Which Elderly Patients with Severe Aortic Stenosis Benefit from Surgical Treatment? An Aid to Clinical Decision Making

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Background and aim of the study: **Clinical decision-making in an individual elderly patient with severe aortic stenosis (AS) is difficult. The prognosis is influenced by increased age and various cardiac morbidity and comorbidity, and the benefit of surgery is uncertain because the prognosis with conservative treatment has rarely been described. The study aim was to identify those patients who would gain from surgical therapy.**

Methods: **The long-term survival of a cohort of elderly patients after an initial diagnosis of severe aortic stenosis was analyzed. Multivariate analysis was used to develop patient profiles on the basis of four main variables of age, severity of AS, cardiac morbidity, and comorbidity, to illustrate the benefit of surgical treatment over conservative treatment.**

Results: **A total of 280 consecutive patients aged ≥70 years (median age 78 years) with a first-time diagnosis of isolated AS made between 1991 and 1993 was included. Of these patients, 120 underwent surgery. The seven-year predicted survival ranged from 6.9% to 83% in surgically treated patient, and from 0.6% to 48% in conservatively treated patients. The benefit of surgical treatment over conservative treatment was greatest in patients aged <80 years, with a more critical AS, cardiac morbidity, and without (7-year survival 78% versus 14%) or with (7-year survival 56% versus 1%) comorbidity. Minimal benefit was seen in patients aged >80 years with a less critical AS and without cardiac morbidity.**

Conclusion: **This model illustrated the benefit of surgical treatment over conservative treatment in 16 different profiles of elderly patients with severe AS. These findings may provide support for clinical decision making in individuals within this patient group**

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As the population of Western society continues to age, aortic valve stenosis represents an expanding health problem. Indeed, in an unselected population a prevalence of 2.5% was found among 72-year-old patients, and 8% among 85-year-olds (1).

The decision to advise surgical or conservative treatment in elderly patients with aortic stenosis (AS) is complicated because it includes not only factors such as AS severity and cardiac symptoms but also the patient's age (i.e., life expectancy) and comorbidity (2). Numerous surgical studies have described the results of surgical treatment (aortic valve replacement, AVR) in a selected population in which the decision to operate had already been taken (3-12). Based on the findings of these investigations, it cannot be inferred whether some patients were - albeit erroneously - denied surgery (13). It is also impossible to determine whether patients really benefited from AVR as compared with conservative treatment. To the present authors' knowledge, no study has yet been reported which describes the clinical course in a cohort of consecutive elderly patients with severe AS, irrespective of the treatment modality (surgical or conservative).

Hence, the study aim was to determine which patients benefited from surgical treatment, and which did not. The clinical course was investigated for 280 consecutive patients with a first diagnosis of isolated AS on the basis of Doppler echocardiography. The study was conducted at three University Hospitals, and all patients were followed up for at least six years, irrespective of any therapeutic decision to perform surgery. Following identification of the determinants of the treatment decision and survival after surgical and conservative treatment, a series of profiles were developed of elderly patients with AS on the basis of four main clinical factors - age, severity of AS, cardiac

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morbidity, and comorbidity. For each patient profile, the benefit of surgical treatment was illustrated by the predicted long-term survival for both treatment modalities.

Clinical material and methods

Patient population

A total of 280 consecutive patients aged over 70 years and with a first-time diagnosis of isolated AS were included in the study. The patients were identified using Doppler echocardiography at three University Hospitals (Amsterdam, Groningen, Maastricht) in the Netherlands between January 1991 and January 1994. Isolated AS was defined as an aortic valve area (AVA) ≤1.0 cm^2 or a maximum gradient of ≥50 mmHg (14,) and an aortic regurgitation not exceeding grade II out of IV as assessed by Doppler echocardiography (15). Patients with serious concomitant valvular diseases were excluded.

Data acquisition

Data on the patients' sociodemographic and clinical characteristics at the time of initial echocardiography were collected from the medical charts. Left ventricular function was qualitatively assessed by echocardiography, and defined as either 'good' or 'impaired'; that is, akinesia of two or more segments or an ejection fraction <45%. In general, coronary angiography was performed only in candidates for surgical treatment. The non-cardiac comorbidity was scored according to Greenfield's classification of diseases, in which each organ system is separately scored for absence of disease activity or presence of any illness at any level of disease activity in that system (16). For example, gastrointestinal disease is defined by the presence of a history of an ulcer, an active gastric ulcer, or diverticulitis. Patients with symptoms that could be attributed to the AS were considered for surgical treatment, and the decision to operate was placed at the discretion of the treating cardiologist (14,17). Concomitant coronary artery bypass grafting (CABG) was performed in the case of significant lesions (≥50%).

