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FOCUS ISSUE: VALVULAR HEART DISEASE

CME

Outcome After Aortic Valve Replacement for Low-Flow/Low-Gradient Aortic Stenosis Without Contractile Reserve on Dobutamine Stress Echocardiography

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Objectives This study investigated whether aortic valve replacement (AVR) is associated with improved survival in patients with severe low-flow/low-gradient aortic stenosis (LF/LGAS) without contractile reserve (CR) on dobutamine stress echocardiography (DSE).

Background Patients with LF/LGAS without CR have a high mortality rate with conservative therapy. The benefit of AVR in this subset of patients remains controversial.

Methods Eighty-one consecutive patients with symptomatic calcified LF/LGAS (valve area $\leq$1 cm^2, left ventricular ejection fraction $\leq$40%, mean pressure gradient [MPG] $\leq$40 mm Hg) without CR on DSE were enrolled. Absence of CR was defined as the absence of increase in stroke volume of $\geq$20% compared with the baseline value. Multivariable analysis and propensity scores were used to compare survival according to whether or not AVR was performed (n = 55).

Results Five-year survival was higher in AVR patients compared with medically managed patients (54 ± 7% vs. 13 ± 7%, p = 0.001) despite a high operative mortality of 22% (n = 12). An AVR was independently associated with lower 5-year mortality (adjusted hazard ratio from 0.16 to 5.21 varying with time [95% confidence interval: 0.12–3.16 to 0.21–8.50], p = 0.00026). In 42 propensity-matched patients, 5-year survival was markedly improved by AVR (65 ± 11% vs. 11 ± 7%, p = 0.019). Associated bypass surgery (p = 0.007) and MPG $\leq$20 mm Hg (p = 0.035) were independently predictive of operative mortality. Late survival after AVR (excluding operative death) was 69 ± 8% at 5 years.

Conclusions In patients with LF/LGAS without CR on DSE, AVR is associated with better outcome compared with medical management. Surgery should not be withheld from this subset of patients solely on the basis of lack of CR on DSE. (J Am Coll Cardiol 2009;53:1865–73) © 2009 by the American College of Cardiology Foundation

Patients with severe low-flow/low-gradient aortic stenosis (LF/LGAS) have a poor prognosis with conservative treatment. In the setting of LF/LGAS, operative risk can be stratified using dobutamine stress echocardiography (DSE) (1–3). According to recent studies, patients with left ventricular contractile reserve (CR) on DSE (i.e., an increase in stroke volume under dobutamine infusion of $\geq$20% compared with the baseline value) have a relatively low operative mortality, about 5% to 7% (2,3). Therefore, patients with

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Abbreviations and Acronyms

AS = aortic stenosis

AVR = aortic valve replacement

CABG = coronary artery bypass graft surgery

CAD = coronary artery disease

CR = contractile reserve

DSE = dobutamine stress echocardiography

EuroSCORE = European System for Cardiac Operative Risk Evaluation

LF/LGAS = low-flow/low-gradient aortic stenosis

LVEF = left ventricular ejection fraction

MPG = mean transaortic pressure gradient

NYHA = New York Heart Association

severe LF/LGAS and CR have an acceptable operative risk, and aortic valve replacement (AVR) improves long-term survival and functional status in most cases (2–4).

Conversely, patients without CR have a high operative mortality, about 30% in a recent series (2). Because of this high reported operative risk, many clinicians consider that the absence of CR on DSE represents a contraindication for AVR. However, actual surgical experience in LF/LGAS without CR on DSE is limited, because very few data on AVR patients have been reported (2,3). Moreover, the prognosis with medical management is extremely poor and a trend toward better survival with AVR was observed in a small series (2). We recently reported that patients without CR who survive the perioperative period improve their functional status in more than 90% of cases and show an increase in left ventricular ejection fraction (LVEF) by >10% in more than 60% of cases (5). Accordingly, the recent American College of Cardiology/American Heart Association guidelines state that some patients without CR could benefit from AVR (1). This European multicenter registry, focusing on a series of consecutive LF/LGAS patients without CR on DSE prospectively enrolled in 10 centers between 1991 and 2006, was retrospectively analyzed to compare survival after AVR and on conservative management and to identify predictors of perioperative mortality and long-term outcome.

Methods

Study sample. Eighty-one patients with low-flow/low-gradient (mean transaortic pressure gradient [MPG] ≤40 mm Hg, LVEF ≤40%) symptomatic calcified AS (aortic valve area ≤1 cm^2) without CR on DSE were prospectively enrolled in 10 centers (Amiens, France; Argenteuil, France; Bordeaux, France; Brest, France; Brussels, Belgium; Créteil, France; Lorient, France; Reims, France; Rennes, France; and Strasbourg, France). The study population was divided into 2 groups according to whether or not aortic valve surgery was performed (AVR group, n = 55; and medical group, n = 26). In patients treated with AVR, the severity of AS was assessed by visual inspection of the valve at the time of surgery. The degree of calcification and commissural fusion was described and the stiffness of each leaflet was assessed in situ to confirm the severity of AS. Preliminary data from this registry were previously published (2,4–6). Forty-four patients from these series (with extended follow-up) were included in the present report. The study was approved by local institutional review boards or ethics committees, in accordance with institutional policies, national legal requirements, and the revised Helsinki declaration. Informed consent was obtained from each patient before any study procedures.

