JACC Vol. 26, No. 5
November 1, 1995:1280–6

Analysis of Risk Factors for Excess Mortality After Aortic Valve Replacement

HANS A. VERHEUL, MD, RENÉE B. A. VAN DEN BRINK, MD, BERTO J. BOUMA, MD, GERARD HOEDEMAKER, MD, ADRIAN C. MOULIJN, MD, EGBART DEKKER, MD, PATRICK BOSSUYT, PHD, AREND J. DUNNING, MD, FACC

Amsterdam, The Netherlands

Objectives. This study sought to identify risk factors for both late observed and late "excess" mortality after aortic valve replacement and to examine the causes of late mortality.

Background. Because operative mortality after aortic valve replacement is very low, the timing of surgical intervention should focus on maximizing long-term survival. However, to judge the effect of valve replacement on long-term survival in an elderly population, it is important to separate mortality resulting from extraneous causes _(background mortality)_ from disease-related mortality _(excess mortality)_. Background mortality can be estimated by calculating expected mortality on the basis of age and gender.

Methods. From 1966 to 1986, 643 patients (mean age 59.6 years, 138 [21%] ≥70 years old) underwent aortic valve replacement, 129 of whom also underwent coronary bypass grafting; 594 patients survived ≥30 days after the procedure. The overall operative mortality rate for isolated aortic valve replacement decreased over time from 25.5% (1966 to 1972) to 2.6% (1980 to 1986). Cumulative total follow-up after discharge was 3,603 patient-years. Multivariate analysis was performed for both observed and excess mortality.

Results. Risk factors for both observed and excess mortality were previous myocardial infarction, coronary artery disease, heart failure and atrial fibrillation. Although age ≥70 years was a risk factor for observed mortality (hazard rate ratio [HRR] 2.4, 95% confidence interval [CI] 1.6 to 3.7), it was not a risk factor for excess mortality. In contrast, isolated aortic regurgitation was an important risk factor for excess mortality only (HRR 3.8, 95% CI 1.3 to 11.2). Late mortality was valve related in 22% of patients, including sudden death in 7% and cerebral vascular accidents in 7%. Congestive heart failure was an important cause of death (21%) irrespective of the time elapsed since aortic valve replacement. In patients with aortic regurgitation, congestive heart failure was the main cause of death (38%); in patients with aortic regurgitation and preoperative heart failure or severe left ventricular dysfunction, heart failure was the cause of death in 44% and 63%, respectively.

Conclusions. Analysis of excess mortality revealed that older age in itself is not a risk factor for late mortality after aortic valve replacement. Aortic regurgitation carries a high risk, probably associated with left ventricular dysfunction at the time of operation. Earlier operation may be warranted in such patients.

(J Am Coll Cardiol 1995;26:1280–6)

Because operative mortality related to aortic valve replacement is now very low, the decision to operate should aim at timing the intervention to maximize long-term survival. However, this timing can be determined only on the basis of clinical studies that randomize the timing of the operation. Nevertheless, some insight can be gained by identifying mortality risk factors that separate patients with a better prognosis from those with a poorer prognosis.

Because aortic valve replacement is usually performed in elderly patients, it is important to distinguish between mortality from extraneous causes ("background" mortality) and disease-related mortality ("excess" mortality). Causes of death can be classified as disease related or not, and background mortality can be estimated from expected mortality. When expected mortality is subtracted from observed mortality, the result is excess mortality. In recent years, several long-term survival studies (1–3) from the Scandinavian countries have indicated the importance of comparing the observed survival after aortic valve replacement with the expected survival in a reference group matched with the study cohort for age, gender and calendar time at operation (1–3).

In the present historical cohort study, we report our experience with aortic valve replacement from 1966 to 1986. The objective of the present study was to identify risk factors for both observed and excess late mortality.

Determining background mortality is problematic in that by comparing the dynamic study cohort with a static reference group drawn from the general population, the heterogeneity of the distribution of observed mortality in younger and elderly patients may result in an increased estimate of background

From the Departments of Cardiology, Cardiopulmonary Surgery and Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, The Netherlands.

Manuscript received July 13, 1994; revised manuscript received May 26, 1995, accepted June 2, 1995.

