Characterization and outcome of patients with severe symptomatic aortic stenosis referred for percutaneous aortic valve replacement

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Objective: Many high-risk patients with severe symptomatic aortic stenosis are not referred for surgical aortic valve replacement. Although this patient population remains ill-defined, many of these patients are now being referred for percutaneous aortic valve replacement. We sought to define the characteristics and outcomes of patients referred for percutaneous aortic valve replacement.

Methods: Between February 2006 and March 2007, 92 patients were screened for percutaneous aortic valve replacement. Clinical and echocardiographic characteristics of patients undergoing surgical aortic valve replacement, percutaneous aortic valve replacement, balloon aortic valvuloplasty, or no intervention were compared. The primary end point was all-cause mortality.

Results: Nineteen patients underwent successful surgical aortic valve replacement, 18 patients underwent percutaneous aortic valve replacement, and 36 patients had no intervention. Thirty patients underwent balloon aortic valvuloplasty, and of these, 8 patients were bridged to percutaneous aortic valve replacement and 3 were bridged to surgical aortic valve replacement. Of the remaining 19 patients undergoing balloon aortic valvuloplasty, bridging to percutaneous aortic valve replacement could not be accomplished because of death ($n = 9$ [47%]), exclusion from the percutaneous aortic valve replacement protocol ($n = 6$ [32%]), and some patients improved after balloon aortic valvuloplasty and declined percutaneous aortic valve replacement ($n = 4$ [21%]). The most common reasons for no intervention included death while awaiting definitive treatment ($n = 10$ [28%]), patient uninterested in percutaneous aortic valve replacement ($n = 10$ [28%]), and questionable severity of symptoms or aortic stenosis ($n = 9$ [25%]). Patients not undergoing aortic valve replacement had higher mortality compared with those undergoing aortic valve replacement (44% vs 14%) over a mean duration of 220 days.

Conclusion: Symptomatic patients with severe aortic stenosis have high mortality if timely aortic valve replacement is not feasible. Twenty percent of the patients referred for percutaneous aortic valve replacement underwent surgical aortic valve replacement with good outcome. Patients undergoing balloon aortic valvuloplasty alone or no intervention had unfavorable outcomes.

See related editorial on page 1315.

Aortic stenosis (AS) is the most common valvular lesion in the aging population, with a prevalence of 4.6% in adults more than 75 years of age.¹⁻³ Surgical aortic valve replacement (SAVR) is the recommended treatment for symptomatic patients.⁴ After the onset of symptoms, average survival can be as low as 1 to 3 years without SAVR.⁴⁻⁸ However, many patients with severe symptomatic AS do not undergo surgical intervention for various reasons.

Some are not referred for intervention because of the presence of comorbidities or patient preference, and others are deemed inoperable by the surgeon because of the presence of coexisting illnesses. This is particularly the case for the elderly. In the Euro Heart Survey on valvular heart disease, 33% of patients with severe symptomatic AS did not undergo surgical intervention.⁹ Other studies have similarly shown that 27% to 41% patients with severe symptomatic AS do not undergo SAVR.^{8,10-12}

These studies included patients who were identified by means of screening echocardiographic laboratory databases for severe AS or those who were referred for SAVR. It is possible that there are other patients who do not come to the attention of cardiologists or tertiary care centers for various reasons. With the advent of percutaneous aortic valve replacement (PAVR),¹³⁻¹⁸ many of these patients are now being referred for this “less invasive” investigational procedure. This provides a unique opportunity to characterize the unmet need for aortic valve replacement. Accordingly, we studied the characteristics and outcomes of patients referred for PAVR.