Echocardiography. All patients underwent a comprehensive Doppler echocardiographic study using commercially available ultrasound systems. The echocardiographic severity of aortic valve calcification was graded qualitatively as previously proposed by Rosenhek et al. (7), and grades 3 (multiple large calcium deposits) and 4 (extensive calcification of all cusps) were considered to be significant valve calcification. Left ventricular outflow tract diameter was assumed to be constant at different flow states, and the baseline value was used to calculate stroke volume at baseline and during dobutamine infusion according to standard formulae (8). Transaortic gradients were calculated using the simplified Bernoulli equation (9). Aortic valve area was calculated by the continuity equation (10). The LVEF was calculated in all patients at inclusion. Dobutamine echocardiographic studies were evaluated off-line in each center by a single experienced echocardiographer. Details of the DSE have been described previously (2,3,5,11). Briefly, after baseline measurements, a dobutamine infusion was started at 5 μg/kg body weight/min, and titrated upward to a maximum dose of 20 μg/kg/min. Absence of CR during DSE was classically defined as the absence of increase in stroke volume of ≥20% compared with the baseline value (2,3,5,11).

Coronary angiography. Pre-operative coronary angiography was performed in all patients. Reduction of the normal diameter ≥50% was considered to define significant coronary artery disease (CAD) in the left main coronary artery. A cutoff value of 70% was used for the right coronary, left anterior descending, and circumflex arteries. Multivessel CAD was defined as the presence of significant stenoses on 2 or more vessels.

Calculation of the European System for Cardiac Operative Risk Evaluation (EuroSCORE). The standard EuroSCORE was calculated retrospectively for each patient using the calculator available online (12). Risk factors integrated in the EuroSCORE are patient-, cardiac-, and operation-related factors. Patient-related factors are: age >60 years, female sex, chronic pulmonary disease, extracardiac arterial disease, neurological dysfunction, previous cardiac surgery, serum creatinine >200 μmol/l, active endocarditis, and critical pre-operative state. Cardiac-related factors are unstable angina, reduced LVEF, recent myocardial infarction, and pulmonary systolic pressure >60 mm Hg. Operation-related factors are: emergency surgery other than isolated coronary artery bypass surgery, thoracic aorta surgery, and surgery for post-infarct septal rupture.

Clinical decision and follow-up. Clinical decisions for each patient were left to the discretion of the referring physician, who was aware of the results of individual DSE. The end point obtained in all patients at follow-up was survival. The mean follow-up was 37 ± 41 months. Perioperative mortality was defined as death within 30 days after AVR or before hospital discharge (2,13), and late mortality was defined as death after the perioperative period. In patients who underwent AVR, overall mortality combined perioperative mortality and late mortality. New York Heart Association (NYHA) functional status and LVEF during follow-up were assessed in 32 (74%) and 34 (79%) of the 43 patients who survived AVR (after the perioperative period), respectively.

Statistical analysis. Continuous variables were expressed as mean ± SD and compared between groups using the 2-sample Student *t* test or the Wilcoxon rank sum test, as appropriate. Categorical variables were expressed as frequency percentages and compared between groups using the chi-square test or Fisher exact test, as appropriate. Changes in NYHA functional status over time were compared using the McNemar test.

The imbalance in baseline variables between AVR and medically managed patients was reduced using propensity scores. The propensity scores for AVR were estimated for each of the 81 patients using a multivariable logistic model (14,15). Characteristics associated with AVR surgery on univariate analysis ($p < 0.5$) were included in the multivariable logistic model in a forward stepwise regression analysis. A propensity score for AVR for each patient was estimated from the resulting selected variables by maximum likelihood regression analysis. Goodness-of-fit, assessed by the Hosmer-Lemeshow test (chi-square = 4.7, $p = 0.69$) and the discriminatory power of the model (area under the receiver-operating characteristic curve, $C = 0.73$) were acceptable. Propensity scores were used to match each medically managed patient to a unique patient in the AVR group with a propensity score within 4%. Each medically matched patient was initially matched with another patient in the AVR group with a similar 5-digit propensity score, and the matched patients were removed from the database. This procedure was repeated on the remaining patients with successive matching by 4-, 3-, 2-, and 1-digit scores. Twenty-one (81%) of the 26 medically managed patients were successfully matched. The mean propensity score in medically managed patients before matching was 0.63054 compared with 0.74375 in patients who underwent AVR ($p = 0.002$). After matching, the mean propensity score was 0.65559 in non-AVR patients, comparable with that of the AVR group (0.65525, $p = 0.98$). The distribution of categorical variables between the 2 groups in the matched cohort was compared with the use of McNemar test. Continuous variables were compared between groups in the matched cohort using paired *t* tests or Wilcoxon signed rank tests, as appropriate.

