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Clinical Utility and Prognostic Value of Appropriateness Criteria in Stress Echocardiography for the Evaluation of Valvular Heart Disease

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We examined the prognostic value of stress echocardiography appropriateness criteria for evaluation of valvular heart disease in 100 consecutive patients. Of the studies, 49%, 36%, and 15% were classified as appropriate, uncertain, and inappropriate, respectively. Over a median of 12.6 months, 24 events (12 deaths and 12 heart failure admissions) occurred. The 12-month event-free survival was significantly reduced in patients with appropriate or uncertain studies compared with patients with inappropriate studies ($p = 0.04$ and $p = 0.005$, respectively). There was no survival difference between patients with an appropriate or uncertain indication ($p = 0.1$). The only independent predictors of events were a positive stress echocardiogram (hazard ratio: 15.5, $p < 0.0001$) and left ventricular ejection fraction (hazard ratio: 0.95, $p = 0.02$). The appropriateness criteria for evaluation of valvular heart disease provide the ability to differentiate between patients at high- (appropriate group) and low- (inappropriate group) risk of cardiac events. Reclassification of the uncertain group may improve the differential value of these criteria.

The growth of cardiovascular imaging over the past 2 decades (1), coupled with increasing associated economic costs, led the American College of Cardiology Foundation to publish appropriateness criteria (2). The purpose was to promote efficient and effective use of cardiovascular imaging. Several investigators have validated the stress echocardiography appropriateness criteria for patients with coronary artery disease (3–5) as a tool to distinguish between patients at high probability of a positive result and an adverse prognosis and those patients with a low probability of a positive result and an excellent prognosis. The application of these criteria in clinical practice may limit the number of unnecessary investigations performed.

Population studies have shown that the prevalence of valvular heart disease increases with age and is associated with excess cardiac mortality (6). The burden of valve disease in the population is likely to increase as the population ages. The physiological effect of valvular heart disease is a dynamic process. Alterations in loading conditions, valve compliance, and ventricular performance that occur on exercise/

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altered flow states can uncover the severity of valve dysfunction and thereby a patient's symptoms status (7). Over the past decade, several investigators have identified the value of stress echocardiography to correlate exercise-induced symptoms with changes in hemodynamics in mitral valve disease in patients with only mild or moderate resting valve disease (8–12) and the prognostic value in asymptomatic patients with severe aortic stenosis (13,14). Furthermore, the use of dobutamine stress echocardiography is useful to identify truly severe aortic stenosis in low-flow, low-gradient aortic stenosis (15,16). Recent guidelines advocate the use stress echocardiography to help risk-stratify patients to aid the diagnosis and, in selected cases, guide decisions for valve intervention (17). No data exist with regard to the value of stress echocardiography appropriateness criteria in these groups.

We therefore sought to investigate the prognostic value of stress echocardiography and the clinical utility of appropriateness criteria in patients referred for stress echocardiography to investigate valvular heart disease.

Methods

One hundred consecutive patients who underwent stress echocardiography in the echocardiography laboratory at our institution between October 2010 and May 2012 were evaluated. The study was approved by the institutional review board.

Valve protocols. For assessment of the severity of exercise-induced mitral regurgitation, mitral stenosis, and asymptomatic severe aortic stenosis and regurgitation, a symptom-limited bicycle test was performed with patients in a semisupine position on a tilting exercise bicycle. Baseline images were acquired. Exercise was performed starting at a workload of 25 W. Every 2 min, the workload increased by 25 W. Two-dimensional and Doppler echocardiography measurements were made at rest and at peak exercise. The test was stopped if limiting symptoms including chest pain and dyspnea occurred or significant adverse hemodynamic changes occurred.

For all tests, both at rest and peak stress, left ventricular systolic and diastolic volumes and left ventricular ejection fraction were calculated using Simpson biplane method, and estimated pulmonary artery systolic pressure was calculated from the transtricuspid pressure gradient using the modified Bernoulli equation, taking inferior vena cava size and respiratory variation into account. The severity of mitral regurgitation at rest and stress was measured using the proximal isovelocity method. A sample of 10 patients was reread to calculate interobserver variability. In rare cases in which this parameter could not be obtained, the vena contracta was measured. The severity of mitral stenosis was assessed by measuring the mean transmitral gradient at rest and at peak stress. For asymptomatic severe aortic stenosis, the change in mean transaortic pressure gradient between rest and stress was measured. For patients with asymptomatic severe aortic regurgitation, left ventricular ejection fraction and left ventricular volumes were assessed at rest and at stress. The criteria used for a positive test are summarized in Table 1.

