SURGERY FOR ACQUIRED HEART DISEASE

THE PREVALENCE OF INFECTIVE ENDOCARDITIS AFTER AORTIC VALVE REPLACEMENT

Replacement valve endocarditis occurred in 3.7% of 2443 patients who underwent primary or redo aortic valve replacements at The Prince Charles Hospital between December 31, 1969, and January 1, 1992, based on a cross-sectional follow-up in 1992 which was 98.8% complete. Because some patients had re-replacements during the study period, a total of 2686 operations were considered for analysis. A variety of replacement devices were used, including 571 allografts (21%), 1152 xenografts (43%), and 880 mechanical valves (36%). Insertion of an allograft valve resulted in a constant risk of endocarditis which, by multivariable hazard function analysis, negated the effect of any early-phase risk factors ($p < 0.0001$). With other replacement devices, the risk of infection peaked early after operation (9 weeks) and then gave way to a constant risk. Compared with the risk associated with allograft valves, constant risk was higher when the replacement device was a Carpentier-Edwards xenograft ($n = 1021, p = 0.02$) and lower when a St. Jude Medical mechanical valve was used ($n = 505, p = 0.05$). In nonallograft recipients, the presence of active preoperative endocarditis ($p < 0.0001$) or a concomitant synthetic aortic root replacement ($p = 0.0006$) increased the magnitude of the early peaking risk. Regardless of replacement device, constant risk was increased in patients with renal dysfunction ($p = 0.01$), in younger patients ($p < 0.0001$), and in those with active or healed preoperative endocarditis ($p = 0.04$). When preoperative endocarditis was caused by *Staphylococcus aureus*, risk was higher than when it was caused by other organisms ($p = 0.04$). A culture-positive postoperative wound infection was associated with increased risk of replacement valve infection ($p < 0.001$) and when it occurred, the same organism was usually responsible (86%). Identification of patients at increased risk for replacement valve infection may lead to reduced morbidity through strategies such as selective use of replacement devices and antimicrobial prophylaxis. (J THORAC CARDIOVASC SURG 1995;110:1708-24)

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Infective endocarditis is a serious and frequently fatal condition, particularly when it occurs on a valve replacement device.¹ In patients with active

endocarditis, the risk of recurrent infection may be lower when an allograft replacement valve is used.^{1,2} However, in patients undergoing aortic valve replacement (AVR) for any reason, usually for reasons other than endocarditis, the prevalence of postoperative endocarditis and the impact of replacement with various modern devices has not been

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fully characterized. Therefore a study to determine the prevalence of replacement endocarditis and its risk factors was undertaken in a series of patients undergoing AVR for any reason, in which a variety of replacement devices were used.

Patients and methods

Study group. A total of 2443 patients had an isolated AVR at The Prince Charles Hospital (TPCH) from January 1, 1970, to January 1, 1992. Among these 2443 patients, 89 had their first AVR and 2 patients had their first two AVRs either before 1970 or at another institution. Among the 2443, 290 (11.9%) had a second AVR at TPCH during this period, 43 (1.8%) had a third, and 1 had a fourth, leading to a total of 2686 operations. Patients with previous mitral or tricuspid valve operations were not included.

A concomitant procedure not involving valve replacement, most frequently coronary bypass grafting, was performed in 856 (32%) of the operations (Appendix Table 1). The average patient age at first TPCH operation was 56 years (± 15 years, standard deviation), and 74% of patients were male. In 243 (9.0%) of the operations the patient had previous (preoperative) endocarditis and the organisms involved are outlined in Appendix Table 2; in 92 (38% of 243) of these cases active endocarditis was an indication for operation. Additional patient characteristics are outlined in Appendix Table 3.

Operative technique. The usual methods of cardiopulmonary bypass were used for the operations. From 1967 to 1978, myocardial protection was provided by continuous coronary perfusion, and from 1978 to 1992, by cold crystalloid cardioplegia supplemented with topical cooling.