Follow up

All patients were followed up until June 2000. Information relating to the patient's NYHA functional class and rate of independence (Rankin score) (18) at the end of follow up was collected via their general practitioner, or by direct telephone contact with the patient.

Statistical analysis

A Cox proportional hazard regression analysis was used to construct three multivariate models.

Model 1 investigated the determinants of surgical treatment during follow up. Time zero was the time point of diagnosis, the event was the time of AVR, and patients without AVR were censored at the time of death for those who died, or at the end of the study for those who survived. The independent variables were the clinical variables as described above. A Cox model was used because in some patients the procedure was performed up to three years after diagnosis.

Model 2 explored the determinants of mortality during conservative treatment. Time zero was the time point of diagnosis, and the dependent variable was death without AVR. Those patients with AVR and those without AVR who were alive at the end of the study were censored.

Model 3 analyzed the determinants of mortality after AVR. Time zero was the time point of AVR. The dependent variable was death following AVR, with censoring at end of the study for those who survived until that time.

Patients who died whilst awaiting AVR were removed from the analysis, because this may have biased the results for conservative treatment (their death was in fact related to the surgical waiting list). As model 2 explores mortality under conservative treatment, it must be based on patients who are actually selected for conservative treatment.

Patient profiles were generated using composite determinants obtained from the previous models. Subsequently, survival after surgical and conservative treatment was predicted for each patient profile. In the prediction model it was assumed (for reasons of simplicity) for surgically treated patients that the operation took place at time zero. Database structuring and data analyses were performed using SAS statistical software (Version 6.12; SAS Institute, Cary, NC, USA).

Results

Patient population

The diagnosis of isolated AS was made for the first time in 280 patients of median age 78 years (range: 70 to 93 years). The baseline characteristics of patients are summarized in Table I. Comorbidity was highly prevalent, being present in 83% of conservatively treated and 67% of surgically treated patients. The most common comorbidities were renal failure, hypertension, a history of stroke or transient ischemic attack (TIA), and peripheral vascular disease. Of the 137 patients who underwent coronary angiography, 70 (51%) had significant coronary artery disease (CAD). Follow up was completed for 99% of the patients (the four missing patients had moved abroad during the follow up period).

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Vol. 13. No. 2
March 2004

Conservative treatment

Among a total of 160 patients treated conservatively, 145 (91%) died during follow up. The median follow up was 7.8 years (10th and 90th percentiles 6.7 and 9.1 years). At the end of follow up, 13 patients were still alive and two had been lost. Nine patients were in NYHA class II, and nine were living independently. The one-, five-, and eight-year unadjusted observed survival rates were 60%, 28% and 8%, respectively. The independent risk factors of mortality are listed in Table IIA. Among 170 patients aged under 80 years, 69 were treated conservatively, and 45 of these were in NYHA class III or IV. Reasons for not proceeding to a surgical procedure were comorbidity (n = 26), absence of complaints or decrease of symptoms after medication (n = 14), other cardiac disease as the main cause of the complaints (mostly CAD), impaired systolic left ventricular function, refusal, or advanced age.

Surgical treatment

During follow up, 120 (45%) patients underwent AVR. Among the surgically treated patients, 71% were operated on within six months of the diagnosis, and this figure increased to 97% within three years. The clinical determinants of surgical treatment are presented in Table IIB. Only 19 of the 107 patients aged over 80 years were operated on, although 64% of these were in NYHA class III or IV. Reasons for not proceeding with surgery were an absence of complaints (n = 17), decrease of symptoms after medication (n = 4),

Table I. Baseline characteristics and mortality during follow up of elderly patients with a first-time diagnosis of aortic valve stenosis stratified to conservative and surgical treatment.