Low-dose dobutamine protocol for low-gradient, low-flow, and low–ejection fraction severe aortic stenosis. The definition of low-flow, low-gradient, low–ejection fraction severe aortic stenosis was aortic valve area $\leq$1 cm^2, mean gradient <40 mm Hg, and ejection fraction $\leq$40%. After comprehensive echocardiography, a dobutamine infusion of 5 μg/kg/min was started. This was increased in 5 μg/kg/min increments every 5 min to a maximum of 20 μg/kg/min. At each stage, the left ventricular outflow tract Doppler (pulse wave), transaortic Doppler (continuous wave) and biplane left ventricular volumes were measured. The transaortic gradient was calculated from the simplified Bernoulli equation. The left ventricular outflow tract diameter was measured at rest and assumed to be constant throughout the test. The aortic valve area was calculated using the continuity equation. The presence of contractile reserve was defined as an increase in stroke volume by $\geq$20%. Severe aortic stenosis was identified when contractile reserve was present, there was an increase in mean transaortic gradient, and the aortic valve area remained <1 cm^2. Moderate aortic stenosis was identified when contractile reserve was present and there was an increase in aortic valve area >1 cm^2. When contractile reserve was

Table 1. Criteria for a Positive Stress Echocardiogram

Valve Assessment	Criteria for Positive Test Results
Assessment of mitral regurgitation in patients with symptoms but mild or moderate mitral regurgitation at rest	Increase in severity of mild or moderate mitral regurgitation to severe. Effective orifice area $\geq$0.4 cm^2 (organic) or $\geq$0.2 cm^2 (functional)
Assessment of asymptomatic severe mitral regurgitation	Increase in pulmonary artery systolic pressure >60 mm Hg
Assessment of mitral stenosis in patients with symptoms but mild or moderate mitral stenosis at rest	Increase in the mean transmitral gradient $\geq$15 mm Hg or estimated pulmonary artery systolic pressure $\geq$60 mm Hg
Assessment of asymptomatic severe mitral stenosis	As above and symptoms
Assessment of asymptomatic severe aortic stenosis (AVA <1 cm^2)	Increase in mean transaortic gradient $\geq$20 mm Hg
Assessment of asymptomatic severe aortic regurgitation	Lack of increase in LVEF $\geq$5% or exercise-induced reduction in LVEF

AVA = aortic valve area; LVEF = left ventricular ejection fraction.

not present, it was not possible to determine the exact severity of aortic stenosis.

Pre-test and outcome data. Demographic factors, risk factors, medical history, medication, and stress echocardiography test indications and results were prospectively collected at the time stress echocardiography was performed. Follow-up and outcome data were derived from the hospital electronic patient record data, which include outpatient and inpatient encounters. Follow-up time was calculated from the initial test date to either the date of a cardiac event or the date of the last contact with the patient. Indications for stress echocardiography were classified as appropriate, inappropriate, or uncertain according to guidelines (2). Worsening heart failure was defined as worsening New York Heart Association functional class or signs of fluid retention.

Each patient was categorized by 2 independent reviewers of the data. In cases in which the classification was not consistent between the 2 reviewers, the patient data was jointly reviewed and a consensus opinion was reached between the 2 reviewers.

Statistics. Data are expressed as median and interquartile range or number and percentage. The chi-square test was used to compare categorical variables. When the number of categorical variables was <5, the Fisher exact test was used. The endpoint was a composite of admission for worsening heart failure or death (whichever occurred first). Logistic regression was used to identify predictors of a positive stress echocardiogram. The Kaplan-Meier method was used for event-free survival analysis. The log-rank test was used to compare differences between survival curves. Cox regression analysis was used to identify predictors of survival. For quantification of mitral regurgitation, interobserver concordance was expressed as exact agreement. All tests of significance were 2 sided. A p value <0.05 was considered statistically significant. Statistical analysis was performed using StatsDirect Version 2.5.7 (StatsDirect, Altrincham, United Kingdom).