Address for correspondence: Dr. Hans A. Verheul, Department of Cardiology, Academic Medical Center, F4-110, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

0735-1097/95/$9.50
0735-1097(95)00303-L

Table 1. Clinical Characteristics According to Type of Valve Dysfunction

	AS or AS/AR (n = 496)	AR (n = 147)	All (n = 643)
Mean (±SD) age (yr)	61.5 ± 11.6	53.2 ± 13.5	59.6 ± 12.6
Age ≥70 yr	126 (25%)	12 (8%)	138 (21%)
Men	308 (62%)	102 (69%)	410 (64%)
NYHA functional class III/IV	381 (77%)	125 (85%)	506 (79%)
Congestive heart failure	111 (22%)	54 (37%)	165 (26%)
Atrial fibrillation	37 (8%)	13 (9%)	50 (8%)
Active endocarditis	1	23 (16%)	24 (4%)
Coronary artery disease	119 (24%)	37 (25%)	156 (24%)
Mitral valve regurgitation	90 (18%)	28 (19%)	118 (18%)
Severely impaired LV function	66 (13%)	24 (16%)	90 (14%)
30-day mortality rate after isolated AVR			
1966–1972	28.6%	15.4%	25.0%
1980–1986	2.4%	3.7%	2.6%

Unless otherwise indicated, data presented are number (%) of patients. AR = aortic regurgitation; AVR = aortic valve replacement; AS = aortic stenosis; LV = left ventricular; NYHA = New York Heart Association.

mortality (4). To overcome this bias and to improve survival analysis, we applied rate adjustment when calculating background mortality, that is, we maintained age, gender and calendar time of the reference group identical at all times to those of each patient still alive and under observation (4).

Methods

Study group. The study group included 643 patients (>20 years old) who underwent aortic valve replacement during 1966 through 1986, of whom 129 (20%) also underwent bypass surgery. Patients who had additional cardiac surgical procedures were excluded. The mean age was 59.6 years (SD 12.6, maximal age 85.7); 138 patients (21%) were >70 years old, and 410 were men (64%).

Angina pectoris was the main indication for operation in 32% of patients without and 64% with coronary bypass surgery. Dyspnea was the clinical indication in 44.3% of patients and syncope in 7.3%. An emergency operation because of a life threatening condition was required in 6% of patients, of whom 24 had active infective endocarditis (4%). Aortic stenosis was diagnosed in 26% of patients, isolated aortic regurgitation in 23% and mixed aortic stenosis and regurgitation in 51%. The clinical characteristics of the patients are presented in Table 1.

Clinical and catheterization data. All clinical documentation, catheterization data and correspondence were collected by retrospective chart review and processed in a structured data base. Preoperative symptoms were classified according to New York Heart Association functional criteria. Prior myocardial infarction was recorded in cases of enzyme level and electrocardiographic (ECG) verification. Congestive heart failure was defined as pulmonary edema or pulmonary vascular congestion, both auscultatory and radiographic, during the year before operation. Atrial fibrillation on the ECG and cardiomegaly (cardiac thoracic ratio ≥50%) on a standard chest radiograph were recorded. Endocarditis was classified using strict criteria (5), and the active phase was defined as <6 weeks of medical treatment.

Left heart catheterization was performed in 556 patients (86%); the remaining 87 patients were examined by Doppler echocardiography or, if they were too ill to sustain cardiac catheterization, by physical examination and two-dimensional echocardiography (before 1986). Aortic valve lesions were classified as *stenotic* (peak to peak gradient ≥30 mm Hg and regurgitation grade ≤2/4), *isolated regurgitation* (peak to peak gradient <30 mm Hg and regurgitation grade ≥3/4) and *mixed* (peak to peak gradient ≥30 mm Hg and regurgitation grade ≥3/4). Left ventricular function was evaluated qualitatively by examination of the 30° right anterior oblique left ventriculogram and classified into categories of normal function and moderate or severe impairment. *Moderate impairment* was defined as dyskinesia of two segments and *severe impairment* as dyskinesia of more than two segments. *Coronary artery disease*, defined as lumen narrowing >50%, was present in 156 patients (24%), of whom 76 had one-vessel disease (12%), 47 had two-vessel disease (7%), and 33 had three-vessel disease (5%).

