Long-Term Survival of Dialysis Patients in the United States With Prosthetic Heart Valves

Should ACC/AHA Practice Guidelines on Valve Selection Be Modified?

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**Background**—Minimal data exist on the long-term survival of dialysis patients after cardiac valve surgery. Current practice guidelines of the American College of Cardiology/American Heart Association Task Force on the management of patients with valvular heart disease prescribe the use of bioprosthetic (tissue) valves in hemodialysis patients.

**Methods and Results**—Dialysis patients hospitalized for heart valve replacement surgery from 1978 to 1998 were retrospectively identified from the US Renal Data System database. Long-term survival was estimated by the life-table method. The impact of demographic differences and comorbidity on outcome were examined in a Cox proportional hazards model. The in-hospital mortality of 5858 dialysis patients undergoing valve surgery was 20.7%. Aortic valve replacement was performed in 3415 patients (58%), mitral valve replacement in 1848 patients (32%), and combined aortic and mitral valve replacement in 562 patients (10%). Tissue valves were used in 881 patients. There was no significant difference in survival related to type of prosthetic valve. The 2-year survival rate was 39.7 ± 3.5% with tissue valves versus 39.7 ± 1.4% for nontissue valves. Compared with nontissue prosthetic valves, the use of tissue valves was not predictive of death (RR 0.98; 95% CI 0.90 to 1.07).

**Conclusions**—There is no significant difference in survival of dialysis patients after cardiac valve replacement with tissue versus nontissue prosthetic valves. Current practice guidelines proscribing the use of bioprosthetic heart valves in hemodialysis patients should be rescinded. (Circulation. 2002;105:1336-1341.)

**Key Words:** dialysis ▪ prosthesis ▪ survival ▪ valves ▪ kidney

Cardiac disease is a major cause of death in patients with end-stage renal disease (ESRD) receiving dialysis, accounting for ≈45% of all-cause mortality. In 1996 to 1998, the estimated all-cause death rate for dialysis patients in the United States was 231 deaths/1000 patient-years at risk, with 103 deaths/1000 patient-years attributable to cardiac causes. Only 1.5 deaths/1000 patient-years were ascribed to valvular heart disease. In France, the estimated annual incidence of valvular heart disease sufficiently severe to warrant surgery was 1.5 to 1.9 cases per 1000 dialyzed patients in 1988 to 1992. Data exist on the long-term survival of dialysis patients in the United States after percutaneous and surgical coronary revascularization, but apart from small published series, comparable data are unavailable for dialysis patients undergoing valve surgery.

Current practice guidelines on the management of patients with valvular heart disease prescribe the use of bioprosthetic heart valves in patients receiving renal replacement therapy with hemodialysis. The use of bioprosthetic valves in hemodialysis patients is classified as a class III indication ("conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful and in some cases may be harmful") by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. In hemodialysis patients, valve replacement with a mechanical prosthesis is classified as a class IIa indication. This recommendation is based on a widely held opinion that the risk of bioprosthetic valve failure mandates the use of mechanical prosthetic valves in hemodialysis patients. The sixth edition of the authoritative textbook *Heart Disease* states that "the high incidence of bioprosthetic valve failure in children and adolescents and in patients on chronic hemodialysis virtually prohibits their use in these groups." Published data support the concept of accelerated bioprosthetic valve failure in children, but data supporting the latter contention in hemodialysis patients are scarce.

Concerns about rapid calcification of bioprosthetic valves in dialysis patients may have initially arisen from 2 early reports of calcification occurring in porcine valves implanted in a total of 4 dialysis patients. Two recent publications have challenged the practice of avoiding insertion of bioprosthetic valves in dialysis patients. 

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The purpose of this study was to compare the long-term survival of dialysis patients in the United States after heart valve replacement with mechanical prosthetic or bioprosthetic cardiac valves. Using the US Renal Data System (USRDS) database, we examined the outcome of 5858 chronic dialysis patients after heart valve replacement.