For multivariable analysis of perioperative mortality, a logistic regression model including a pre-defined covariate (EuroSCORE) and variables associated with perioperative mortality on univariate analysis ($p < 0.10$) was applied to calculate odds ratios and 95% confidence intervals for the set of variables independently associated with an adverse outcome.

The association between AVR and 5-year overall mortality was analyzed first in the overall cohort. Survival curves were generated using Kaplan-Meier survival estimates. Differences in time to death between groups were analyzed using a 2-sided log-rank test. The most common approach for analyzing survival data and identifying predictors of outcome is the Cox model, which assumes constant hazard ratios throughout a subject's time course (proportional hazards assumption). However, this assumption probably does not hold after cardiac surgery, because the hazard ratio for death will likely decrease after the perioperative period (6). Gray's piecewise-constant time-varying coefficients survival model is an extension of the Cox proportional hazards model that allows the regression coefficients to change over different time intervals (16). It has, therefore, the ability to estimate how the hazards of individual risk factors change over time (6,16) and may be better suited for modeling survival after cardiac surgery. We used single-variable Gray models to identify variables associated with 5-year overall mortality. These models were fitted using 5 intervals: the perioperative period and 4 subsequent time intervals, each containing approximately equal numbers of deaths (16). The duration of each interval was determined automatically, based on when the events occur. Gray's model has its own test of proportionality, a value of $p < 0.10$ assuming nonproportionality. In the multivariable model we included a predefined covariate (EuroSCORE) and variables associated with overall mortality on univariate analysis ($p < 0.10$). For each variable, a specific hazard ratio for each of the 5 time intervals was found. For proportional variables, the mean of these values of hazard ratios were reported with the mean of 95% confidence interval limits. For nonproportional variables, the range from minimum to maximum hazard ratio is reported. The overall significance of the nonproportional variables is given by the p value. In the matched cohort, Kaplan-Meier survival curves were estimated for patients who underwent AVR and for medically managed patients. The survival curves of matched patients were compared according to methods appropriate for matched data (17). For all tests, a value of $p < 0.05$ was considered statistically significant. All p values are results of 2-tailed tests. Statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, Illinois), and the R Project for Statistical Computing (release 2.8.1, CICT, Toulouse, France). Gray's program, written for R, is available from the author's website (18).

Results

Baseline characteristics of the study population. The study included 81 patients (22 women, 59 men) with a mean age of 71 ± 10 years, mean aortic valve area of 0.75 ± 0.16

cm^2, mean indexed aortic valve area of 0.40 ± 0.09 cm^2/m^2, mean cardiac index of 2.29 ± 0.56 l/min/m^2, MPG of 28 ± 7 mm Hg, and mean LVEF of 29 ± 7%. Significant valve calcification was observed at echocardiography in all patients (7). All patients complained of dyspnea, and 67 patients (83%) were classified in NYHA functional class III to IV. Seven patients had associated angina, and 2 had a history of syncope. Forty-two patients (52%) had significant CAD; multivessel CAD was identified in 33 patients (41%). Eighteen patients (22%) had a history of myocardial infarction, and 1 patient (1.2%) had previously undergone coronary artery bypass graft surgery (CABG). Baseline characteristics of the study population are presented in Table 1. The severity of AS was confirmed by the surgeon in all AVR patients except for 1 patient, in whom the surgeon considered AS to be moderate.

Compared with the medically managed group (n = 26), patients who underwent AVR (n = 55) were younger (age 70 ± 11 years vs. 75 ± 8 years), had a lower frequency of chronic renal failure, and tended to more frequently suffer from diabetes mellitus. The EuroSCORE was similar in AVR patients and medically managed patients. Mean LVEF was comparable between patients operated for AVR and medically managed patients (29 ± 7% vs. 27 ± 7%, p = 0.14). AVR patients had higher MPG (29 ± 7 mm Hg vs. 24 ± 6 mm Hg, p = 0.001). Forty-six percent (n = 25) of the 55 AVR patients received a mechanical prosthesis, and 54% (n = 30) received a bioprosthesis.