Table 2. Baseline Demographic Factors

	Appropriate (n = 49)	Uncertain (n = 36)	Inappropriate (n = 15)	p Value
Age, yrs	65.3 ± 17.5	71.9 ± 11.5	62.5 ± 19	0.17
Female	26 (53.0)	20 (55.6)	8 (53.3)	0.97
Median follow-up, months	12.2 (7.3–15.6)	13.0 (8.4–23)	13.0 (12–14.5)	0.19
Smoker	5 (10.2)	3 (8.3)	2 (13.3)	0.86
Hypertension	18 (36.7)	16 (44.4)	6 (40.0)	0.78
Diabetes	5 (10.2)	5 (13.9)	3 (20.0)	0.61
Hyperlipidemia	10 (20.4)	12 (33.3)	5 (33.3)	0.22
Previous CABG	5 (10.2)	4 (11.1)	2 (13.3)	0.94
Previous PCI	7 (14.3)	5 (13.9)	2 (13.3)	0.99
LVEF, %	50.8 ± 14.5	58.9 ± 10.4	57.5 ± 14.4	0.08
LVEDD, cm	5.4 ± 0.7	5.3 ± 0.5	5.1 ± 0.8	0.44
Interventricular septum thickness, cm	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.1	0.21
Left atrial diameter, cm	4.4 ± 0.8	4.5 ± 0.9	4.0 ± 0.5	0.22
Mitral stenosis	3 (6.1)	2 (5.6)	3 (20.0)	0.18
Mitral regurgitation				
Functional	10 (20.4)	14 (38.9)	6 (40.0)	0.12
Degenerative	7 (14.3)	10 (27.8)	5 (33.3)	0.17
Aortic stenosis				
Low gradient, low flow	26 (53.1)	0 (0.0)	0 (0.0)	<0.0001
Severe, asymptomatic	0 (0.0)	8 (22.2)	0 (0.0)	0.001
Aortic regurgitation	3 (6.1)	2 (5.5)	1 (6.6)	0.98

Values are mean ± SD, n (%), or n (interquartile range).
CABG = coronary artery bypass graft; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Results

Between October 2010 and May 2012, 100 consecutive patients who underwent stress echocardiography were identified. Baseline demographic factors are documented in Table 2.

Of the 100 patients who were assessed with stress echocardiography for the evaluation of valvular heart disease, 34 (34%), 52 (52%), 8 (8%), and 6 (6%) studies were for assessment of aortic stenosis, mitral regurgitation, mitral stenosis, and aortic regurgitation, respectively. Of the 100 patients, 49 (49%), 36 (36%), and 15 (15%) were classified as appropriate, uncertain, and inappropriate, respectively.

A positive test result was identified in 32 patients (32%). A positive test result occurred in 19 patients (38.8%) with an appropriate indication, in 13 patients (36.1%) with an uncertain indication, and in no patients with an inappropriate indication ($p < 0.0001$). Exact agreement between graders was obtained in 92 (92%) patients. In 8 patients, a consensus opinion was reached. Mitral regurgitation quantification by the proximal isovelocity method was achieved in 46 (88.5%) of the 52 patients undergoing mitral regurgitation assessment. Interobserver differences ranged from 0% to 5% (mean, 1.7%). Exact agreement between graders was reached in 70% of patients. The remaining 6 patients were graded using a combination of vena contracta and jet area.

During a median follow-up of 12.6 months (interquartile range, 8.8 to 17.5 months), a total of 24 events (12 heart failure admissions and 12 deaths) occurred. Of the 32 patients with positive test results, events occurred in 18 (56.3%) patients compared with only 6 (8.8%) events in the 68 patients with a negative stress echocardiogram ($p < 0.001$). Figure 1 shows the Kaplan-Meier survival curves of the patients with positive and negative stress echocardiograms. Logistic regression showed no baseline demographic or clinical features were independent predictors of a positive valve stress echocardiogram (Table 3).

Events occurred in 11 patients (22.4%) with an appropriate indication, in 13 patients (36.1%) with an uncertain indication, and in no patients with an inappropriate indication. Kaplan-Meier curves (Fig. 2) showed that event-free survival was significantly reduced in patients with an appropriate indication compared with those with an inappropriate indication ($p = 0.04$) and in patients with an uncertain indication compared with those with an inappropriate indication ($p = 0.005$). There was no significant survival difference between patients with an appropriate or uncertain indication ($p = 0.1$). Cox regression analysis showed that a positive stress echocardiogram (hazard ratio: 15.5; interquartile range, 4.2 to 57.4; $p < 0.0001$) and left ventricular ejection fraction (hazard ratio: 0.95, interquartile range, 0.91 to 0.98; $p = 0.02$) were the only independent predictors of events among prognostically important clinical and echocardiographic variables (Table 4). Although there was a higher mortality rate in the appropriate group (8 deaths [16.3%]) and uncertain group (4 deaths [11.1%]) compared with the inappropriate group (no deaths), this was not statistically significant.