Methods
All data were derived from the USRDS. The accuracy of these data has been validated previously. The study was a retrospective analysis of dialysis patients hospitalized for the first heart valve replacement surgery after initiation of renal replacement therapy from January 1978 to December 1998. Patients were identified from the USRDS database of 1 100 654 patients by International Classification of Diseases code (ICD-9-CM) 35.2X for cardiac valve replacement (excluding pulmonic valve replacement [35.25, 35.26]): for aortic valve replacement (35.21, 35.22), mitral valve replacement (35.23, 35.24), and tricuspid valve replacement (35.27, 35.28). The type of prosthetic valve (ie, bioprosthetic or mechanical) was determined from ICD-9-CM codes for “tissue valves” (35.21, 35.23, 35.27) and nontissue valves (35.22, 35.24, 35.28). Concomitant coronary artery bypass surgery (CABG) was determined from ICD-9-CM code 36.1X. Eligible patients were receiving renal replacement therapy for ≥90 days and were on dialysis for ≥60 days before valve surgery. Patients were excluded for dialysis duration of <60 days before valve surgery. The subset of dialysis patients receiving only hemodialysis for renal replacement therapy was also identified. Patient demographic data included age, sex, ethnicity (Hispanic patients not identified in database), year of valve surgery, and primary renal diagnosis. The impact of comorbid conditions was examined, because dialysis patient survival is significantly affected by comorbidity. We used a previously developed comorbidity profiling methodology based on ICD-9-CM diagnosis and procedure codes in the Medicare Part A institutional inpatient claims. Co-morbid conditions were identified by ICD-9-CM codes from previous hospitalizations occurring before the valve surgery. Comorbid conditions include prior acute myocardial infarction, other atherosclerotic heart disease, congestive heart failure, other cardiac conditions (including valvular heart disease, arrhythmia, and arrhythmia requiring pacemaker), nonskin malignancies, peripheral vascular disease, cerebrovascular ischemia (cerebrovascular accident and transient ischemic attack), chronic obstructive pulmonary disease, gastrointestinal disease, gallbladder disease, and liver disease. Previous coronary revascularization (percutaneous or surgical coronary revascularization) was analyzed separately in the Cox proportional hazards model.

In-hospital mortality was determined. Survival time was calculated from time of valve surgery to censor or end point. Study end points were all-cause death and cardiac death. In the USRDS database, the primary source for information regarding cause of death is the revised Health Care Financing Administration ESRD Death Notification Form (HCFA-2746). Censoring occurred if a patient underwent renal transplantation, had no event at end of study, or was lost to follow-up.

Long-term survival was estimated by the life-table method. The log-rank test was used to compare the difference in cumulative survival in different groups. Patients who received both tissue and nontissue valves were excluded from the survival comparison of tissue versus nontissue valves. Only patients receiving aortic and/or mitral valve replacement were included in the survival analysis. A Cox proportional hazards model was used to evaluate the impact of independent predictors (demographics, comorbidity, duration of ESRD before valve surgery, concomitant CABG, and type of valve surgery by valve site and prosthesis) on patient survival. The reported probability values in the Cox model are based on the Wald test statistic. All reported probability values are 2-sided. All statistical analyses were performed under the SAS system for Windows version 8 (SAS Institute, Inc).

Results
Valve replacement surgery was identified in 5858 dialysis patients. The mean follow-up time (±SD) was 18.8±22.5 months (25th to 75th percentile range, 1.7 to 27.5 months). A total of 44 patients were lost to follow-up after valve replacement (7 in year 1, 31 in year 2, 5 in year 3, and 1 in year 6). Table 1 summarizes demographic characteristics of the patients. By sex, the group was 57% men and 43% women. The age distribution was ≤44 years, 20%; 45 to 64 years, 39%; 65 to 74 years, 29%; and ≥75 years, 12%. The group was 65% white, 31% black, 1% Native American, and 3% other races or ethnic groups. The cause of renal failure was diabetes in 19%, hypertension in 29%, and other conditions in 52%.

Most valve surgery was done within the past decade: 4449 patients (76%) in 1992 to 1998, 1276 patients (22%) in 1985 to 1991, and 133 patients (2%) in 1978 to 1984. In 33 patients, the valve replacement surgery was performed either for tricuspid valve replacement (22 patients) or for unspecified valve site (11 patients), with the remaining 5825 patients receiving aortic and/or mitral valve replacement. In an additional 33 patients, tissue and nontissue valves were used simultaneously. Aortic valve replacement was performed in 3415 patients (58%), mitral valve replacement in 1848 patients (32%), and combined aortic and mitral valve replacement in 562 patients (10%). Concomitant CABG was performed in 2024 patients (35%). Tissue valves were used in 881 patients (15%).
The in-hospital death rate for the entire cohort was 20.7%. Of the 133 patients who had surgery before 1985, there were 26 in-hospital deaths (19.5%); 337 of 1276 patients undergoing valve surgery in 1985 to 1991 died in-hospital (26.4%), and 848 of 4449 patients with valve replacement in 1992 to 1998 died in-hospital (19.1%). There were 4389 deaths (75% of patients) during the study period.