Outcome. Forty-six deaths were recorded during follow-up. The 5-year overall survival of the study population was

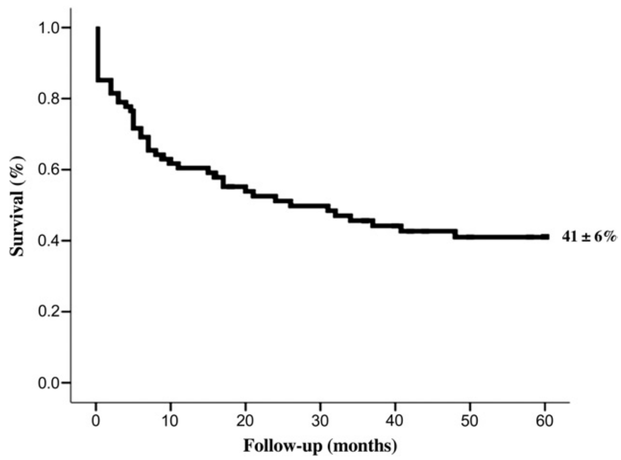

Figure 1 **Probability of Survival in LF/LGAS Patients Without CR on DSE**

Kaplan-Meier estimate of the probability of survival of the total study population (n = 81). CR = contractile reserve; DSE = dobutamine stress echocardiography; LF/LGAS = low-flow/low-gradient aortic stenosis.

41 ± 6% (Fig. 1). Survival was significantly lower in patients with significant CAD, MPG ≤20 mm Hg, and medically managed patients (Table 2). Five-year overall survival was 15 ± 10% in patients with MPG ≤20 mm Hg versus 46 ± 6% in patients with MPG >20 mm Hg (Fig. 2A), and 32 ± 7% in patients with significant CAD versus 51 ± 8% in patients without CAD (Fig. 2B).

Table 1 **Clinical Characteristics of the Overall Population and Comparison Between AVR and Medically Managed Patients Before and After the Matching Procedure**

	Before Match (n = 83)				After Match (n = 42)		
Variable	Overall (n = 81)	No AVR (n = 26)	AVR (n = 55)	p Value	No AVR (n = 21)	AVR (n = 21)	p Value
Age (yrs)	71 ± 10	75 ± 8	70 ± 11	0.03	74 ± 8	73 ± 10	0.74
Male sex	59 (73)	16 (62)	43 (78)	0.11	14 (67)	16 (76)	0.73
Body mass index (kg/m^2)	25 ± 3	24 ± 3	25 ± 3	0.78	25 ± 4	24 ± 3	0.71
Hypertension	19 (24)	5 (19)	14 (26)	0.53	3 (14)	5 (24)	0.69
Chronic renal failure	12 (15)	7 (27)	5 (9)	0.04	6 (29)	4 (19)	0.73
Diabetes mellitus	12 (15)	1 (4)	11 (20)	0.09	1 (5)	4 (19)	0.22
COPD	12 (15)	3 (12)	9 (16)	0.56	3 (14)	3 (14)	1.00
History of cancer	7 (9)	3 (12)	4 (7)	0.67	2 (10)	1 (5)	1.00
EuroSCORE >10	27 (33)	11 (42)	26 (47)	0.21	8 (38)	9 (43)	0.85
Coronary artery disease	42 (52)	16 (62)	10 (18)	0.23	11 (52)	12 (57)	1.00
Prior myocardial infarction	18 (22)	8 (31)	21 (38)	0.20	7 (33)	4 (19)	0.45
MVD	33 (41)	12 (46)	46 (84)	0.49	7 (33)	8 (38)	1.00
Congestive heart failure	67 (83)	21 (81)	16 (29)	0.75	16 (76)	17 (81)	1.00
Aortic valve area (cm^2)	0.75 ± 0.16	0.74 ± 0.18	0.74 ± 0.15	0.89	0.74 ± 0.18	0.75 ± 0.18	0.82
Left ventricular outflow tract (cm)	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.1	0.58	2.1 ± 0.2	2.0 ± 0.1	0.70
LVEF (%)	29 ± 7	27 ± 7	29 ± 7	0.14	27 ± 6	26 ± 7	0.50
MPG (mm Hg)	28 ± 7	24 ± 6	29 ± 7	0.001	25 ± 5	25 ± 4	0.74
MPG ≤20 mm Hg	13 (16)	7 (27)	6 (11)	0.10	5 (24)	5 (24)	1.00
Systolic PAP (mm Hg)	48 ± 13	51 ± 10	47 ± 14	0.53	49 ± 10	46 ± 15	0.55

Values are n (%) or mean ± SD.

AVR = aortic valve replacement; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MPG = mean transaortic pressure gradient; MVD = multivessel coronary artery disease; no AVR = medically managed patients; PAP = pulmonary artery pressure.

