measured as recommended (28). Aortic and mitral regurgitation were graded on the basis of color flow imaging. Mitral valve area was calculated according to transmittal pulsed-wave Doppler spectrograms as 1) restrictive, if the E/A ratio was ≥2 or E/A ratio was between 1 and 2 and E-wave deceleration time was ≤140 ms (29); 2) prolonged relaxation, if the E/A ratio was less than the 95% CIs of normal age-matched subjects or the deceleration time was above 95% CI limits (30); and 3) normal, if neither restrictive or prolonged relaxation criteria were met.

In the retrospective cohort, measurements of outflow tract diameter and pulsed-wave spectrogram required to calculate AVA were performed when peak jet velocity was >3 m/s or LV function was abnormal. This represents current clinical practice in our laboratory and follows cost-efficacy recommendations (31). Patients in whom outflow tract diameter and spectrograms were not recorded were included in Group A but not in Group B. Measurements were averaged from 4 to 6 beats of patients in sinus rhythm and from 6 to 10 consecutive beats in patients in atrial fibrillation. Valve area and ΔP were calculated using the continuity and Bernoulli equations, respectively. Valve resistance was calculated as 28 · √ΔP/AVA (10). Left ventricular SWL was expressed as percentage and obtained as 100 · ΔP/(ΔP + SPB) (9,15). Reproducibility values of indices of AS in our laboratory have been reported (10).

In the prospective group, a low-dose dobutamine infusion protocol was begun after the baseline study at 5 µg/kg body weight/min up to 20 µg/kg/min, titrated upwards at steps of 5 µg/kg/min every 5 min (10). Doppler spectrograms of LV outflow tract and AS jet velocity were obtained within the last 2 min of each dose. Blood pressure was monitored using automatic sphygmomanometry. All concomitant vasodilator and beta-blocker therapy was suspended 24 h before the index examination. Dobutamine-induced aortic orifice enlargement was calculated as the absolute difference between values of AVA observed at peak flow rate and at baseline.

**Patient outcome and definition of end points.** Clinical and Doppler echocardiographic patient follow-up was performed on a yearly basis in the prospective cohort. At the end of the four-year follow-up period, medical charts from the whole study group were reviewed and patients alive were directly interviewed. The composite outcome end point was defined as cardiac death or aortic valve replacement during the follow-up period. Death was classified as either cardiac or noncardiac according to patient medical records, information provided by the referring physician, and autopsy data when available. Identical criteria were used in the retrospective cohort. Aortic stenosis was defined in clinical terms as critical when the patient’s aortic orifice was small enough to cause symptoms and require valve replacement or induce cardiac death during the three months following patient enrollment. This three-month criterion was established at the time of study design because it is the maximum time recommended for valve replacement for patients who develop symptoms (25); also, three months is above the time for performing valve replacement once indicated at our institution. The decision to indicate valve surgery was made by the patient’s physician, according to his own interpretation of symptomatic status. Valve area and ΔP were reported to the referring physician, whereas AVR, SWL, and the response to dobutamine were withheld. Patients dying from noncardiac causes were censored at the date of death, and patients still alive without valve replacement were censored at the end of the follow-up period.

**Statistical analysis.** Variables are described as mean ± SD. Association among hemodynamic indices was assessed by cluster analysis based on Spearman’s correlation coefficient. All predictive models were designed multivariate. Logistic regression models were used to assess symptom correlation and identification of critical AS, whereas long-term outcome was analyzed by Cox proportional-hazards survival analysis. Five AS indices (peak transaortic jet velocity [Vmax], ΔP, AVA, AVR, and SWL) as well as dobutamine-induced increase in AVA were compared. For covariable testing, a composite severity score was computed as the first term of the principal components analysis based on the correlation matrix of all indices. This score therefore synthesizes average prediction capability of the five indices, providing equal weight to each of them. Factors previously reported to correlate with disease symptoms or outcome (age, comorbidity, rhythm, symptomatic status, functional class, LV mass, volumes, diastolic profile, and EF) were tested as covariables and entered in full saturated models for each prediction, including only the composite score as index of severity. Then, relevant covariables were selected by backward stepwise variable selection based on Alkaike’s information criterion (32). Next, each severity index was consecutively substituted in place of the composite severity score. Finally, dobutamine-induced increase in AVA was forced in the model of the index showing best baseline relationship with outcome.
prediction (prospective cohort). Models were validated by resampling 400 bootstrap replications to exclude overfitting. Agreement between each dataset (training sample) and the original data (test sample) was excellent (slope shrinkage factor 0.9; maximum absolute error in predicted probability 0.02) (32). Efficacy was compared computing bias-corrected and adjusted areas under the receiver-operator characteristic (ROC) curves for models containing each of the severity indices (33). Using these models in Group A, cutoff values were obtained using classification-and-regression trees (34), followed by the log-rank test when appropriate. All analyses were performed using S-Plus software (MathSoft, version 2000), expanded by public-domain libraries “survcart” (35), and “design” and “hmisc” (32,36). Statistical significance was assumed at \( p < 0.05 \).