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Abbreviations and Acronyms

AS	= aortic stenosis
BAV	= balloon aortic valvuloplasty
MR	= mitral regurgitation
PAVR	= percutaneous aortic valve replacement
REVIVAL	= Transcatheter Endovascular Implantation of Valves
SAVR	= surgical aortic valve replacement
STS	= Society of Thoracic Surgeons

MATERIALS AND METHODS

All patients screened at our institution for PAVR have been included in a prospective registry. These were patients who were thought to be at very high risk for SAVR by the referring doctors. Ninety-two consecutive patients screened for PAVR from February 2006 through March 2007 were included in this prospective cohort study. At baseline, all patients underwent a structured assessment, including history and physical examination, electrocardiogram, Doppler echocardiography, and coronary and peripheral angiography. All patients with severe AS, irrespective of the previous recommendations from referring institutions, were independently evaluated by 2 surgeons for aortic valve replacement. The decision to perform either SAVR or PAVR was made by a multidisciplinary team consisting of cardiologists with expertise in clinical, interventional, and imaging fields; cardiothoracic surgeons; and cardiac anesthesiologists with extensive experience in SAVR in high-risk patients. The decision-making process was a complex interplay of clinical presentation, physical examination, and various diagnostic tests, along with consideration of social situation (Figure 1). If patients were not candidates for cardiac surgery, they were evaluated for the Transcatheter Endovascular Implantation of Valves (REVIVAL) trial. The Society of Thoracic Surgeons (STS) score was primarily used to make this determination; however, factors that are not captured in the STS score, such as prior chest radiation, porcelain aorta, anatomic issues (eg, grafts or cardiac chambers adherent to sternum and lack of sternum), and severe debilitation, were also taken into account to determine the candidacy for SAVR. Under the REVIVAL study protocol, PAVR was performed only in patients who were deemed inoperable or had an estimated operative mortality of greater than 15%, as per the inclusion criteria. Patients who were excluded from PAVR for reasons such as thrombocytopenia ($n = 2$), cancer ($n = 2$), severe left ventricular dysfunction with an ejection fraction of less than 20% ($n = 1$), and age of less than 70 years ($n = 1$) underwent balloon aortic valvuloplasty (BAV). Patients who were neither accepted for cardiac surgery nor for the REVIVAL trial were clinically evaluated and medically managed. BAV was offered to those patients who could be considered for surgical intervention in the future if their general status improved and to those who could not leave the hospital because of AS-related congestive heart failure. All patients who underwent BAV were re-evaluated for SAVR. For analysis, patients who were bridged to SAVR or PAVR after BAV were included in the respective groups (SAVR or PAVR). Clinical and echocardiographic characteristics were compared among these patients based on the modality of treatment. The primary end point for outcome was all-cause mortality. Mortality was assessed by querying the Social Security Death Index or by directly referring to patient charts in case of in-hospital mortality. Length of hospital stay and postoperative complications were determined by means of chart review. The institutional review board waived requirements for informed consent.

Continuous data are presented as means $\pm$ standard deviation. Student's t test was used to compare mean values for continuous variables. Multiple groups were compared by using 1-way analysis of variance. Post-hoc analysis was performed with the Newman-Keuls test. The χ^2 or Fisher's exact test was used to find significant associations between categorical variables.

FIGURE 1. Decision process. AVR, Aortic valve replacement; REVIVAL, Transcatheter Endovascular Implantation of Valves; STS, Society of Thoracic Surgeons; BAV, balloon aortic valvuloplasty.

All tests were 2-tailed. Statistica 6.1 (Statsoft, Inc, Tulsa, Okla) software was used for analysis.

RESULTS

Patient Characteristics

Baseline characteristics of the 4 groups are shown in Table 1. Of the 92 patients screened, 53 (58%) were 80 years or older, and 36 (39%) were 85 years or older. There were 35 (39%) patients who had at least 1 prior cardiac surgery, 30 (34%) who had previously diagnosed severe lung disease (forced expiratory volume in 1 second ≤ 1 L or on home oxygen), and 10 (11%) who had chronic kidney disease (serum creatinine value, >2 mg/dL). There were 23 (25%) patients with a left ventricular ejection fraction of 30% or less and 10 (11%) patients with an ejection fraction of 20% or less. Additionally, 14 (15%) patients had severe mitral regurgitation (MR), and 33 (36%) patients had severe pulmonary hypertension (systolic pulmonary artery pressure, ≥ 50 mm Hg; Figure 2). The mean Logistic EuroSCORE of all patients was 26, with 51% of patients having a score of greater than 20. The mean STS score of all patients was 12.8, with 43% of patients having a score of 10 or greater.