Unavailability of information was due to limited clinical registration in the early period, incomplete catheterization (no coronary angiography because of young age or endocarditis; no transvalvular gradient because of an inability to access the left ventricle) or loss of information.

Surgical technique. Two methods of myocardial preservation were used: before 1978, continuous selective perfusion of the coronary arteries combined with local and general hypothermia, and beginning in 1978, cardioplegia by anterograde perfusion with St. Thomas's Hospital's solution into the coronary arteries. After excision of the valve and, when necessary, thorough annular debridement of calcium, the largest prosthesis that could be fitted into the annulus was implanted using interrupted everting mattress sutures. Before 1973, Starr-Edwards prostheses were used (n = 70 [11% of the study group]). These were followed by use of Björk-Shiley prostheses until 1984 (n = 292 [45%]). After 1984, the Medtronic-Hall valve became the principal choice of prosthesis (n = 149 [23%]). St. Jude Medical prostheses were used in cases of a small orifice (n = 21 [3%]). Bioprostheses were nearly all Carpentier-Edwards (n = 86 [13%]) and were used since 1980 in some patients >70 years old and when anticoagulation was contraindicated. Infrequently, other valve prostheses were implanted (4%).

All patients with mechanical prostheses received lifelong anticoagulation (target international normalized ratio 3 to 4.5); patients with bioprostheses received anticoagulation within the first 3 months of implantation. Since 1976, concomitant coronary artery bypass grafting was performed if significant lesions were present in the major branches. The average number of grafts was 1.6, and the average number of distal anastomoses was 2.1/patient. The operative mortality rate for isolated aortic valve replacement decreased from 25.5% in the period from 1966 to 1972 to 2.6% from 1980 to 1986. The operative mortality rate in patients <70 years old and without active infective endocarditis was 0.6% for combined aortic stenosis and regurgitation and 0% for isolated aortic regurgitation (1980 to 1986). The overall operative mortality rate for patients who underwent concomitant coronary artery bypass grafting was 13.9%.

Follow-up data and outcome events. Death after 30 days was classified as *late mortality*. A collective review of all evidence, including clinical records, postmortem examination and information from the Census Bureau (Central Bureau of Statistics), if present, was used to classify deaths into the following categories: surgical death, valve-related death, cardiac-related death, other causes and "circumstances unknown" (6). *Surgical death* was caused by intractable bleeding, major infection or sepsis, respiratory failure or multiorgan failure. *Valve-related mortality* was defined as death caused by structural deterioration (leaflet tear or stress fracture), nonstructural dysfunction (paravalvular leakage, entrapment), thromboembolism, anticoagulant-related bleeding, prosthetic valve endocarditis (death within 30 days after reoperation), sudden unexpected and unexplained death or fatal cerebrovascular accident. *Cardiac death* was defined as death due to myocardial infarction, heart failure or secondary cardiac arrhythmias. Other causes of death were mainly from malignancy and trauma. If absolutely no information on causes or circumstances of death was available (e.g., patients who emigrated), patients were classified as "circumstances unknown."

Data on clinical course and functional status at the end of follow-up of hospital survivors were collected by one of us (B.J.B.) from the outpatient clinical records. If this approach was not feasible, a questionnaire was answered by the attending cardiologist. The end of the follow-up period was January 1988.

Statistical analysis. Continuous variables are reported as mean value ±SD. Chi-square analysis was used to test differences between categoric variables. The Student *t* test was used for differences between continuous variables.

Cumulative survival was estimated by the Kaplan-Meier method (7). Potential risk factors were dichotomized into two categories: an index group, for which the risk was assumed to be increased, and a reference group that consisted of all other cases, including the unclassified. Factors studied were age, gender, preoperative functional class (class III or IV vs. other), previous myocardial infarction, congestive heart failure, active infective endocarditis, atrial fibrillation, cardiomegaly, coronary artery disease, aortic regurgitation (isolated regurgitation vs. stenosis/mixed lesion), mitral valve regurgitation, left ventricular function (severe impaired vs. normal/moderately impaired), valve size (≤23 vs. >23) and prosthesis type (bioprosthesis vs. mechanical prosthesis).