The estimated survival for all-cause death in patients receiving tissue and nontissue prosthetic valves is displayed in the Figure. For the entire cohort of 5858 patients, the estimated 1-, 2-, 3-, 5-, and 10-year all-cause survival (±SE) was 54.0±1.3%, 39.6±1.3%, 28.1±1.3%, 14.8±1.3%, and 4.4±1.1%, respectively. The estimated cardiac survival at 1, 2, 3, 5, and 10 years was 73.2±1.2%, 62.9±1.5%, 52.5±1.7%, 38.8±2.2%, and 22.5±3.4%, respectively. The estimated all-cause survival with tissue prosthetic valves at 1, 2, 3, 5, and 10 years was 54.7±3.4%, 39.7±3.5%, 27.2±3.5%, 13.8±3.4%, and 5.4±3.1%, respectively. The estimated all-cause survival with nontissue valves at 1, 2, 3, 5, and 10 years was 54.0±1.4%, 39.7±1.4%, 28.2±1.4%, 14.9±1.3%, and 4.3±1.1%, respectively. As shown in the Figure, the survival curves are nearly identical for patients receiving tissue and nontissue prosthetic valves. There was no significant difference in all-cause or cardiac survival (not shown) between these 2 groups.

The effects of independent predictors of all-cause and cardiac death were examined in the Cox proportional hazards model. Table 2 summarizes independent predictors of all-cause death. The most powerful predictors of death were older age (≥75 years, RR [relative risk] 1.72; 95% CI 1.52 to 1.95), diabetic ESRD (RR 1.40; 95% CI 1.29 to 1.52), liver disease (RR 1.26; 95% CI 1.09 to 1.46), and double valve replacement (RR 1.36; 95% CI 1.22 to 1.51). Patients undergoing surgery in 1992 to 1998 had a 20% decreased death risk in the Cox model compared with 1978 to 1984 (RR 0.80; 95% CI 0.66 to 0.98). Sex and race were not predictive of all-cause death. Patients receiving concomitant CABG had an 8% increased death risk, which was of borderline statistical significance (RR 1.08; 95% CI 1.00 to 1.16). Single mitral valve replacement had a 23% increased death risk versus aortic valve replacement (RR 1.23; 95% CI 1.15 to 1.32). Compared with nontissue prosthetic valves, the use of tissue valves was not predictive of death (RR 0.98; 95% CI 0.90 to 1.07).

Table 3 summarizes independent predictors of cardiac death. Older age, diabetic ESRD, and double valve replacement were the most powerful predictors of cardiac death. Concomitant CABG was associated with a 13% increased risk of cardiac death (RR 1.13; 95% CI 1.02 to 1.25). Single mitral valve replacement had a 19% increased cardiac death risk compared with aortic valve surgery (RR 1.19; 95% CI 1.08 to 1.31). Compared with nontissue prosthetic valves, the use of tissue valves was not predictive of cardiac death (RR 1.00; 95% CI 0.89 to 1.13).

In the subset of dialysis patients receiving hemodialysis, there was no difference in survival related to the use of tissue versus nontissue prosthetic valves. Nontissue prosthetic valves were used in 3870 hemodialysis patients, and 675 patients received tissue valves. The estimated 2-year survival rate with nontissue prosthetic valves was 41.8±1.7% versus 42.0±4.0% with tissue valves. The risk of all-cause death was not different for tissue valves versus nontissue prosthetic valves in hemodialysis patients (RR 1.00; 95% CI 0.90 to 1.10).

Discussion

Previous studies on prosthetic cardiac valve replacement in dialysis patients have generally reported on small, retrospective series. In a 30-year literature overview, Horst et al summarized the perioperative mortality of patients with ESRD undergoing cardiac surgery, and there was a total of only 230 patients undergoing valve replacement. In this retrospective analysis, the perioperative mortality was 19.3% for isolated cardiac valve procedures in 192 patients and 39.5% for combined CABG and valve replacement in 38 patients. With the inclusion of recent publications by Lucke et al, Baglin et al, Frenken and Krian, Ura et al, and Kaplon et al, an additional 146 dialysis patients have...
been reported in published series on the outcome of cardiac valve replacement. The present study using the USRDS database details the long-term survival of >5800 patients and provides a point of national reference for survival outcome of dialysis patients after cardiac valve replacement.