A variety of replacement devices were used (Appendix Table 4), but biologic valves predominated (xenografts in 43% of the operations, allografts in 21%), and some patients early in the experience received what would now be regarded as obsolete valves (fascia lata valves or Braunwald-Cutter prostheses, Cutter Biological, Berkeley, Calif.). Mechanical and xenograft valves were inserted with an interrupted suture technique. Allograft valves were inserted by a variety of methods,³ including the subcoronary technique, the cylindrical technique, and as an aortic root replacement. Valve selection was at the discretion of the surgeon, but an allograft aortic valve was more likely to have been inserted in the latter part of the experience. Abscess cavities were not specifically closed unless closure was necessary for anchoring of valve prostheses.

Routine postoperative antimicrobial therapy consisted of intravenous antibiotics for the first 2 days, then oral antibiotics for an additional 2 or 3 days. The antibiotics used were ampicillin/cloxacillin from January 1970 through December 1979, ampicillin/flucloxacillin from January 1980 through August 1982, and cephalothin (intravenously)/cephalothin (orally) from September 1982 through January 1992.

Definitions

Preoperative endocarditis. Patients were considered to have had preoperative endocarditis if morphologic, histo-

logic, or bacteriologic evidence of aortic valve infection was present at the time of their valve replacement. Such patients were subdivided into two groups. Patients with positive cultures of operative specimens or positive blood cultures in the immediate preoperative period were considered to have *active* preoperative endocarditis. Patients lacking positive cultures, but with morphologic evidence of previous disease, were considered to have *remote* endocarditis, and an attempt was made to identify from the medical record the previous episode of endocarditis and the identity of the causative organism(s).

Replacement valve endocarditis. Replacement valve endocarditis was defined as infection occurring on the AVR device. Replacement valve infection was considered to be present (1) if typical clinical symptoms of endocarditis developed, including fever, splenomegaly, peripheral skin or mucocutaneous lesions, or a regurgitant murmur, along with positive blood cultures with no obvious extracardiac source of infection, (2) if blood cultures were positive for infection with consistent findings at reoperation or autopsy, or (3) if organisms were cultured from the removed prosthetic valve at the time of reoperation.⁴

Two patients who had active native valve infection at the time of AVR continued to show clinical signs of valve infection in the early postoperative period, leading to an early diagnosis of replacement valve endocarditis. In these cases, the event *endocarditis* was considered to have occurred on the date of the first positive blood culture in the postoperative period.

Data collection and follow-up. Information was obtained from hospital and outpatient medical records and by direct contact with the patients' families, local physicians, and cardiologists. Information was collected from January 15, 1992, through November 9, 1992.

Of the 2443 patients, 2413 (98.8%) were either known to be dead or were contacted during the follow-up interval. The remaining 30 patients were lost to follow-up at some time in their postoperative period, but only three were not contacted after hospital dismissal. The mean period from operation to most recent follow-up was 6.9 years (83 months; standard deviation ± 5 years). Seventy-five percent of patients were followed up for more than 15 months, 50% for more than 5.7 years (68 months), and 25% for more than 14 years (172 months).

Data analysis. Simple contingency tables and comparisons of means were made for all variables. Actuarial analyses were performed by the Kaplan-Meier method.⁵ The overall hazard function (instantaneous risk of endocarditis) was estimated by a generic three-phase model,⁶ facilitating multivariable, parametric analysis of risk factors within individual phases of risk.⁷ A *p* value of 0.1 was used as the criterion for retaining a variable in the model (this level was chosen because, despite the large number of operations, there were relatively few events), but for each identified risk factor the *p* value is provided, allowing for independent assessment as to its believability.

For the Kaplan-Meier estimates and for the multivariable analysis, patients were censored at the time of their death or at the time of a heart transplant (one patient). Because of the prevalence of more than one AVR, two

techniques were used for patients in the study group who had multiple AVRs. In one, each patient was entered into the data set once, at the time of the initial AVR procedure at TPCB. The patient was then followed up in the usual way (intention-to-treat analysis). In other words, crossovers were simply accepted. This method had the number of patients as the N . The second method took account of the time-varying covariate of repeated AVRs by using the modulated renewal process.⁸ In this process patients who underwent a second AVR were removed from the study group (censored) at the time of the second replacement and were entered into a second study group in which time zero was the time of the second replacement. Those with a third AVR were censored and entered into a third study group, and so forth. This resulted in a complete depiction of the 2686 operations among the 2443 patients. The multivariable analysis was made of the composite group of 2686 operations by a modulated renewal process, which properly evaluated the possibility that the time-varying covariate "AVR number" 2 or 3 (or more) was itself an incremental risk factor (explanatory variable). In this, patients with an initial AVR elsewhere or before this study received a value of "2" for "number of previous AVRs" in their first entry in the study.