RESULTS

Correlation among hemodynamic indices. Figure 1 shows the association among the five indices of severity. Non–flow-corrected indices (Vmax, \( \Delta P \), and SWL) correlated closely into a single cluster, whereas flow-corrected indices (AVA and AVR) were grouped in another one. Correlation between these two clusters was fair (\( \rho = 0.37 \)).

Patient outcome. The follow-up period was 14 ± 16 months (range 10 days to 55 months, median 6 months). For patients without early events, the follow-up period was 22 ± 14 (median 21) months. Outcome of Groups A and B is summarized in Figure 2. There were fewer symptomatic and critical AS patients in Group A than in Group B (71% vs. 81%, \( p = 0.02 \); and 39% vs. 55%, \( p = 0.002 \), respectively). A very high event rate was observed in the study population, resulting in the fact that only 28% were alive without valve replacement at the end of the follow-up period. Probability for performing valve replacement in symptomatic patients was related (multivariate logistic regression) to younger age (95% CI odds ratio [OR] for \( \Delta \) 14 years: 0.15 to 0.47; \( p < 0.0001 \)), higher \( \Delta P \) (95% CI OR \( \Delta \) 34 mm Hg: 3.70 to 13.6; \( p < 0.0001 \)), and less comorbidity (95% CI OR \( \Delta \) 2 score points: 0.34 to 0.85; \( p = 0.007 \)).

The ROC analysis of clinical efficacy end points is shown in Figure 3, best unadjusted cutoff values for hemodynamic indices to predict outcome are summarized in Table 2, and the results of multivariate prediction models are shown in Table 3.

Prediction of symptomatic status. No covariables were retained in the models of symptomatic status prediction. Box plots of severity indices according to symptomatic status demonstrated significant overlap of values of AVA
and AVR between symptomatic and asymptomatic patients; among non-flow-corrected indices, the discriminative power of SWL was highest (Figs. 3 and 4). Sensitivity, specificity, and positive and negative predictive values (95% CI) for the SWL criterion of \( \leq 23\% \) vs. >23\% were 0.54 (0.48 to 0.59), 0.81 (0.74 to 0.87), 0.89 (0.83 to 0.93), and 0.42 (0.36 to 0.48), respectively. The dobutamine test did not increase predictive accuracy to the model based on SWL in the prospective cohort (Wald chi-squared \( \chi^2 \) = 1.30; \( p = 0.2 \); area under the ROC curve 0.80 vs. 0.80 with and without dobutamine increase in AVA).

**Identification of critical aortic stenosis (early cardiac events).** Other than AS severity, symptomatic status and EF at enrollment were identified as independent covariables related to critical disease. Non-flow-corrected indices of AS performed better than AVA and AVR and, among them, SWL was the index showing highest area under the ROC curve (Fig. 3); also in the validation group, SWL showed the best predictive accuracy. Figure 5A illustrates the regression tree for predicting a critical AS in Group A. Entering dobutamine test information added no prognostic information to the previous model in the prospective cohort.