Baseline characteristic	Conservatively treated		Surgically treated	
	All*	Deaths+	All*	Deaths+
All	157	142 (90)	120	46 (38)
Age group (years)				
70-74	32	26 (81)	60	22 (37)
75-79	37	32 (92)	41	12 (29)
80-84	50	46 (92)	15	10 (67)
≥85	38	36 (95)	4	2 (50)
Female gender	106	96 (91)	74	33 (45)
Angina NYHA III/IV	100	90 (90)	83	33 (39)
History of infarction	40	40 (100)	14	8 (57)
History of cardiac surgery	12	11 (92)	8	6 (75)
Clinical heart failure	62	58 (94)	27	10 (37)
Max gradient (mmHg)‡				
<50	31	30 (97)	3	3 (100)
50-63	49	44 (90)	14	6 (43)
64-99	68	59 (87)	54	21 (39)
≥100	9	9 (100)	49	16 (33)
Moderate MR	81	77 (95)	52	22 (42)
TR (moderate or severe)	63	60 (95)	27	11 (41)
LVF (impaired)	72	69 (96)	32	12 (37)
Renal failure	68	63 (93)	24	15 (52)
Hypertension	53	49 (92)	37	17 (46)
Stroke or TIA	42	39 (93)	22	8 (36)
Peripheral vascular disease	32	29 (91)	18	13 (72)
Pulmonary disease	31	30 (97)	14	8 (57)
History of malignancy	33	31 (97)	10	4 (40)
Diabetes	21	19 (90)	18	13 (72)
Arthritis	27	24 (89)	10	3 (30)
Gastrointestinal disease	12	12 (100)	8	3 (37)
Hepatobiliary disease	12	10 (83)	2	0 (0)

*No. of patients.
+No. of deaths during follow up; values in parentheses are percentages.
‡Aortic valve area ≤1.0 cm^2.
LVF: Left ventricular function; MR: Mitral regurgitation; TIA: Transient ischemic attack; TR: Tricuspid regurgitation.

advanced age (n = 16), comorbidity (n = 16), and impaired systolic left ventricular function.

The 30-day postoperative mortality in the 120 surgically treated patients was 5%. The median follow up was 7.8 years (10th and 90th percentiles 6.7 and 9.1 years). During follow up, 47 (39%) patients died and two were lost. At the end of follow up, 57 (80%) patients were in NYHA class I or II, and 47 (66%) were living independently. The one-, five-, and eight-year unadjusted observed survival rates after surgery were 91%, 71% and 59%, respectively. Among the 79 (66%) patients who underwent AVR as an isolated procedure, the one-, five-, and eight-year survival was 94%, 73% and 66%, respectively. Among those patients who had additional bypass surgery, the one-, five-, and eight-year observed survival was decreased to 85%, 66% and 45%, respectively. Comorbidity, age, and a history of cardiac surgery determined the prognosis (Table IIC).

Patient profiles

The three multivariate models identified age over 80 years, severity of AS and 12 other clinical variables as influencing treatment decision and survival after surgical or conservative treatment (Table III). The corresponding hazard ratios of the latter 12 variables were of the same order of magnitude. The patient information obtained from these models was expressed in two newly created variables. First, cardiac morbidity was defined as being present when at least two of the cardiac characteristics were present (angina III/IV, clinical heart failure, history of infarction, tricuspid regurgitation, impaired LV function, or history of CABG). Second, comorbidity was defined as present if one or more of the following applied: diabetes, history of malignancy, pulmonary disease, gastrointestinal disease, peripheral vascular disease, or renal failure.

Three final models were constructed with four composite independent variables: age (70-80 or over 80 years), severity of AS (severe: maximum gradient 50-64 mmHg or AVA 0.8-1.0 cm^2) or critical (maximum gradient >64 mmHg or AVA <0.8 cm^2), cardiac morbidity (for definition, see above) and comorbidity (defined above), as the independent variables. The first model describes the influence on the decision to perform AVR, and the two other models on the mortality after conservative and after surgical treatment, respectively. The results are presented in Table III. Age over 80 years and comorbidity restrained the possibility of a surgical treatment, whilst critical AS favored surgical treatment. Mortality after conservative treatment was mainly determined by cardiac morbidity and comorbidity, with a limited influence of age and severity of AS. In the surgically treated group, mortality was determined by advanced age and comorbidity, but not by cardiac morbidity.