The Cox proportional hazards model was used to examine the impact of covariates (risk factors or determinants) on observed late mortality. "Hazard" was defined as the probability of dying within a short interval, as a function of time, given that the patient survived until the beginning of the interval. The ratio of the mortality hazard in the index group to that in the reference group is the *hazard rate ratio*.

Expected survival and excess mortality were estimated as follows: Background mortality was estimated by extracting from life-table data from the Dutch Census Bureau (Centraal Bureau voor de Statistiek), for each day that each patient was observed, the mortality fraction for that same day of a counterpart from the general population matched with the patient for age, gender and year of observation. Thus, by this method, whenever a patient was lost to follow-up, either by death or by end of the study, we withdrew his or her referent from the reference group. Together, these referents formed the *reference group*. Finding the mean mortality per day of these referents, a procedure known as rate adjustment, ensures that the reference parameters remain comparable at all times between the patient group and the reference group (4). This adjusted mortality rate indicates the probable mortality rates for the patient group if they had the same rates as those of the normal population. When this mortality fraction is dealt with analogously to the instantaneous mortality that is calculated after the death of each patient by the Kaplan-Meier method (7), it leads to the *expected survival curve*. *Excess mortality* is the difference between observed and expected survival. The hazard was separated into an expected (background) component and an excess component. Risk factors for excess mortality were identified through Poisson regression, as described by Hakulinen and Abeywickrama (8).

To control for overall improvement of surgical performance, the analysis was first stratified for date of operation; the study period was divided in two intervals (early experience [1966 to 1976] and current experience [1977 to 1986]).

Cox proportional hazard regression was performed with the BMDP package (9). Poisson regression of excess mortality was performed with the GLIM package (10).

Results

Late mortality and long-term survival. Of the 643 patients, 49 did not survive >30 days. Follow-up after discharge was complete in 583 (98%) of the remaining 594 patients, a

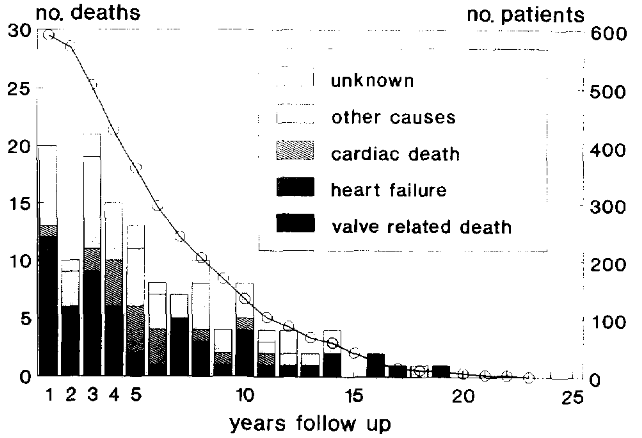

Figure 1. Causes of death after discharge for 594 patients according to follow-up time. **Solid line** = number of patients at risk; **columns** = mortality.

cumulative total of 3,603 patient-years. Mean follow-up time was 73 months. In total, 135 (late) deaths occurred.

Late mortality was valve related in 22% of patients and included all sudden and unexplained deaths (7%) and all cerebrovascular accidents (7%). Cardiac death was responsible for 34% of late mortality (mostly congestive heart failure [21%]), other causes for 36%, and no information was available for 8%.

Figure 1 shows the causes of death according to follow-up time. Valve-related deaths and deaths due to congestive heart failure and other cardiac causes remained essentially constant over time. Of 29 patients who died at age <50 years, 6 (21%) died of valve-related causes and 9 (31%) of congestive heart failure. Congestive heart failure was the main cause of death in patients with aortic regurgitation (38%), whereas in patients with aortic stenosis, this was the cause in less than half (14%).

In patients with aortic regurgitation who had preoperative congestive heart failure or severe left ventricular dysfunction, death was due to congestive heart failure in 44% and 63%, respectively.