Patient Management

Further information on patient management is shown in Figure 3. Of the 92 patients who were screened for possible PAVR, 19 (21%) underwent SAVR, and 18 (20%) underwent PAVR. Of the patients who underwent aortic valve replacement, 3 were bridged to SAVR after BAV, and 8 were bridged to PAVR after BAV. Nineteen (21%) patients could not be bridged to aortic valve replacement after BAV. Of these 19 patients who underwent BAV alone, 9 (47%) died while waiting for PAVR, 4 (21%) improved after

TABLE 1. Baseline patient characteristics

	All patients (n = 92)	No intervention (n = 36)	SAVR (n = 19)	PAVR (n = 18)	BAV alone (n = 19)	P value
Clinical characteristics						
Age (y)	81 ± 7	83 ± 8	78 ± 7	81 ± 6	81 ± 8	.52
Male sex (%)	51 (55)	17 (47)	10 (53)	12 (67)	12 (63)	.48
NYHA class III	54 (59%)	19 (53%)	14 (74%)	6 (33%)	15 (79%)	.12
NYHA class IV	38 (41%)	17 (47%)	5 (26%)	12 (67%)	4 (21%)	.07
Peripheral arterial disease	26/89 (29%)	12/34 (35%)	3/19 (16%)	6/18 (33%)	5/18 (28%)	.48
Severe chronic obstructive pulmonary disease	30/88 (34%)	8/33 (24%)	5/19 (26%)	8/18 (44%)	9/18 (50%)	.18
Previous coronary artery bypass graft surgery	35/89 (39%)	13/34 (38%)	8/19 (42%)	7/18 (39%)	7/18 (39%)	.81
Creatinine (mg/dL)	1.5 ± 1.2	1.7 ± 1.7	1.2 ± 0.5	1.4 ± 0.6	1.5 ± 0.9	.48
Porcelain aorta	8/67 (12%)	2/18 (11%)	2/15 (13%)	3/18 (17%)	1/16 (6%)	.80
Additive EuroSCORE	10.8 ± 2.8	10.8 ± 2.8	9.6 ± 2.1	11 ± 3	11.7 ± 3.2	.73
Logistic EuroSCORE	25.6 ± 17.4	25.4 ± 17.6	18.3 ± 8.4	27.8 ± 18.8	35.2 ± 20.9	.42
STS score	12.8 ± 9.8	12.6 ± 9.2	9.2 ± 6.7	11.4 ± 7.5	17.9 ± 13.6	.047
Follow-up (d)	218 ± 121	179 ± 105	266 ± 106†	278 ± 128†	179 ± 122	.002
Echocardiographic characteristics						
Aortic valve area (cm ²)	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	.6
Peak gradient (mm Hg)	75 ± 31	72 ± 29	87 ± 37	80 ± 25	65 ± 29	.11
Mean gradient (mm Hg)	43 ± 18	41 ± 17	51 ± 23	46 ± 16	37 ± 17	.09
Mitral regurgitation	1.6 ± 0.8	1.5 ± 0.8	1.2 ± 0.6	1.9 ± 0.7*	1.8 ± 0.9*	.01
Aortic incompetence	1.3 ± 0.8	1.3 ± 0.8	1.4 ± 0.8	1.2 ± 0.8	1.3 ± 0.6	.70
Ejection fraction (%)	46 ± 16	48 ± 16	49 ± 14	46 ± 17	38 ± 17‡	.02

SAVR, Surgical aortic valve replacement; PAVR, percutaneous aortic valve replacement; BAV, balloon aortic valvuloplasty; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons. *Patients who underwent percutaneous aortic valve replacement and those undergoing balloon aortic valvuloplasty alone had a higher degree of mitral regurgitation compared with those who underwent surgical aortic valve replacement. †Follow-up was longer for patients undergoing surgical or percutaneous aortic valve replacement. ‡Patients who underwent balloon aortic valvuloplasty alone had lower ejection fraction compared with other groups.