Of the 32 patients with a positive test result, 25 (78.1%) underwent a valve intervention, of whom 12 patients had an event before intervention. Seven patients (21.9%) with a positive test result were medically managed, 6 of whom had an event. The 25 valve interventions were 6 surgical aortic valve replacements, 8 mitral valve replacements, 7 transcatheter aortic valve implantation, and 4 percutaneous mitral valve repair. No patient with a negative test result underwent valve intervention. Valve intervention was performed in 12 patients (24.5%) with an appropriate indication, in 13 patients (36%) with an uncertain indication, and in no patients with an inappropriate indication ($p < 0.0001$). The 30-day periprocedure mortality rate was 8% (2 patients). At 6 months, no further patients had died.

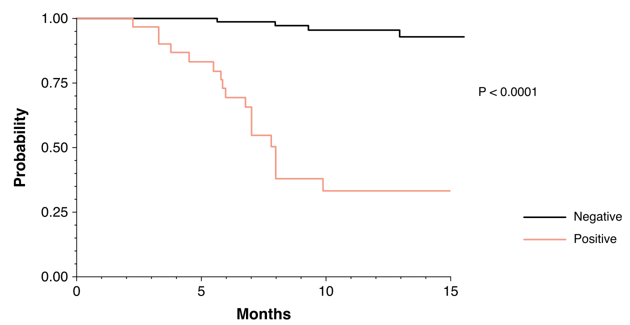

Figure 1. Kaplan-Meier Survival Curves Stratified by a Positive or Negative Stress Echocardiogram

Significantly reduced event-free survival in patients with a positive stress echocardiogram compared with patients with a negative stress echocardiogram.

Discussion

This study identifies the clinical value of performing stress echocardiography in patients with valvular heart disease. Second, it demonstrates the benefits of applying appropriateness criteria to this patient group. Third, it also demonstrates that appropriateness criteria in valvular heart disease need to be further refined.

Fifty-six percent of patients with a positive stress echocardiography test result had an event within 12 months, whereas only 9% of those with a negative test result had an event. Indeed, a positive stress echocardiogram and reduced left ventricular ejection fraction were the only independent predictors of events among all prognostically important clinical and resting echocardiographic parameters. This illustrates the prognostic value of stress echocardiography

Table 3. Clinical and Demographics Predictors of a Positive Stress Echocardiogram

	Odds Ratio (95% CI)	p Value
Age, yrs	1.01 (0.98–1.05)	0.51
Female	0.67 (0.68–5.61)	0.21
Smoker	0.99 (0.12–8.12)	0.99
Hypertension	1.91 (0.64–5.66)	0.99
Diabetes	0.29 (0.04–1.95)	0.20
Hyperlipidemia	0.55 (0.16–1.92)	0.35
LVEF, %	0.99 (0.96–1.04)	0.95
LVEDD, cm	0.77 (0.32–1.84)	0.55
Interventricular septum thickness, cm	0.37 (0.02–6.72)	0.50
Left atrial diameter, cm	0.75 (0.33–1.73)	0.06
Appropriate indication	6.2 (0.61–7.22)	0.98
Inappropriate indication	2.48 (0.22–3.56)	0.98
Uncertain indication	4.1 (0.42–5.1)	0.99

CI = confidence interval; other abbreviations as in Table 2.

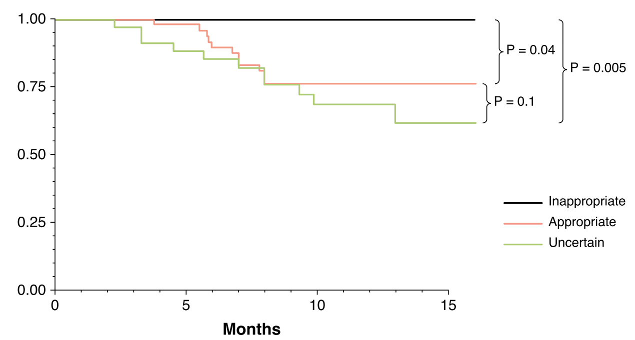

Figure 2. Kaplan-Meier Survival Curves Stratified by Stress Echocardiography Appropriateness Criteria: Appropriate, Uncertain, and Inappropriate

Significantly reduced event-free survival in patients classified as appropriate and uncertain compared with patients classified as inappropriate.

in the assessment of patients with valvular heart disease. Previous studies examined the diagnostic utility and prognostic role of stress echocardiography in specific patient groups (e.g., severe asymptomatic aortic stenosis, severe asymptomatic mitral regurgitation, mild mitral stenosis in research protocols within specialist echocardiography laboratories with research interests in valvular heart disease) (8–16). This study demonstrates the feasibility and prognostic value of stress echocardiography when incorporated into a clinical service where procedures are performed by several operators for the evaluation of multiple different valve lesions.