The overall cumulative 5-, 10-, 15- and 20-year survival rate was estimated to be 83%, 67%, 55% and 36%, respectively. For patients <70 years old undergoing isolated aortic valve replacement, the cumulative 5-, 10- and 15-year survival rate was 87%, 75% and 61%, respectively; after combined valve replacement and coronary artery bypass grafting, the 5- and 10-year survival rate was 83% and 49%, respectively. For patients ≥70 years old undergoing isolated valve replacement, the cumulative 5- and 10-year survival rate was 76% and 41%, respectively. After combined valve replacement and coronary artery bypass grafting, the 5-year survival rate was 55%.

A first analysis of the association between potential risk factors for late mortality, stratified according to the timing of operation (before and after 1977), revealed no significant differences between the two periods. Although there were substantial differences in patient characteristics between the two subgroups, the direction and magnitude of the risk factors were the same in the precardioplegic era. Therefore, only the results of the pooled analysis, combining the two subgroups, are reported here.

Multivariate analysis of long-term survival (observed mortality) showed an increased risk in elderly patients (hazard rate ratio [HRR] 2.4, 95% confidence interval [CI] 1.6 to 3.7), patients with documented myocardial infarction (HRR 1.8, 95% CI 1.1 to 3.1) or coronary artery disease (HRR 2.1, 95% CI 1.4 to 3.1) and patients with heart failure (HRR 1.7, 95% CI 1.1 to 2.5). Patients with atrial fibrillation showed the highest risk (HRR 2.6, 95% CI 1.5 to 4.4).

Expected survival and excess mortality. Expected 5-, 10- and 15-year survival rate was 89%, 80% and 72%, respectively. Figures 2 and 3 show observed and expected survival in our

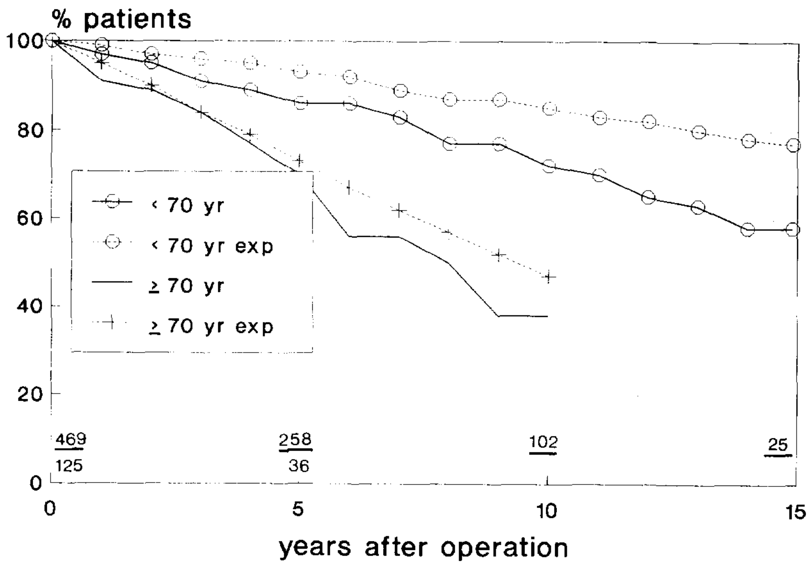

Figure 2. Survival after aortic valve replacement. Cumulative observed survival and expected (exp) survival after discharge for 594 patients according to age (<70 years old, n = 469, 5- and 10-year observed survival rates 86 ± 2% and 72 ± 3%, respectively; ≥70 years old, n = 125, 5- and 10-year observed survival rates 70 ± 5% and 39 ± 11%, respectively).