Patients who received allograft valves were found to have only a single constant phase of hazard (lacking the early phase present in patients who received other valves). In previous studies, discrepancies of this type precluded the inclusion of all operations in a single multivariable analysis, in part because of computational intractabilities introduced by the complete absence of a hazard phase.² In this study, estimates when the allograft and nonallograft recipients were combined were not found to be intractable, and the absence of an early phase in the former group was represented by a large negative coefficient. The assumption was that a previously undetectable early phase of hazard was present in the allograft group. The analyses were repeated with the allograft group evaluated independently and the results were found to be similar. In this manuscript results from the combined analyses are presented.

As a means of internal validation of the multivariable model, Kaplan-Meier estimates were made of several subgroups, and solutions for the same groups of patients were computed by averaging the individual patient-specific predictions from the multivariable equation. The comparison was made in the time-related domain and also by comparing the total number of events (Appendix Table 5).

Results

Overall prevalence. The non-risk-adjusted actuarial freedom (Fig. 1, *A*) from endocarditis among the 2443 patients followed up after their first AVR at TPCB was 94.6% at 10 years and 89.8% at 20 years. The parametric estimate was similar, and its corresponding hazard function had two phases (Fig. 1, *B*), with an early peak at 9 weeks that gave way to a constant risk by about 6 months after operation.

Factors affecting the prevalence of replacement valve endocarditis. Patient and operative characteristics associated with an increased prevalence of replacement valve infection were identified by non-risk-adjusted (Appendix Tables 1, 3, and 4) and risk-adjusted (multivariable) analysis (Table I).

Prereplacement endocarditis. The prevalence of replacement valve endocarditis was higher by non-risk-adjusted analysis in those with preoperative endocarditis than in those without it (Fig. 2). In risk-adjusted analyses, preoperative endocarditis was associated with increased constant-phase hazard, but early-phase risk was increased only when there was active endocarditis at the time of AVR. The constant-phase risk was not equal for all patients with preoperative endocarditis; risk was higher in patients with *Staphylococcus aureus* endocarditis than in those with preoperative endocarditis caused by other organisms ($p = 0.05$) (Fig. 3).

Replacement with an allograft valve. Regardless of the presence of early-phase risk factors, patients who received an allograft replacement device did not demonstrate an increased early risk of replacement valve endocarditis, having only a single (constant) risk. This negation of increased early risk is represented in the multivariable equation (see Table I) as a large negative coefficient in the early phase.

Replacement with other devices. In non-risk-adjusted and risk-adjusted analyses, patients who received the now obsolete fascia lata valve had a higher prevalence of postoperative endocarditis at any time after operation. Late postoperative endocarditis was less prevalent ($p = 0.05$) after AVR with a St. Jude Medical mechanical valve (St. Jude Medical, Inc., St. Paul, Minn.). In risk-adjusted analysis only, other valve-specific differences in risk were identified, including an increased constant-phase risk for endocarditis in patients receiving the Carpentier-Edwards xenograft valve (Baxter Healthcare Corp., Edwards Division, Santa Ana, Calif.) (see Table I).

Figs. 4A, 4B, and 4C depict the estimated freedom from replacement valve endocarditis after replacement with the three most commonly used devices in patients with differing preoperative endocarditis histories.