Table 2 **Predictors of Overall Mortality on Univariate Analysis in the 81 Patients With Low-Flow/Low-Gradient Aortic Stenosis Without Contractile Reserve**

Variable	Alive (n = 35)	Dead (n = 46)	Association With Mortality		
			Cox p Value	Gray p Value	p Value for Nonproportionality*
Age (yrs)	71 ± 9	72 ± 11	0.34	0.15	0.08
Male sex	25 (71)	34 (74)	0.81	0.70	0.20
Body mass index (kg/m^2)	25 ± 3	24 ± 3	0.66	0.19	0.07
Hypertension	5 (14)	14 (30)	0.05	0.17	0.90
Chronic renal failure	3 (9)	9 (20)	0.23	0.07	0.10
Diabetes mellitus	6 (17)	6 (13)	0.54	0.61	0.66
COPD	4 (11)	8 (17)	0.27	0.51	0.66
History of cancer	4 (11)	3 (7)	0.37	0.72	0.63
EuroSCORE >10	9 (26)	18 (39)	0.21	0.52	0.81
Coronary artery disease	14 (40)	28 (61)	0.03	0.04	0.50
Prior myocardial infarction	7 (20)	11 (24)	0.55	0.86	0.87
MVD	12 (34)	21 (46)	0.11	0.14	0.29
CABG	5 (14)	11 (24)	0.07	0.01	0.03
Congestive heart failure	28 (80)	39 (85)	0.83	0.18	0.06
Aortic valve area (cm^2)	0.73 ± 0.16	0.76 ± 0.15	0.48	0.71	0.68
Left ventricular outflow tract (cm)	2.0 ± 0.2	2.1 ± 0.2	0.49	0.67	0.68
Left ventricular ejection fraction (%)	30 ± 6	28 ± 8	0.16	0.56	0.82
MPG (mm Hg)	30 ± 6	26 ± 7	0.009	0.0006	0.003
MPG ≤20 mm Hg	2 (6)	11 (24)	0.003	0.0015	0.06
Systolic PAP (mm Hg)	47 ± 15	49 ± 11	0.90	0.78	0.59
Aortic valve replacement	31 (89)	24 (52)	0.001	0.000003	0.00007

Values are n (%) or mean ± SD. *Nonproportionality was tested using the Schoenfeld residuals ($p < 0.10$ assuming nonproportionality).
CABG = coronary artery bypass graft surgery; other abbreviations as in Table 1.

Operative mortality and post-operative outcome. Among the 55 patients who underwent AVR, 12 died during the perioperative period. Perioperative mortality was therefore 22%. The main cause of perioperative mortality was cardiogenic shock in 10 patients (83.4%). One patient died from multiorgan failure, and another died from septic shock. On univariate analysis, CABG associated with AVR (p = 0.001), MPG ≤20 mm Hg (p = 0.01), longer cardiopulmonary bypass time (163 ± 54 min vs. 101 ± 51 min, p = 0.003), and longer aortic cross-clamp time (116 ± 37 min vs. 70 ± 36 min, p = 0.001) were associated with increased perioperative mortality. Associated CABG (odds ratio: 9.7, 95% confidence interval [CI]: 1.9 to 49.9, p = 0.007) and MPG ≤20 mm Hg (odds ratio: 10.0, 95% CI: 1.2 to 84.9,

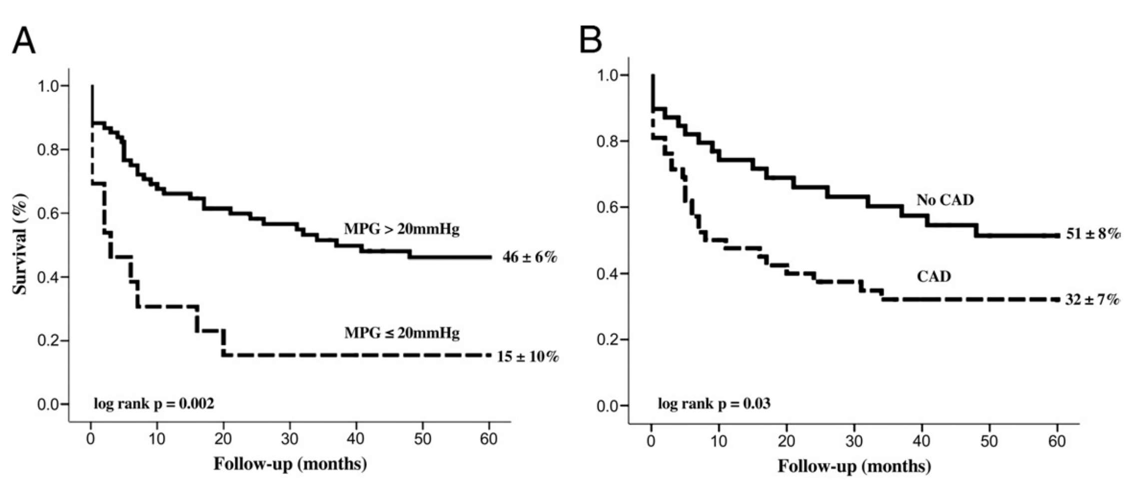

Figure 2 **Influence of MPG and CAD on Survival in LF/LGAS Patients Without CR on DSE**

Kaplan-Meier estimates of the probability of survival of the total population (n = 81) according to: **(A)** mean pre-operative transvalvular gradient (MPG) ≤20 and >20 mm Hg, and **(B)** presence of significant coronary artery disease (CAD). Abbreviations as in Figure 1.