In total, 16 different patient profiles were created representing each combination of the four composite variables. The latter two Cox models were used to predict the survival after conservative and surgical treatment for each patient profile (Fig. 1a and b). The predicted survival for patients with similar treatment differed dramatically. The seven-year predicted survival in surgically treated patients ranged from 6.9% to 83%, depending on the patient profile. For example,

Table II. Multivariate analysis of determinants of surgical therapy and mortality after conservative and surgical treatment.

A) Mortality after conservative treatment.

Model	Hazard ratio	95% CI
Clinical heart failure	1.6	1.1-2.4
History of infarction	1.8	1.2-2.7
Tricuspid regurgitation	1.7	1.1-2.4
Impaired LV function	1.7	1.2-2.4
History of malignancy	1.6	1.1-2.4
Pulmonary disease	2.2	1.4-3.4
Gastrointestinal diseases	2.5	1.3-4.6

B) Clinical determinants of surgical treatment.

Model	Hazard ratio	95% CI
Severity of AS (mmHg)		
50-63	1.9	0.6-6.7
64-99	6.2	1.9-20
≥100	26	7.9-85
Age ≥80 years	0.23	0.1-0.4
Angina (NYHA class III/IV)	2.1	1.4-3.2
Diabetes	2.1	1.3-3.6
History of malignancy	0.5	0.2-0.9

C) Mortality after surgical treatment.

Model	Hazard ratio	95% CI
Age ≥ 80 year	2.5	1.2-5.0
Diabetes	2.5	1.2-5.0
PVD	2.6	1.3-5.2
Renal failure	2.0	1.1-3.8
History of CABG	4.0	1.6-10

CABG: Coronary artery bypass grafting; PVD: Peripheral vascular disease

J Heart Valve Dis
Vol. 13. No. 2
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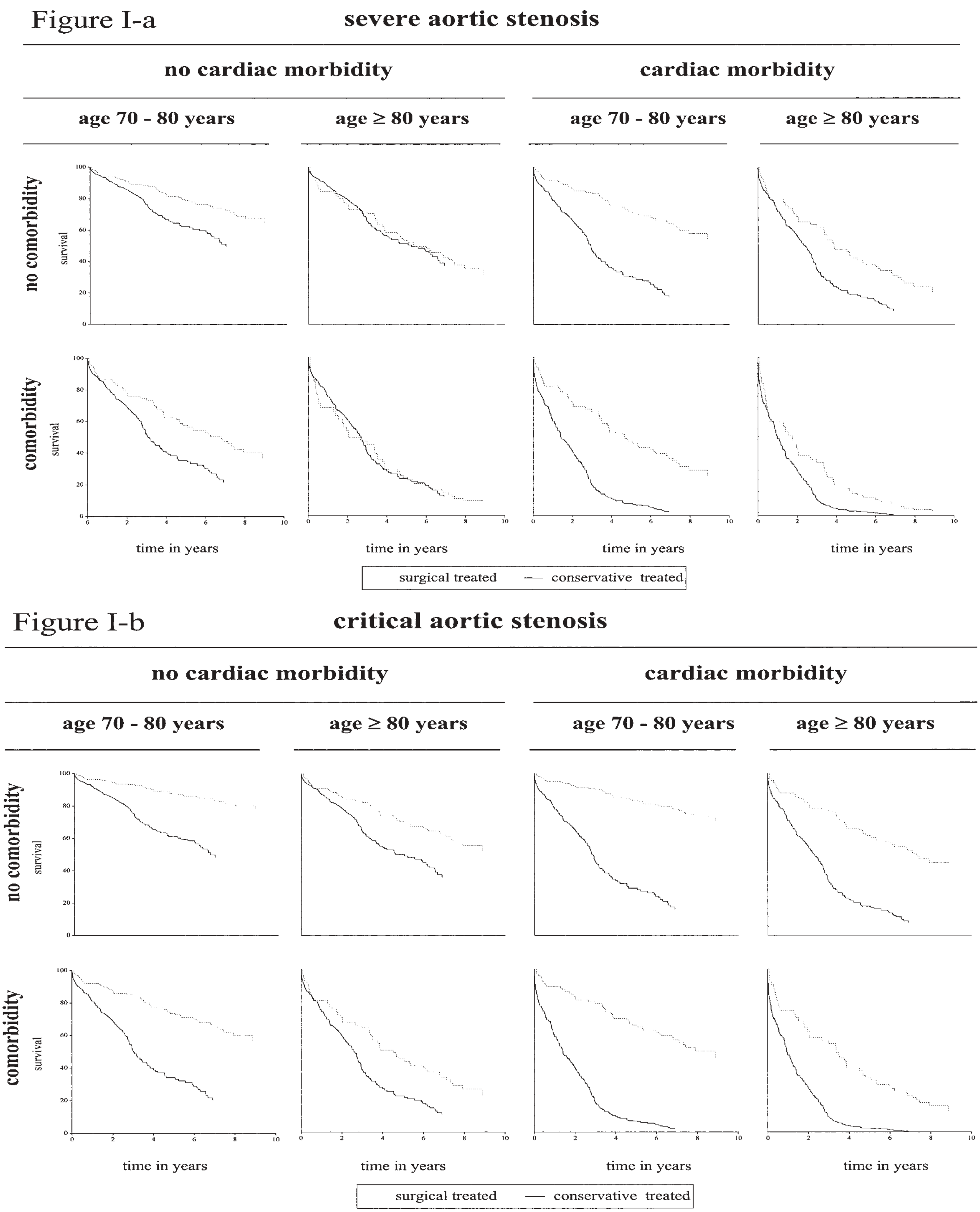