**Table 2. Unadjusted Best Cut-Off Values of AS Indices to Predict Clinical Outcome**

<table>
<thead>
<tr>
<th>Index Study Group</th>
<th>( V_{\text{max}} ) (m/s)</th>
<th>( \Delta P ) (mm Hg)</th>
<th>SWL (%)</th>
<th>AVA (cm²)</th>
<th>AVR (dynes/s/cm⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Clinical efficacy objective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS symptoms</td>
<td>3.4</td>
<td>3.2</td>
<td>29</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Late AS events</td>
<td>4.1</td>
<td>4.1</td>
<td>46</td>
<td>46</td>
<td>25</td>
</tr>
<tr>
<td>Critical AS</td>
<td>3.4</td>
<td>3.7</td>
<td>30</td>
<td>41</td>
<td>26</td>
</tr>
<tr>
<td>Average</td>
<td>3.6</td>
<td>3.7</td>
<td>35</td>
<td>38</td>
<td>23</td>
</tr>
</tbody>
</table>

AS = aortic valve stenosis; AVA = aortic valve area; AVR = aortic valve resistance; \( \Delta P \) = mean transvalvular pressure gradient; SWL = LV percentage stroke work loss; \( V_{\text{max}} \) = peak transaortic jet velocity.
model for assessing the risk of cardiac death were SWL (95% CI HR Δ13%: 1.13 to 1.92), comorbidity (95% CI HR Δ2 points: 1.02 to 1.26), age (95% CI HR Δ14 years: 1.35 to 2.52), presence of AS symptoms (95% CI HR ∆1.09 to 2.68) and EF (95% CI HR Δ15% 0.52 to 0.86).

The superiority of non-flow-corrected indices over AVA and AVR was corroborated in patients in sinus rhythm for the three major efficacy end points.

**DISCUSSION**

Onset of dyspnea, angina, or syncope identifies a critical point in the natural history of AS (37). Once symptoms appear, average survival rapidly falls and prompt valve replacement is warranted. Because the risk of sudden death while patients remain asymptomatic does not outweigh the complications of artificial prostheses, valve replacement should be withheld until patients become symptomatic (1). Although they are well established, it is recognized that these guidelines are based on retrospective studies that defined the spontaneous course of mostly congenital and rheumatic disease (20,22,37,38). Today’s clinical spectrum of AS is different. Calcific-degenerative has become the most frequent etiology, and AS is now a highly prevalent disease in the elderly (39,40). These changes are frequently responsible for uncertainty regarding the definition of optimal timing of valve replacement in individual patients. First, defining symptomatic status is particularly difficult in the elderly (5). Second, whether mild exertion dyspnea should be considered an index symptom in order to recommend surgery also remains controversial (25). Third, degenerative AS is known to be related to widespread cardiovascular involvement (41), and even when symptoms are clear, it may be impossible to discern whether they are related to the disease or to associated ischemic or hypertensive cardiomyopathy. Finally, concomitant obstructive lung disease, a common disease in the elderly, may account for patients’ dyspnea instead of AS (5).

A robust measurement of disease severity is mandatory in these contexts. It is recognized that clinical outcome is the only end point available for defining severity, owing to the lack of any hemodynamic gold standard (2). This is the first study to compare clinical efficacy of different indices of AS and demonstrates the superiority of non-flow-corrected indices in a broad population. Multiple theoretical and technical studies have demonstrated that AVA is the index that best characterizes the severity of the outflow obstruction caused by a stenotic valve (42,43). However, best technical efficacy does not necessarily imply superior clinical outcome efficacy (18). Although they are limited to measuring AS severity from a fluid-dynamic viewpoint, non-flow-corrected indices account for additional factors such as LV and systemic response to the outflow obstruction.

Among non-flow-corrected indices, SWL showed highest clinical efficacy, even in patients with impaired LV function. The present study demonstrates that if SWL is
Probability of showing symptoms attributable to AS is >23%, probability of showing symptoms attributable to AS is >80% at the time of the echo-Doppler exam; if SWL is ≥25%, median cardiac survival without valve replacement is close to one year, or slightly better if the patient is asymptomatic; and if SWL is >26%, probability of events is 30% in the following three months, increasing to 87% if the patient is symptomatic. Although it may be argued that valve replacement is a "soft" end point that is arbitrarily determined during the natural history of the disease, it is noteworthy that referring physicians based their decision to operate on AVA and ΔP, unaware of the values of SWL. Furthermore, 67 out of 198 AS events (34%) were cardiac deaths, thereby allowing assessment of the natural history of the disease in a relatively large number of patients.