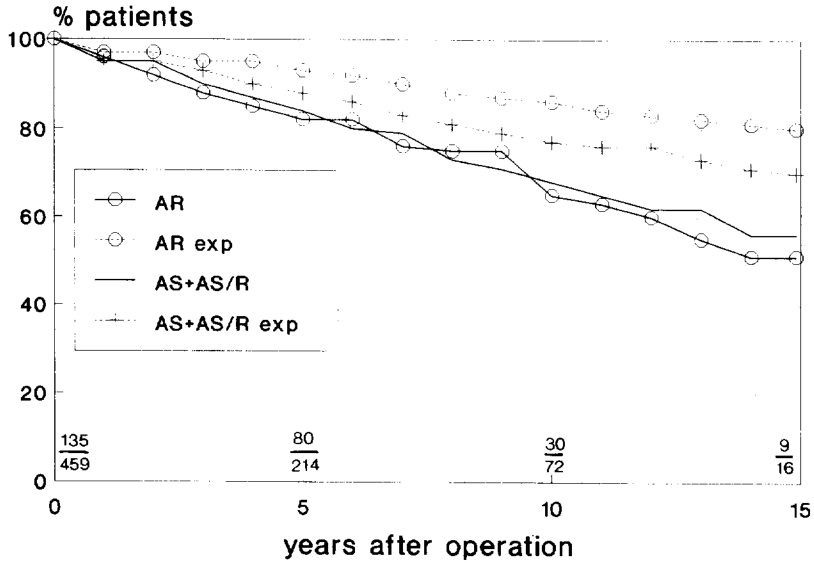

Figure 3. Survival after aortic valve replacement. Cumulative observed survival and expected (exp) survival after discharge for 594 patients according to type of valve dysfunction (isolated aortic regurgitation [AR], n = 135, 5- and 10-year observed survival rates 81 ± 3% and 65 ± 5%, respectively; aortic stenosis [AS]/mixed lesion, n = 459, 5- and 10-year observed survival rates 83 ± 2% and 68 ± 3%, respectively).

study group stratified according to age (cutoff point 70 years) (Fig. 2) and valve dysfunction (isolated aortic regurgitation vs. aortic stenosis or mixed lesion) (Fig. 3).

For excess mortality as well, no significant differences in risk factors could be found between the subgroups operated on in the early period (1966 to 1976) and the more recent period (1977 to 1986).

Multivariate analysis of excess mortality showed that patients with atrial fibrillation were at highest risk (excess mortality hazard rate ratio [EHRR] 4.3, 95% CI 1.4 to 13.2), followed by patients with aortic regurgitation (EHRR 3.8, 95% CI 1.3 to 11.2), patients with a previous myocardial infarction (EHRR 3.6, 95% CI 1.3 to 11.2) and coronary arjtery disease (EHRR 2.9, 95% CI 1 to 8.3) and patients with heart failure (EHRR 2.7, 95% CI 1.05 to 7.1).

Discussion

Timing of aortic valve replacement. Published reports (3,11–13) are inconclusive regarding optimal timing of aortic valve replacement. Management of valvular heart disease is based mainly on surgical outcome, valve-related morbidity, residual heart disease and long-term survival. The present study, based on 20 years of experience in 643 patients undergoing aortic valve replacement (combined with coronary artery bypass surgery in 129 patients), was undertaken to identify determinants of differences in long-term survival and causes of death, which may guide risk assessment of patients with aortic valve disease.

An evident and strong decrease in operative mortality after aortic valve replacement has been reported (3,11,13–17), which must be attributed to better myocardial preservation (cold cardioplegia since 1978), shorter extracorporeal circulation time and overall improved surgical technique. Our experience shows a similar strong decrease in operative mortality, although the patients operated on later were much older and more often had coronary artery disease and preoperative patient status, as reflected by an unchanged functional class. Between 1980 and 1986, operative mortality for isolated aortic valve replacement (without coronary artery bypass surgery) in patients <70 years old and without active infective endocarditis was 0.6% for isolated aortic stenosis or combined stenosis and regurgitation and 0% in isolated aortic regurgitation.

Mortality. After patients receive a prosthetic valve, new potential causes of death prevail, such as prosthetic valve dysfunction, anticoagulant-related bleeding and thromboembolism. The incidence of valve-related death is highest in the first 3 months after operation. Thereafter, it decreases to a yearly incidence of 0.7% to 1.0% and seems to be mainly linked to patient-related variables (18–21). It is often stated that in these patients, native valve disease is exchanged for prosthetic valve disease and that the operation should be postponed until (marked) symptoms appear, despite medical treatment or whether asymptomatic patients develop progressive cardiomegaly (11,12,22–24). This management strategy, which was also applied in the present study, is based on our knowledge of the natural history of aortic valve disease and on the results of studies reporting the long-term survival after aortic valve replacement.