Concomitant procedures. In risk-adjusted analysis, concomitant replacement of the aortic root with a synthetic graft (but not root replacement with tissue) was associated with a higher early risk of replacement valve endocarditis. Although the prevalence of postoperative endocarditis after concomi-

Fig. 1. A, Time-related prevalence of freedom from endocarditis after first AVR at TPCH ($n = 2443$). Note that the vertical axis representing freedom from endocarditis (the complement of prevalence of endocarditis) is expanded. Circles represent the occurrence of endocarditis in an individual, positioned along the horizontal axis at the interval between operation and the time of occurrence and actuarially (Kaplan-Meier method) along the vertical axis. The vertical bars represent 70% confidence limits (± 1 standard deviation). Numbers in parentheses represent the number of patients continuing to be followed up after that time. The solid line represents the parametrically estimated freedom from endocarditis, and the dashed line encloses the 70% confidence limits of that estimate. The table represents the parametric estimates at specified intervals. **B,** Hazard function for the rate of endocarditis (events/month) after the first AVR at TPCH. The horizontal axis is expanded for better visualization of the early risk. The hazard function has two phases, an early peaking phase that gives way to the constant phase of hazard at about 5.5 months. The depiction is similar to that in A.

Fig. 2. Time-related prevalence of freedom from replacement valve endocarditis stratified by presence of previous (preoperative) endocarditis. Symbols represent the occurrence of replacement valve endocarditis in an individual: circles for patients without preoperative endocarditis, squares for patients with remote preoperative endocarditis, and triangles for patients with active preoperative endocarditis. Symbols are positioned along the horizontal axis at the interval between operation and the time of occurrence and actuarially along the vertical axis. Vertical bars represent 70% confidence limits.

Table I. Incremental risk factors for endocarditis after AVR (N = 2686; 95 events)

Risk factor	Hazard phase			
	Early		Constant	
	Coefficient	P	Coefficient	P
Demographic				
Age (younger)*			-0.9272	<0.0001
Clinical history				
Renal dysfunction			1.005	0.01
Preoperative endocarditis			0.6686	0.04
If <i>Staph. aureus</i> was the causative organism			0.9026	0.05
If active endocarditis at operation	3.526	<0.0001		
Replacement device				
Allograft	-13.17	<0.0001		
Medtronic Intact	2.612	0.002		
Fascia lata	2.081	0.01	1.484	0.0001
Carpentier-Edwards			0.6154	0.02
St. Jude Medical			-2.062	0.05
Concomitant procedures				
Aortic root replacement with synthetic graft	3.084	0.0006		
Support technique				
Bypass time (longer)			0.1898	0.01
Intercept	-6.207	<0.0001	-7.727	<0.0001

Note: Age, in years, was transformed as: age' = (age/50)². Bypass time, in minutes, was transformed as: bypass time' = exp (bypass time/120).

*Younger patients are at increased risk.

Fig. 3. Nomograms (specific solutions from the multivariable equation) depicting risk-adjusted freedom from replacement valve endocarditis. *Lines* shown are specific solutions to the multivariable equation for a 50-year-old patient, without renal dysfunction, and with the preoperative history indicated. The *lines* represent the overall response for all replacement valve types. The confidence intervals are not shown to improve clarity, but those for “no preoperative endocarditis” overlapped no others.

tant mitral valve repair and concomitant false aneurysm closure was increased by non-risk-adjusted analysis (Appendix Table 1), during subsequent risk-adjusted analysis these differences were found to be explained by the prevalence of other patient-specific risk factors.

Primary versus redo AVR. When examined in a non-risk-adjusted manner, primary AVR was followed by a lower prevalence of replacement valve endocarditis than was redo AVR (Wilcoxon $p = 0.03$). The small group ($n = 43$) of patients having a second redo operation (the third AVR operation) did not have a believably higher non-risk-adjusted prevalence of postoperative endocarditis than those having their first redo operation (Wilcoxon $p = 0.76$). However, redo AVR was not found to be a risk factor for replacement valve endocarditis in risk-adjusted analyses. This is likely a result of the differences in risk factors (explanatory variables) among those having primary and redo operations (Appendix Table 6).

Age. Younger age at operation increased constant-phase risk ($p < 0.0001$). By correlation analysis, younger patients were more likely to be male ($p = 0.0001$) and were more likely to have had preoperative endocarditis ($p = 0.0001$). When

younger patients had preoperative endocarditis, the organism was more likely to be *Coxiella burnetii* (Q fever) than when older patients had preoperative endocarditis ($p = 0.002$).