Although SWL was proposed more than 30 years ago (15), little attention has been paid to its clinical application. From a fluid-dynamic basis, this index represents the amount of energy the LV dissipates as heat because of outflow obstruction (15,44). Invasive studies have demonstrated an inverse and quadratic correlation between SWL and AVA, and values >30% predict a critically narrow orifice (44); this value is close to the cutoff values identified in the present study. A number of reasons may account for the highest outcome efficacy of this index. According to its formula, SWL can be interpreted as a blood-pressure normalization of ΔP. Low systolic blood pressure is a hallmark of severe AS (45), and SWL accounts for such effect: higher values are obtained as blood pressure falls for a given ΔP. Blood pressure response to AS is known to be subject to a number of factors, particularly age. Therefore the findings of our study, demonstrating maximal prognostic value of SWL in a cohort with a majority of elderly patients, justify further investigation on peripheral adaptation to AS. Also, even though flow-normalized indices such as AVA are theoretically the most robust measurements of severity, follow-up studies of unselected patients have found prognostic value to be highest for non–flow-corrected indices such as Vmax and ΔP (8,25,46). Placed above the other diagnostic goals, increased clinical outcome efficacy is probably the consequence of improved technical and diagnostic-accuracy efficacy (19). Stroke-work loss is based only on pressure estimates, without the need of measuring flow rate. Because the latter is the most important source of error and variability, both in Doppler and cardiac catheterization-derived hemodynamic calculations (10,46), SWL can be more accurately obtained than AVA and AVR, particularly in patients in atrial fibrillation. Also, ΔP has shown to correlate with symptomatic status (47), and its combination with blood pressure has been demonstrated to powerfully predict survival in unoperated patients (48). Stroke-work loss mathematically incorporates both ΔP and systolic blood pressure, and therefore adds their individual statistical value.

The demonstration of flow-mediated changes in AVA led some authors to postulate that stress interventions may unmask the opening reserve available for patients to increase

![Figure 4](image-url)
their cardiac output (9,16,49). As valves become stiffer, valvular reserve would decline and limit the capability of the ventricle to increase output. Once valvular reserve reaches a critical point, patients would develop characteristic exercise symptoms. Because valve stiffness is not directly related to baseline AVA, stress interventions are required to assess it (10,50). However, both the present and a previous (2) study have failed to find any additive clinical value of stress testing in cohorts of patients with mostly normal LV function.

Figure 5. Validation of clinical efficacy models in Group A. (A) Regression tree for calculating the probability of suffering critical aortic stenosis (AS) (prob) according to stroke-work loss (SWL), presence or absence of symptoms, and ejection fraction (EF). (B) Cumulative probability of long-term outcome according to SWL and symptomatic status. Patients with critical AS have been excluded. (C) Probability of early and late AS events in patients with impaired left ventricular function (EF < 0.45). p = probability of long-rank test for comparisons between categories.
Study limitations. Stroke-work loss in the retrospective cohort was calculated using non-simultaneous measurements of \( \Delta P \) and SBP. As stated earlier, systolic blood pressure in the echocardiography laboratory was higher than values registered in the clinical records. However, the impact of this small bias on calculated SWL is negligible: an increase of SBP of 11 mm Hg (upper 95% CI of bias) translates to only a 1% absolute decrease in SWL (23% to 22%, for average values of \( \Delta P \) and SBP in Group A).

The purpose of the study was to assess clinical performance of AS diagnostic tests and not to analyze natural-history predictors. Hence, the goal was to recruit a representative sample of most subjects in whom clinical indices are employed to guide clinical management, as recommended for test evaluation designs (51). Furthermore, the data analysis strategy was designed to minimize the number of variables tested, and the stability of the final models was demonstrated by resampling techniques. Using these methods, overfitting is remarkably reduced, allowing validation populations to include groups used for model definition (32).

Conclusions. The present study demonstrates that non-flow-corrected indices of AS are the most clinically efficient in terms of predicting symptomatic status and outcome. Among them, SWL is the Doppler-echocardiographic index that best accounts for clinical severity of adult AS. Patients showing values >25% are likely to be symptomatic and have an adverse outcome, irrespective of symptomatic status. Thus, SWL should be incorporated in clinical assessment of AS and used to aid patient management in unclear situations. Inotropic stimulation is of no prognostic value in unselected patients.

Acknowledgment
We are indebted to Catherine M. Otto for her suggestions on data presentation.

Reprint requests and correspondence: Dr. Javier Bermejo, Laboratory of Echocardiography, Department of Cardiology, Hospital General Universitario Gregorio Marañón, Dr. Esquerdo 46. 28007 Madrid, Spain. E-mail: javbermejo@jet.es.

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