Figure 1: Predicted survival after surgical and conservative treatment for elderly patients with (A) severe and (B) critical aortic valve stenosis varying with age, cardiac morbidity, and comorbidity.

surgically treated 'younger' patients (aged 70-80 years) with a severe AS (maximum gradient 50-64 mmHg or AVA 0.8-1.0 cm^2), with cardiac morbidity but without comorbidity, had a seven-year survival of 64%, whereas those with comorbidity had a predicted survival of 36%. The predicted survival after conservative treatment ranged from 0.6% to 48%.

The predicted survival in surgically treated patients was similar to or better than - but never worse than - the predicted survival with conservative treatment. The biggest difference in predicted survival was found in 'younger' patients with a critical AS and cardiac morbidity. No difference was found among 'older' patients with a severe AS and without cardiac morbidity.

Discussion

The benefit of surgical treatment in elderly patients with AS was illustrated graphically in 16 different patient profiles, using a model of four variables, namely age (70-80 or >80 years), severity of AS (severe or critical), cardiac morbidity, and comorbidity (Fig. 1a and b). These four variables enabled patient profiles to be distinguished in which surgical treatment either did, or did not, result in a substantial improvement of prognosis, taking all relevant clinical characteristics into account. These findings should provide support in the decision-making process relating to surgery in elderly patients with AS. The long-term follow up of at least six years strengthened these findings.

The decision to apply surgical or conservative treatment in elderly patients with AS is complicated, as shown by the identification of 14 independent clinical variables influencing treatment choice and survival after conservative and surgical treatment (Table II). Clinical decision making is hampered by the lack of randomized controlled trials (19). The available studies on the success of valve replacement in elderly patients with aortic valve stenosis have been performed in selected populations, and do not provide information about the rejected and conservatively treated patients. Therefore, data from those studies cannot easily be transferred to the routine elderly patient with severe AS in everyday clinical practice (3-12). This leads to a wide variation in treatment (19), together with doubts relating to the justification of treatment choices in certain cases (13).

The determinants of mortality were found to differ between conservatively and surgically treated patients. In the latter situation, cardiac morbidity and AS severity were, as expected, modified by surgery and no longer influenced survival. Advanced age and comorbidity determine the prognosis in surgically treated patients. Against this, in conservatively treated patients, neither age nor AS severity are significant determinants. In these patients, cardiac morbidity and comorbidity determine prognosis.

As opposed to patients aged <70 years, comorbidity often dominates the discussion about the treatment of elderly patients with AS. In accordance with other studies, comorbidity occurs frequently, but more often in conservatively (83%) than in surgically (67%) treated patients (3-12). In the present study, eight different organ systems were identified (besides the heart) in which disease activity influenced treatment decisions and the prognosis in conservative and surgical treatment. This hampers clinical decision making and leads to heterogeneity in treatment (19). The findings of the present study may be helpful in reducing heterogeneity and in taking correct decisions, though further research should be carried out to confirm these findings.