There are several notable findings in our study. Chronic dialysis patients have poor long-term survival after cardiac valve replacement. We found a 19% in-hospital mortality for 4449 patients undergoing surgery in 1992 to 1998. The estimated survival was only ∼40% at 2 years. This
contrasts with the 12.5% in-hospital mortality and ∼57% 2-year survival with nondiabetes patients undergoing CABG (without other concomitant procedures) in the United States.² Our findings on outcome after valve replacement mirror those reported in small series. Baglin et al² reported a 30-day survival of 74% and a 2-year survival of 54% in 61 dialysis patients undergoing valve surgery (of whom 60 had valve replacement) in France. In a series of 19 patients described by Lucke et al,⁶ the 30-day mortality was 16%, and the estimated survival was 60±12% at 1 year and 42±14% at 5 years. Horst et al⁴ reported perioperative mortality in 7 of 32 dialysis patients (22%) undergoing valve replacement at the University of Cologne in Germany.

In the present study, we found no difference in the survival of dialysis patients in the United States receiving cardiac valve replacement with tissue compared with nontissue prosthetic valves. This finding is buttressed by the results of 2 small published series. Kaplon et al⁵ analyzed the Cleveland Clinic experience in 42 dialysis patients with cardiac valve replacement. The estimated 3-year survival for the 25 patients receiving bioprostheses was 36% (95% CI 16% to 56%) and for 17 patients with mechanical valves, it was 50% (95% CI 25% to 75%). The 5-year survival was 27% (95% CI 5% to 49%) for patients with bioprosthesis valves and 33% (95% CI 2% to 65%) with mechanical valves. Although the small sample size (and attendant large 95% CIs) makes the interpretation of survival data in the study by Kaplon et al problematic, their study is noteworthy because it is the only clinical series that even attempted to compare the long-term survival of dialysis patients receiving bioprothetic and mechanical heart valves. Importantly, Kaplon et al found no convincing evidence for accelerated calcification as a major cause of bioprosthetic valve failure and resultant adverse morbidity and mortality. Five patients underwent reoperation. The indications were prosthetic valve endocarditis in 1 patient with a mechanical prosthesis and in 3 patients with bioprostheses, but only 1 patient with a bioprosthesis underwent repeat surgery (10 months after surgery) for calcific degeneration. In the series by Lucke et al,⁹ 9 patients received bioprosthetic valves and 10 patients mechanical valves. No reoperations were performed for prosthetic valve dysfunction or endocarditis. One aortic bioprosthetic valve failed at 13 years after implantation. Despite the small sample size, Lucke et al reported statistically significant reductions in both cerebrovascular accident and hemorrhagic complications in patients receiving bioprosthetic valves. In the study by Kaplon et al,⁵ however, there was no significant difference in morbidity between the 2 groups.

There are several limitations to our study. The USRDS database provides few clinical data. Important prognostic factors such as left ventricular function and functional class are not identified in the database. The present study provides little insight into the actual cause of the adverse survival of dialysis patients after valve replacement. The ascertainment of the type of valve replacement is based on claims data in this study. Although published data exist on the accuracy of claims information compared with clinical data in patients with ischemic heart disease,²³ we are unaware of any specific studies on the validation of claims data accuracy in patients receiving cardiac valve replacement. Our survival analysis is based on a retrospective study design, and it is possible that selection bias for a particular choice of valve may have occurred.

We conclude that dialysis patients suffer poor long-term survival after cardiac valve replacement, but this outcome is not related to the type of prosthetic valve selected. Until new data (preferably generated in a prospective, randomized clinical trial) become available, we find no compelling reason for the designation of valve replacement with a bioprosthesis as a class III indication in patients on hemodialysis. We respectfully urge the American College of Cardiology/American Heart Association Task Force on Practice Guidelines pertaining to the management of patients with valvular heart disease to rescind the current prescription of bioprosthetic heart valves in hemodialysis patients.

Note Added in Proof

After the submission of this manuscript, the authors became aware of newly published data concerning operative mortality after valve replacement surgery (Edwards FH, Peterson ED, Koombs LP, et al. Prediction of operative mortality after valve replacement surgery. Am J Coll Cardiol. 2001;37:885–892). This paper offers statistical models to accurately predict operative mortality after valve replacement surgery. Included in these data are operative mortality values for dialysis patients. The reported operative mortality was 17.07% for aortic valve replacement only, 22.45% for mitral valve replacement only, 24.59% for combined CABG and aortic valve replacement, and 36.89% for combined CABG with mitral valve replacement. These data independently confirm the high operative mortality in dialysis patients reported in the present study.

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References


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