The development of appropriateness criteria were a step to improve effectiveness of noninvasive testing by reducing the number of unnecessary noninvasive tests. The criteria were based on score and classification by expert opinion. Therefore, the only way to validate the criteria is to test them in patient populations and modify them depending on these results. To our knowledge, our study is the first study to examine the clinical applicability of appropriateness criteria for valvular heart disease.

Table 4. Baseline Clinical and Echocardiographic Predictors of Cardiac Events

	Hazard Ratio (95% CI)	p Value
Age, yrs	0.98 (0.94–1.02)	0.38
Female	0.68 (0.20–2.31)	0.54
Smoker	1.01 (0.37–6.24)	0.25
Hypertension	2.43 (0.69–8.53)	0.16
Diabetes	2.94 (0.54–16.04)	0.21
Hyperlipidemia	0.82 (0.20–3.39)	0.79
LVEF, %	0.95 (0.91–0.98)	0.02
LVEDD, cm	1.39 (0.54–3.54)	0.49
Interventricular septum thickness, cm	2.9 (0.55–7.23)	0.22
Left atrial diameter, cm	1.00 (0.50–2.00)	0.99
Positive stress echocardiogram	15.49 (4.18–57.38)	<0.0001
Appropriate indication	2.1 (0.67–6.25)	0.99
Inappropriate indication	5.4 (0.89–9.23)	0.99
Uncertain indication	1.52 (0.45–5.20)	0.98

Abbreviations as in Table 3.

Our data show that the clinical value of the appropriateness criteria is the ability to differentiate between those who have a high probability of a positive stress test result and subsequent cardiac event/intervention (appropriate studies) and those with a low probability of a positive test result and cardiac events (inappropriate studies). Patients deemed inappropriate by current appropriateness criteria are unlikely to have a positive test result and have an excellent prognosis without any intervention.

However, there was no significant difference in outcome between the appropriate and uncertain groups. The majority of studies classified by the appropriateness criteria as uncertain were for asymptomatic severe aortic stenosis or symptomatic patients with mild or mild to moderate mitral regurgitation/stenosis. There is a growing body of evidence that demonstrates the poor prognosis of an increase in the mean transaortic gradient of >20 mm Hg in patients with severe asymptomatic aortic stenosis (13,14). Recently published European Society of Cardiology guidelines for valvular heart disease now recommend consideration of valve intervention for asymptomatic severe aortic stenosis in which the exercise mean transaortic gradient increases by ≥20 mm Hg as a class IIb indication for aortic valve replacement (17). Studies have demonstrated that in patients with mild mitral regurgitation or stenosis, severe dysfunction may develop after exercise (8–11). Furthermore, the worsening exercise-induced mitral regurgitation correlates with symptoms. Quantification of mitral regurgitation is based on the combination of multiple parameters and maybe classified being of mild to moderate severity (18); this entity is not recognized in the appropriateness criteria. Given the evidence base, guideline changes and the demonstration that patients in the uncertain group have the same number of adverse events as those in the appropriate group may mean that these indications should be reclassified as appropriate. The inappropriate group had no valve interventions/cardiac events or positive test results. Therefore, an updated classification would allow differentiation between patients with a high likelihood of significant valve disease and intervention and those in whom the test is unlikely to uncover significant valve disease.

Previous studies, validating the stress echocardiography appropriateness criteria for evaluation coronary artery disease, identified a number of limitations. A number of assumptions were needed to classify the patients, and in 1 study, 19% of studies were graded differently by 2 graders (4). Our data show good agreement between the 2 graders. The grading of studies for valvular heart disease was a simpler process, mainly requiring identification of symptoms and the severity of valve dysfunction.

Study limitations. The sample size of this study is a limitation. However, referrals for stress echocardiography assessment of valvular heart disease are substantially less frequent than those for assessment of coronary artery disease. This study is the first to identify the clinical value of stress echocardiography for valvular heart disease when incorporated into routine clinical practice.

Conclusions

Stress echocardiography for the dynamic assessment of valvular heart disease provides prognostic data in a range of valve lesions when incorporated into clinical practice. The appropriateness criteria for the evaluation of valvular heart disease provide the ability to differentiate between patients at high- (appropriate group) and low- (inappropriate group) risk of subsequent cardiac events. Reclassification of the uncertain group may improve the differential value of these criteria and improve their applicability to current clinical practice.

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Key Words: dobutamine ■ exercise ■ stress echocardiography ■ valvular heart disease.