Nevertheless, the benefit of surgical treatment

Table III. Multivariate analysis of determinants of surgery, and mortality after conservative and surgical treatment.

Determinant	Surgery		Mortality after			
			Conservative treatment		Surgical treatment	
	HR	95% CI	HR	95% CI	HR	95% CI
Age ≥80 years	0.3	0.2-0.4	1.1	0.8-1.5	2.6	1.4-5.2
Severe aortic stenosis	4.5	2.7-7.7	1.2	0.9-1.7	0.6	0.3-1.2
≥ 2 cardiac characteristics*	1.1	0.8-1.6	2.2	1.5-3.1	1.4	0.8-2.4
≥ 1 factor of comorbidity+	0.6	0.4-0.9	1.8	1.2-2.7	2.3	1.2-4.4

*Cardiac characteristics (angina NYHA class III/IV, clinical heart failure, history of infarction, tricuspid regurgitation, impaired LV function, history of CABG).
+Factors of comorbidity (diabetes, history of malignancy, pulmonary disease, gastrointestinal disease, peripheral vascular disease, renal failure).
HR: Hazard ratio.

should be judged not only on its capacity to prolong life but also on an ability to improve the quality of life. In this respect, it is encouraging that of the 71 surgically treated patients who were alive at the end of follow up, the vast majority (n = 57; 80%) was in NYHA class I or II, and 47 (66%) lived independently. Thus, surgery not only prolongs life, but also improves its quality.

Study limitations

This retrospective study was the first in which the observation period commenced at the time of the initial diagnosis of AS. This contrasted with most studies, where observation was commenced at the time of AVR. The present methodological concept was seen to fit better with clinical practice, wherein the cardiologist examines an elderly patient with AS and decides whether or not to refer them for cardiac surgery. Starting an observation period at the time of diagnosis rather than at AVR hinders a straightforward analysis, and hence three analytical strategies were used. First, patients were grouped on the basis of whether they underwent surgery during follow up, or not. This approach might be criticized for creating a division based on an event that transpires after time zero. Second, a multi-state model was constructed to calculate the chance of being alive, taking into account all possible stages (to be alive before surgery, the chance of surgery, and to be alive after surgery) (20). This model was statistically elegant, but did not provide useful clinical information. To overcome these limitations, the authors resorted to the analysis as presented, wherein the concession was made that the three patients who died on the waiting list were rejected as these data may have biased the results for conservative treatment (this proved not to be the case). The predicted survival with and without surgery for 16 different patient profiles (see Fig. 1) enhances clinical simplicity and clarity at the expense of some predictive detail because the information was reduced to four baseline characteristics. In predicting survival, it was assumed that surgery would take place on the day of diagnosis, thereby avoiding a preoperative period during which the patient is at risk of mortality. As most patients were operated on shortly after diagnosis, and the follow up was long, the effect of this concession was limited.

The long follow up employed provided an insight into the impact of treatment decisions in the long term. However, treatment decisions made in 1993 differ greatly from those of today. For example, today an impaired left ventricular function would be a reason for operation, whereas 10 years ago it would be considered a relative contraindication. Also, in the present study only 19 of 107 patients aged >80 years were treated surgically, implying that today's results might be different.

Coronary angiography was only performed in patients who were candidates for surgery. For this reason, the presence of CAD was not used in the model predicting either surgery or mortality in conservatively treated patients, though the presence of CAD is clearly a major risk factor for mortality. In the surgically treated group, the CAD presence was a strong univariate predictor of late mortality, but in the multivariate analysis its presence failed to reach statistical significance because of its correlation with other risk factors such as diabetes and peripheral vascular disease.

In conclusion, various clinical characteristics influence the treatment and prognosis of elderly patients with a first-time diagnosis of severe AS. The benefit of surgical treatment in these patients may be satisfactorily predicted using patient profiles incorporating four variables of age, AS severity, cardiac morbidity, and comorbidity. Patients aged <80 years, with critical AS and more then one cardiac characteristic seem to benefit most from surgery. In patients aged >80 years, with severe AS and no (or one) cardiac characteristics, the prognosis after surgery is similar to that after conservative treatment. These findings may be useful in clinical decision making in individual elderly patients with severe AS.

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