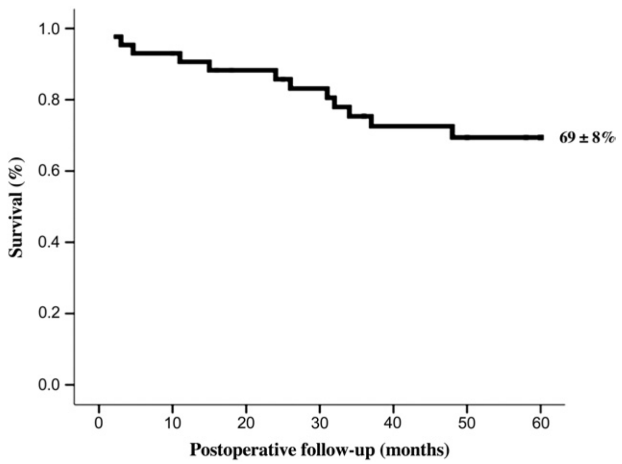

Figure 3 **Late Survival in Operated LF/LGAS Patients Without CR on DSE**

Kaplan-Meier estimate of the probability of late survival (excluding perioperative mortality) of aortic valve replacement patients (n = 55). Abbreviations as in Figure 1.

p = 0.035) were the 2 independent predictors of perioperative mortality. Operative mortality of the subgroup of patients with MPG ≤20 mm Hg was 67% (n = 4 of 6) compared with 16% (n = 8 of 49) in patients with MPG >20 mm Hg. Patients in whom CABG was performed at the time of AVR had an operative mortality of 53% (n = 8 of 15) compared with 10% (n = 4 of 40) for patients in whom associated CABG was not performed at the time of AVR. Late survival (excluding perioperative mortality) of patients in whom AVR was performed was 69 ± 8% at 5 years (Fig. 3).

Among AVR patients (n = 55), 5-year overall mortality was significantly higher in patients with MPG ≤20 mm Hg (83 ± 15% vs. 41 ± 7%, p = 0.003) and in patients with CAD (60 ± 10% vs. 33 ± 9%, p = 0.02). Among the 32 AVR patients in whom functional status was assessed after AVR, 81% (n = 26) were in NYHA functional class III to IV pre-operatively, compared with 9.4% (n = 3) post-operatively (p < 0.001). In the 34 patients who had post-operative LVEF assessment, LVEF improved significantly, from 31.2 ± 6.2% pre-operatively to 46.6 ± 10.2% after AVR (p < 0.001).

AVR versus medical management. During the 5-year follow-up, 34 deaths occurred after the index hospital discharge. In almost 80% of cases (n = 27), the cause of death was cardiovascular (pump failure in 18 patients, sudden cardiac death in 7, and vascular noncardiac death in 2 cases). Six patients (17%) died of noncardiovascular causes after discharge. In 1 patient (3%), the cause of death remained unknown. The 5-year overall survival in patients operated for AVR was 54 ± 7%, significantly higher than that of medically managed patients (13 ± 7%, p = 0.001) (Fig. 4A). On univariate Gray's piecewise-constant time-varying coefficients analysis, AVR was associated with a significantly lower risk of 5-year mortality (p = 0.000003) (Table 2). On multivariable analysis, after adjustment for EuroSCORE (including age) and variables associated with 5-year mortality on univariate analysis, AVR was associated with a lower subsequent mortality (adjusted hazard ratio: 0.16 to 5.21 varying with time, 95% CI: 0.12–3.16 to 0.21–8.50, p = 0.00026). The impact of aortic valve surgery on survival was not constant over time (Fig. 5). The excess perioperative mortality related to AVR was outweighed by the significant and sustained survival benefit of AVR patients throughout the 5-year follow-up. Both MPG ≤20 mm Hg (adjusted hazard ratio: 0.57 to 11.25 varying with time, 95% CI: 0.12–2.48 to 0.83–14.73, p = 0.012) and