The association of postoperative complications to replacement valve endocarditis. The presence of a postoperative wound infection or postoperative cardiac dysfunction was associated with an increased prevalence of postoperative endocarditis (Appendix Table 7), even when adjustments were made for identified risk factors (Table II). Among the seven patients who had wound infections and later had endocarditis, the mean period from wound infection to diagnosis of endocarditis was 6 weeks. In six of the seven patients (86%) the organism cultured from the infected wound was subsequently responsible for the valve infection, and in the remaining patient endocarditis occurred many months after operation. Patients having an early reoperation for excessive bleeding (reentry) had a higher prevalence of replacement valve endocarditis, but this finding could be due to chance alone ($p = 0.2$).

The prevalence of staphylococcal versus streptococcal replacement valve endocarditis. Staphylococcal organisms were most commonly responsible for postoperative endocarditis, followed by strepto-

Fig. 4A. Nomogram (specific solution from the multivariable equation) depicting risk-adjusted freedom from replacement valve endocarditis (risk adjusted) for a patient receiving a Carpentier-Edwards (xenograft) valve. Estimates were made for a 50-year-old patient, without renal dysfunction, who did not receive a concomitant aortic root replacement, and with the pre-replacement endocarditis history specified. *Solid lines* are parametric estimate and *dashed lines* represent 70% confidence limits.

Fig. 4B. Nomogram (specific solution from the multivariable equation) depicting risk-adjusted freedom from replacement valve endocarditis (risk adjusted) for a patient receiving an allograft valve. Estimates were made for a 50-year-old patient, without renal dysfunction, who did not receive a concomitant aortic root replacement, and with the pre-replacement endocarditis history specified. *Solid lines* are parametric estimate and *dashed lines* represent 70% confidence limits.

Fig. 4C. Nomogram (specific solution from the multivariable equation) depicting risk-adjusted freedom from replacement valve endocarditis (risk adjusted) for a patient receiving a St. Jude Medical (mechanical) valve. Estimates were made for a 50-year-old patient, without renal dysfunction, who did not receive a concomitant aortic root replacement, and with the pre-replacement endocarditis history specified. *Solid lines* are parametric estimate and *dashed lines* represent 70% confidence limits.

Table II. Correlates of endocarditis after AVR considering postoperative variables (N = 2686; 95 events)

Risk factor	Hazard phase			
	Early		Constant	
	Coefficient	P	Coefficient	P
Demographic				
Age (younger)			-0.9300	<0.0001
Clinical history				
Renal dysfunction			0.9682	0.02
Preoperative endocarditis			0.6469	0.05
If <i>Staph. aureus</i> was the causative organism			0.8632	0.07
If active endocarditis at operation	3.045	<0.0001		
Replacement device				
Allograft	-12.92	<0.0001		
Fascia lata	2.731	0.005	1.465	0.0001
Carpentier-Edwards			0.5805	0.02
St. Jude Medical			-2.3188	0.08
Support technique				
Bypass time (longer)			0.1929	0.01
Postoperative course				
Wound infection	3.975	<0.0001		
Cardiac dysfunction	3.052	<0.0001		
Intercept	-7.244	<0.0001	-7.703	<0.0001

Note: Age, in years, was transformed as: age' = (age/50)². Bypass time, in minutes, was transformed as: bypass time' = exp (bypass time/120).