BAV but did not want PAVR, and 6 (32%) remained unsuitable for SAVR and were excluded from the PAVR study protocol for various reasons, as mentioned in the Methods section. Thirty-six (39%) patients did not undergo any intervention. The most common reasons for no intervention included mortality before definitive treatment because of

limitation in the number of patients who could be enrolled for PAVR (n = 10 [28%]), patients not interested in the study (n = 10 [28%]), and patients with symptoms not clearly attributable to severe AS (n = 9 [25%]).

There were no differences in the baseline clinical characteristics among the 4 groups of patients: those undergoing

FIGURE 2. Patient characteristics.

FIGURE 3. Patient management. PAVR, Percutaneous aortic valve replacement; SAVR, surgical aortic valve replacement; BAV, balloon aortic valvuloplasty; MSOF, multisystem organ failure; AI, aortic insufficiency.

SAVR, PAVR, BAV, or no intervention (Table 1). Among echocardiographic characteristics, patients who underwent BAV alone had lower left ventricular ejection fractions compared with the other groups ($38\% \pm 17\%$ vs $49\% \pm 14\%$, $46\% \pm 17\%$, and $48\% \pm 16\%$, respectively; $P = .02$). Additionally, 8 (42%) patients with ejection fractions of less than 30% underwent BAV alone compared with 3 (16%) patients in the SAVR, 5 (25%) in the PAVR, and 7 (19%) in the no intervention groups. Also, patients who underwent PAVR and those undergoing BAV alone had a higher degree of MR compared with those who underwent SAVR (1.9 ± 0.7 and 1.8 ± 0.9 vs 1.2 ± 0.6 , respectively; $P = .01$). Patients undergoing surgical intervention had lower logistic EuroSCOREs compared with other patients (18 ± 8 vs 27 ± 18 , respectively; $P = .04$). Patients undergoing surgical intervention had lower STS scores compared with patients undergoing BAV alone (9.2 ± 6.7 vs 17.9 ± 13.6 , $P = .02$).

Outcome

Further information on outcomes is available in Figure 4. Of the 92 patients in this study, overall mortality was 32% (29 patients), with a mean follow-up of 220 days. In-hospital/30-day mortality for the SAVR group was 0%, with total mortality of 5% on follow-up (1 patient died 2 months after surgical intervention from an unknown cause). In-hospital/30-day mortality in the PAVR group was 5% (1 patient died of renal failure and sepsis on postprocedure day 10). The mortality in the PAVR group on follow-up was 22% (4 patients: 1 in-hospital death, as noted above; 1 had unsuccessful PAVR and died 2 months later of congestive heart failure; 1 died after 3 months of complications from liver cirrhosis after refusing liver transplantation; and 1 died after 4 months from multiple myeloma diagnosed after PAVR). Length of hospital stay and complications after SAVR and

FIGURE 4. Kaplan–Meier survival curve: Patients referred for percutaneous aortic valve replacement.

PAVR are shown in Table 2. Four patients in the PAVR group had 3+ MR before PAVR. Postoperatively, 3 of these patients had 2+ MR and 1 had 1+ MR on follow-up.

Mortality in the BAV-only group was 47% (9 patients) after a mean duration of 55 days after BAV. Of these patients, 1 died of severe aortic insufficiency after BAV, 1 died of cancer after 5 months, 5 died of multisystem organ failure, and 2 experienced sudden death. In patients not undergoing any intervention, 1-year mortality was 42% (15 patients). Mortality was 9% (1/11) in patients bridged to SAVR or PAVR after BAV.

DISCUSSION

Our findings demonstrate that patients with advanced age and comorbidities, such as renal insufficiency, lung disease, previous cardiac surgeries, and poor left ventricular function, are being referred for PAVR. These symptomatic patients with severe AS have high mortality if SAVR or PAVR is not performed in a timely manner. About 20% of the patients referred for PAVR were found to be surgical candidates and underwent AVR with no operative deaths in an experienced center. High-risk patients who had no intervention or who were not bridged to either PAVR or SAVR after BAV had an excessive mortality rate of 44%.