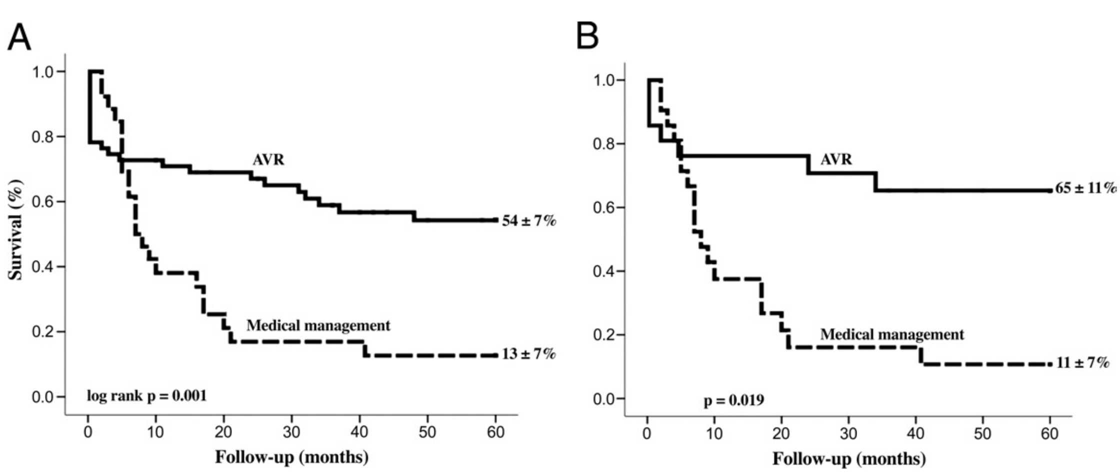

Figure 4 **Prognostic Impact of AVR in LF/LGAS Patients Without CR on DSE**

Kaplan-Meier estimates of the probability of survival according to whether aortic valve replacement (AVR) was performed: **(A)** total population (n = 81), and **(B)** matched patients (n = 42). Abbreviations as in Figure 3.

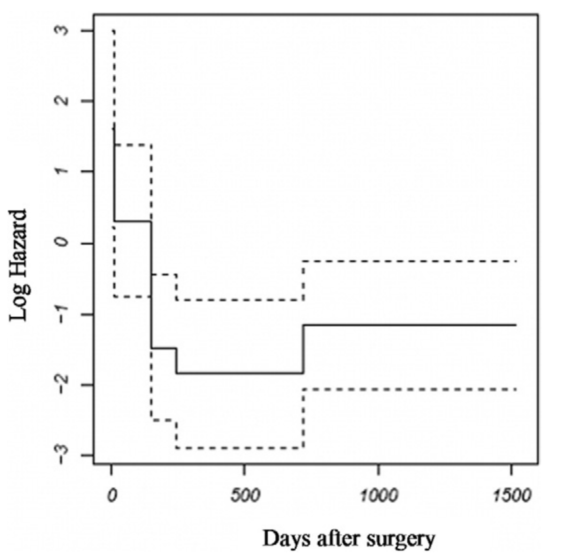

Figure 5 **Nonproportionality of the Effect of Aortic Valve Replacement on Mortality According to the Gray Model**

The **solid line** represents the evolution of the hazard ratio for mortality over time, and the **dashed lines** represent 95% confidence intervals.

significant CAD (adjusted hazard ratio: 1.30, 95% CI: 1.08 to 2.07, $p = 0.03$) were independently predictive of 5-year overall mortality. By propensity scores matching, 21 of the 26 patients not treated by AVR were successfully matched. After matching, no difference in baseline variables was observed between the 2 groups (Table 1). In the 42 matched patients, 5-year survival was 65 ± 11% for the AVR group and 11 ± 7% for medically managed patients (Fig. 4B). In the matched cohort, AVR remained associated with a significant survival benefit during the 5-year follow-up ($p = 0.019$).

Discussion

The present study is derived from an international multicenter registry of LF/LGAS and outlines the prognostic implications of surgery in LF/LGAS patients without CR on DSE. These results show that LF/LGAS without CR on DSE has a catastrophic long-term outcome on conservative management with a 5-year mortality as high as 87%, compared with a 5-year mortality of 31% in patients operated for AVR. Using multivariable analysis and propensity scores to reduce the imbalance in baseline covariates between medically managed patients and AVR patients, surgery was shown to be associated with a marked reduction of long-term mortality. Therefore, despite high operative mortality (22%), surgery should not be contraindicated for LF/LGAS patients on the sole basis of absence of CR on DSE because these patients present unacceptably high mortality on medical management and have an acceptable long-term outcome after AVR with significant functional and LVEF improvement (5).

In selected patients with LF/LGAS, AVR is associated with a dramatic long-term survival benefit compared with medical management (2,19,20). Moreover, patients who survive surgery usually improve their functional status, and in more than 80% of cases LVEF increases by at least 10% post-operatively (5). Recent studies conducted in LF/LGAS have reported operative mortality rates between 8% and 16% (2–4,20). We have recently reported that operative mortality in LF/LGAS has significantly decreased to approximately 10% over the last 5 years (4). Operative mortality and poor long-term outcome are mainly related to older age, comorbidities, low MPG (≤20 mm Hg), severe associated CAD, history of myocardial infarction, and absence of CR on DSE (2,4,13,20).

Currently DSE is used to stratify operative risk in patients with LF/LGAS (2,3,19,21). Patients with severe LF/LGAS and CR on DSE have an acceptable operative mortality of 5% to 7% (2,3), and AVR improves long-term survival and functional status in most cases (2,3). European guidelines recommend surgery for this group of patients (19). Patients who do not experience a 20% increase in stroke volume on DSE are considered to have LF/LGAS without CR (2,3,5,11). In this setting, the assessment of the true severity of the AS remains a difficult issue. In our experience, pseudosevere AS (mild to moderate AS associated with an alternative cause of left ventricular dysfunction) is relatively rare, being observed in only 5% of LF/LGAS patients (2), and severe aortic valve calcification on echocardiography, fluoroscopy, or computed tomography is a valuable element in favor of significant AS (7,22). B-type natriuretic peptide may also be useful for identifying true severe LF/LGAS (23).