In our series, the overall cumulative 5- and 10-year survival rate after hospital discharge after aortic valve replacement was 83% and 67%, respectively, which is in accord with the findings of others (1–3,13–15,17,24). Although an evident decrease in operative mortality is shown and prosthetic valve design improved, it is striking that the 5- and 10-year survival rate remained unchanged in our series as well as in others (25). This result is probably related to postponement of aortic valve replacement until life expectancy with native aortic valve disease is lower than that after operation and is based on studies that consider only observed long-term survival.

Survival studies after aortic valve replacement often describe an elderly patient population with an extended observation period. This dynamic study population is then, in nearly all survival studies, compared with a static reference group (matched for age, gender and calendar time) drawn from the general population at the time of valve replacement, which tends to increase the estimate of background mortality. This overestimation of background mortality partly obscures the excess mortality that is disease related. To overcome this bias, we applied rate adjustment to the calculation of background mortality.

Analysis of excess mortality. To our knowledge, this is the first study to report a multivariate analysis of excess mortality after valve replacement. This multivariate analysis of excess mortality demonstrated that older age (≥70 years), which is a risk factor for observed mortality, is not a determinant of excess mortality. Background mortality becomes increasingly important in patients ≥70 years old. Five risk factors for excess mortality were identified: myocardial infarction, coronary artery disease, atrial fibrillation, congestive heart failure and aortic regurgitation. Aortic regurgitation, which is not a risk factor for observed mortality (in many young patients) is a strong risk factor for excess mortality (fourfold increase). This finding was obscured in the traditional analysis of observed long-term survival. Noteworthy is that early experience (1966 to 1976), the precardioplegic era, is not a risk factor for excess mortality. Although many improvements in anesthetic and surgical techniques have decreased operative mortality, survivors operated on in the early period are not at increased risk for late death compared with those operated on in the current period.

Valve-related death is not the main cause of death in patient groups with at least one risk factor. Moreover, we used the guidelines of the Society of Thoracic Surgery to define valve-related mortality, which probably results in an overestimation (22%) when all fatal strokes (7%) and all sudden and unexplained deaths (7%) are included. However, the incidence of fatal strokes also strongly increases in elderly patients without valvular heart disease (26). Furthermore, not all of the sudden and unexplained deaths (7%) may have been valve related. In a study (27) on the incidence of complications in patients with Bjork-Shiley valves with a very high necropsy rate (77%), it was found that of all sudden and unexplained deaths only 18% were due to valve-related complications.

During long-term follow-up, congestive heart failure was a major cause of death (21%), irrespective of the time that had elapsed since aortic valve replacement. Subgroup analysis revealed that patients with aortic regurgitation had the highest mortality rate owing to congestive heart failure (38%); this figure was even higher in patients with preoperative congestive heart failure (44%) or severe impaired left ventricular function (63%).

Limitations of the study. Expected survival curves and excess mortality based on mortality data derived from the general population must be interpreted cautiously. Patient groups are not random samples from the general population that differ only by disease entity under study. Mortality is determined by many factors, few of which are taken into account when matching for demographic variables and other important indexes of survival, such as race or socioeconomic class, which are rarely available. In particular, patients selected for cardiac surgery tend not to have serious comorbidity, which could be reflected in the mortality pattern. Differences in the distribution of such variables can bias any comparison.

Conclusions. In our opinion, management of valvular heart disease should be guided primarily by an analysis of excess mortality rather than observed mortality and causes of late mortality. In the present cohort, older age itself was not a risk factor for excess mortality. We believe that elderly patients should not be denied aortic valve replacement on the basis of age alone. Although aortic regurgitation was not a risk factor for observed mortality, it was a strong risk factor for excess mortality. In these patients, congestive heart failure was the principal cause of death, especially when congestive heart failure or severe impaired left ventricular function was present preoperatively. The present evidence may warrant earlier operation in patients with aortic regurgitation, before advanced left ventricular dysfunction and possible irreversible injury occur.