TABLE 2. Length of stay and complications

Postoperative complications	SAVR (n = 19)	PAVR (n = 18)	P value
Length of stay (d)	12 ± 4	12 ± 6	.3
Transfusion	7 (37%)	7 (39%)	.94
Stroke	0	0	1.0
Infection	2 (11%)	2 (11%)	1.0
Myocardial infarction	0	0	1.0
Prolonged ventilation	1 (5%)	1 (6%)	1.0
Nursing home	0	1 (5%)	.84
Permanent pacemaker	1 (5%)	1 (6%)	1.0

SAVR, Surgical aortic valve replacement; PAVR, percutaneous aortic valve replacement.

ACD

There are 4 retrospective studies in the literature characterizing patients with severe AS who did not undergo SAVR.^{8-10,12} Patients were selected in these studies by either searching echocardiographic laboratory databases^{8,10} or by means of a survey of patients referred for SAVR.⁹ Inherently, these studies might have excluded patients not referred for SAVR and occurred before the availability of PAVR. Our study is the first to characterize and report outcomes of patients screened for PAVR, thus including patients with severe symptomatic AS, many of whom would probably not have been referred for SAVR otherwise. Of the 92 patients screened, 20% could undergo conventional surgical intervention with a good outcome (only 1 death at 2 months and no operative mortality) at our institution with high surgical volume. This is in concurrence with existing data that show an association of surgeon and hospital volume with surgical mortality.^{19,20}

Past studies have shown that although BAV can result in temporary relief of symptoms, restenosis is certain within 6 to 12 months.²¹⁻²⁴ This led to clinical guidelines recommending BAV as a reasonable bridge to surgical intervention in hemodynamically unstable patients at high risk for AVR or as a palliative procedure in patients with AS at high risk for SAVR (class IIb indication).⁴ Patients undergoing BAV (n = 30) had lower mortality compared with patients not undergoing any intervention (33% vs 42%). This was mainly due to 11 patients who could be bridged to SAVR or PAVR. Patients undergoing BAV who could not be bridged had a high mortality rate of 47% on follow-up, which is similar to that seen in patients who had no intervention. Most of these patients were waiting for PAVR after undergoing BAV. With the advent of PAVR and the rapid developments in this field, there has been a resurgence of interest in BAV procedures that otherwise offer little long-term benefit. Future studies will help to define this emerging role of BAV in bridging patients to PAVR.

Many patients with AS and heart failure have moderate-to-severe MR. In our patient population 14 patients had at least moderate MR, and 6 (42%) underwent BAV initially. Two of these patients were subsequently bridged to PAVR. The ongoing randomized study for PAVR excludes patients with severe MR. Use of BAV in patients who are not surgical candidates in this population remains uncertain.

Our study shows that patients with severe symptomatic AS who did not undergo aortic valve replacement had a high mortality, which concurs with the existing data.⁴⁻⁸ Most of the deaths in this group occurred while patients were in the process of being screened for PAVR or waiting for the procedure. Our study shows that replacing the aortic valve in these very sick elderly patients with severe symptomatic AS improves survival. Undoubtedly, a multifaceted management plan is required for successful management of elderly patients with severe AS. However, it appears that definitive treatment with valve replacement is imperative for

any plan to succeed. It is conceivable that wider availability of PAVR, timely intervention, and earlier referral to centers experienced in multidisciplinary treatment of high-risk patients with AS will result in better outcomes.

Although this study brought to light many more patients with severe AS who could not be included in the previous studies, there are potentially many more patients who were not referred for PAVR, mainly because of the novelty of the approach. There might be a selection bias in that this is a single-center study from a tertiary care center with expertise in valvular heart surgery. Despite this limitation, our findings highlight the potential of new treatment paradigms that will emerge with PAVR.

CONCLUSION

In summary, patients with advanced age, renal insufficiency, lung disease, previous cardiac surgeries, and poor left ventricular function are referred for PAVR. Symptomatic patients with severe AS have high mortality if aortic valve replacement is not feasible in a timely manner. Approximately 20% of the patients referred for PAVR could undergo surgical AVR with a good outcome. Patients managed with BAV or without any intervention have unfavorable outcomes.

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