The management of LF/LGAS without CR is difficult and controversial because few studies have included patients without CR (2,3,11,21). Patients with LF/LGAS but without CR on DSE have been reported to present a high operative risk with an operative mortality of about 30% (2,5). In the present study, the operative mortality was 22%. The subgroup with MPG ≤20 mm Hg had dramatically higher operative mortality. The absence of CR on DSE could therefore be interpreted as a contraindication for surgery, especially in patients with MPG ≤20 mm Hg. However, the limited available data portend a grim outcome for medically managed LF/LGAS patients without CR (2,3,21). Based on a small preliminary series, we have previously reported that medically managed patients without CR have a 2-fold higher 2-year mortality rate compared with patients in whom AVR is performed, but this difference was not significant (2). Moreover, the majority of patients without CR on DSE who survive AVR have a significant increase in post-operative LVEF and improvement in functional status (5), a finding that was confirmed by the present study. Therefore, the main determinant for low pre-operative LVEF in these patients without CR on

JACC Vol. 53, No. 20, 2009
May 19, 2009:1865–73

DSE who survive AVR is probably an afterload mismatch that cannot be corrected by inotropic stimulation with dobutamine infusion. Consequently, the lack of CR on DSE is not systematically related to irreversible left ventricular dysfunction. The results of the present study suggest that a conservative therapeutic strategy is not an option for these severely diseased patients because the 5-year survival of the medically managed group is extremely poor. Despite a high operative mortality, the group in which AVR was performed had a better outcome, and the late survival of AVR patients was acceptable. To reduce the impact of baseline characteristics, a propensity score analysis was performed and each medically managed patient was matched to a unique AVR patient. After matching, AVR was still associated with an impressive survival benefit.

Study strengths and limitations. The number of patients in this cohort is relatively small, but this is the largest study focusing on LF/LGAS without CR on DSE. The decision to perform AVR was left to the referring physician. Because of the small number of perioperative fatal events, the multivariable analysis on perioperative mortality is overfitted. The potential inclusion of patients with moderate AS and severe left ventricular dysfunction with exhausted CR on DSE represents a limitation. Nevertheless, the uniform presence of severe aortic valve calcification on fluoroscopy and/or echocardiography supports the assumption that AS was severe in almost every case (22). Computed tomography, which offers the advantage of objective quantification of calcification, was not performed in this study (22). Although the distinction of moderate and severe AS by surgical judgment may be questionable, the severity of AS was confirmed by the surgeon in all but 1 of the patients in whom AVR was performed. The outcome of medically managed patients if they had been treated by AVR remains unknown. Although the small number of patients limits the ability of this study to draw definitive conclusions on the management of this high-risk subset of LF/LGAS patients, our results provide evidence that caution is warranted when therapeutic decisions in LF/LGAS are made and call for further rigorous prospective studies to evaluate the implications of AVR in the management of LF/LGAS patients. Although the propensity analysis emphasized that AVR significantly improves long-term survival in patients with LF/LGAS without CR, the association between AVR and outcome might have been influenced by factors beyond the documented variables.

In our study, B-type natriuretic peptide was not systematically determined and its potential role was therefore not analyzed (23). A history of myocardial infarction was not associated with poorer outcome in our study. However, the extent of scar and the amount of viable myocardium have certainly an important role in the pathophysiology of the contractile dysfunction in LF/LGAS and should be investigated in future studies. This study used the standard EuroSCORE to assess the risk for cardiac surgery. The EuroSCORE has a reasonable predictive ability for both coronary and valve surgery, but may have limited predicted capacity for patients at high risk and for combined valvular and coronary surgery (24).

Clinical implications. This multicenter study shows that the long-term outcome of calcified LF/LGAS without CR on DSE is extremely poor when patients are treated conservatively. Despite a high operative mortality of 22%, AVR was clearly associated with improved survival in this category of patients. These results suggest that AVR could be the treatment of choice for most patients with calcified LF/LGAS without CR on DSE. The decision not to perform surgery in calcified LF/LGAS should be made case by case, taking into account risk factors resulting in a very high operative risk. In our opinion, AVR should be considered in patients with calcified LF/LGAS without CR on DSE when MPG is >20 mm Hg, and in the absence of excessive comorbidities or severe CAD with large scarring caused by extensive myocardial infarction. Heart transplantation should also be considered in eligible patients as an alternative to AVR. Percutaneous or transapical AVR could also possibly represent a valuable alternative to classic AVR in these patients at high risk for surgical AVR. Actually, in the near future, these new procedures may considerably change the therapeutic strategies in patients with calcified LF/LGAS without CR. This issue will need to be addressed in further studies.

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