References

1. Abdelnoor M, Nitter Hauge S, Trettli S. Relative survival of patients after heart valve replacement. Eur Heart J 1990;11:23–8.
2. Lindblom D, Lindblom U, Qvist J, Lundstrom H. Long-term relative survival rates after heart valve replacement. J Am Coll Cardiol 1990;15:566–73.
3. Lund O. Preoperative risk evaluation and stratification of long-term survival after valve replacement for aortic stenosis. Circulation 1990;82:124–39.
4. Verheul HA, Dekker E, Bossuyt P, Moulijn AC, Dunning AJ. Background mortality in clinical survival studies. Lancet 1993;341:872–5.
5. von Reyn CF, Ley BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. Ann Intern Med 1981;94:505–18.
6. Edmunds LH, Clark RE, Cohn LH, Miller G, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 1988;46:257–9.
7. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
8. Hakulinen T. Abeywickrama KH. A computer program package for relative survival analysis. Comput Methods Programs Biomed 1985;19:197–207.
9. Dixon WJ. Brown MB, Engelman L. Jennrich RI. BMDP statistical software manual to accompany the 1990 release software manual, vol 2. Berkeley (CA): University of California Press, 1990:775.
10. Aitkin M, Anderson D, Francis B, Hinde J. Statistical modelling in GLIM. Oxford Statistical Science Series 4. Oxford (UK): Oxford University Press, 1990.
11. Turina J, Hess O, Sepulci F, Krayenbuehl HP. Spontaneous course of aortic valve disease. Eur Heart J 1987;8:471–83.
12. Nishimura RA, McGoon DC, Schaff HV, Giuliani ER. Chronic aortic regurgitation: indications for operation—1988. Mayo Clin Proc 1988;63: 270–80.
13. Pilegaard HK, Lund O, Nielsen TT, Knudsen MA, Magnussen K. Early and late prognosis after valve replacement in aortic regurgitation: preoperative risk stratification and reasons for a more aggressive surgical approach. Thorac Cardiovasc Surg 1989;37:231–7.
14. Czer LSC, Gray RJ, Stewart ME, De Robertis M, Chaux A, Matloff JM. Reduction in sudden late death by concomitant revascularization with aortic valve replacement. J Thorac Cardiovasc Surg 1988;95:390–401.
15. Lytle BW, Cosgrove DM, Taylor PC, et al. Primary isolated aortic valve replacement. Early and late results. J Thorac Cardiovasc Surg 1989;97:675–94.
16. Bergus BO, Feng WC, Bert AA, Singh AK. Aortic valve replacement (AVR): influence of age on postoperative morbidity and mortality. Eur J Cardiothorac Surg 1992;6:118–21.

17. Magovern JA, Pennock JL, Campbell DB, et al. Aortic valve replacement and combined aortic valve replacement and coronary artery bypass grafting: predicting high risk groups. J Am Coll Cardiol 1987;10:38–43.
18. Blackstone EH, Kirklin JW. Death and other time related events after valve replacement. Circulation 1985;72:753–67.
19. Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart valve replacement with a mechanical valve or bioprosthesis. N Engl J Med 1993;328:1289–96.
20. Mitchell RS, Miller DC, Stinson EB, et al. Significant patient-related determinants of prosthetic valve performance. J Thorac Cardiovasc Surg 1986;91:807–17.
21. Rahimtoola SH. Lessons learned about the determinants of the results of valve surgery. Circulation 1988;78:1503–7 (Erratum, Circulation 1989;79: 732).
22. Brandenburg RO. Cardiology: Fundamentals and Practice. Chicago: Year Book, 1987:1284, 1302.
23. Braunwald E. Heart Disease: A Textbook of Cardiovascular Disease. Philadelphia: WB Saunders, 1992:1042, 1052.
24. Louagie Y, Brohet C, Robert A, et al. Factors influencing postoperative survival in aortic regurgitation. J Thorac Cardiovasc Surg 1984;88:225–33.
25. Lund O, Vaeth M. Prediction of late results following valve replacement in aortic valve stenosis. Seventeen years of follow-up examined with the Cox regression analysis. Thorac Cardiovasc Surg 1987;35:295–303.
26. Cerebral Embolism Task Force. Cardiogenic brain embolism. Arch Neurol 1986;43:71–84.
27. Lindblom D, Bjork VO, Semb BKH. Mechanical failure of the Bjork Shiley valve: incidence, clinical presentation and management. J Thorac Cardiovasc Surg 1986;92:894–907.