Table III. Causative organisms in postoperative endocarditis

Organism	n	% of 95
Gram positive		
<i>Staphylococcus</i>	36	37
<i>Staph. aureus</i>	31	33
<i>Staph. epidermidis</i>	3	3.2
Unspecified	2	2.1
<i>Streptococcus</i>	28	27
<i>S. viridans</i>	6	6.3
<i>S. sanguis</i>	8	8.4
<i>S. faecalis</i>	4	4.2
<i>S. mitis</i>	3	3.1
Other <i>Streptococcus</i> *	3	3.1
Unspecified sp.	4	4.2
<i>Corynebacterium</i>	4	4.2
<i>Micrococcus</i>	1	1.1
<i>Bacillus</i> (otherwise unspecified)	1	1.1
Gram negative	15	14.7
<i>Coxiella burnetii</i>	7	7.4
<i>Eikenella corrodens</i>	2	2.1
<i>Pseudomonas</i> sp.	2	2.1
<i>Haemophilus</i> sp.	1	1.1
<i>Klebsiella pneumonia</i>	1	1.1
<i>Neisseria gonorrhea</i>	1	1.1
<i>Proteus mirabilis</i>	1	1.1
Mycotic	4	4.2
<i>Mucor</i> sp.	2	2.1
<i>Aspergillus fumigatus</i>	1	1.1
<i>Candida albicans</i>	1	1.1
Unidentified	9	8.4

Note: Although organisms were not identified in nine patients, some of the remaining 86 patients had polymicrobial infections, leading to a total of 98 identified organisms.

*Includes the following streptococcal species: *bovis* (1), *pneumoniae* (1), and *salivarius* (1).

coccal organisms (Table III). Staphylococcal endocarditis tended to occur early after operation, whereas the risk of streptococcal infection was constant across time (Fig. 5). The risk of endocarditis caused by other organisms was similar to that for staphylococcal organisms. In a separate risk-adjusted analysis of the event *replacement valve staphylococcal endocarditis*, patients with preoperative endocarditis were found to be at increased risk of staphylococcal endocarditis ($p < 0.001$) only if their preoperative infection was caused by a staphylococcal organism (Table IV).

Mortality after AVR and diagnosis of replacement valve endocarditis. Among the 2443 patients, there were 678 deaths (28%) during the follow-up period. The actuarial freedom from death after a first AVR was 93.9% at 1 year, 84.3% at 5 years, 65.7% at 10 years, and 37.6% at 20 years. Among the 93 patients in whom replacement valve endocar-

ditis developed, there were 47 deaths (50.5%). Actuarial survival after diagnosis of replacement valve endocarditis was 81.7% at 1 year, 58.2% at 5 years, and 37.1% at 10 years.

Discussion

Method. This analysis is made more specific by the use of parametric, phase-specific, multivariable methods. These techniques have been used previously for the analysis of endocarditis after AVR.^{9,10} In an attempt to increase clarity, but also for reasons of mathematical tractability, we have designated some characteristics as *negative risk factors*, instead of using positive coefficients and the absence of a characteristic. For example, we have designated *use of allograft valve* as a negative risk factor instead of *nonuse of an allograft valve* as a positive risk factor.

Patients with previous nonaortic valve operations were not included in the study group. This exclusion was an attempt to eliminate ambiguity regarding the location of postoperative endocarditis in patients with clinical evidence of valve infection. For similar reasons, we excluded those with double valve operations (concomitant non-AVRs) and censored patients at the time of any subsequent valve replacement.

This analysis does not address risk factors for mortality, reoperation, or morbidity (other than endocarditis). Admittedly, such information would be prerequisite to definitive recommendations regarding treatment strategies, such as valve selection for particular patients, because replacement valve endocarditis is a relatively uncommon cause of morbidity or mortality.

Prevalence of replacement valve endocarditis. The overall estimate of incidence of prosthetic valve endocarditis in this report is low (3.8%) and consistent with data from previous reports.¹¹⁻¹⁴ In actuarial estimates, we censored patients at the time of death, reoperation, or non-AVR. It is important to remember that the reported actuarial estimates cannot be used independently to estimate a percentage of patients in whom endocarditis will develop.¹⁵ For example, although the actuarial occurrence of endocarditis at 20 years is 9.7%, the expected number of endocarditis cases for a large group of patients followed up for 20 years would be less than 9.7%, because some patients will die and still others will have reoperations before endocarditis develops.

Recurrent endocarditis. Previous work has shown that patients with preoperative (native or

Fig. 5. Separately determined hazard functions for the non-risk-adjusted rate of staphylococcal and streptococcal endocarditis. The *horizontal axis* is expanded to allow better visualization of early phase differences. *Solid lines* represent the hazard estimates, and the corresponding *dashed lines* enclose 70% confidence limits. Note that the risk of staphylococcal endocarditis is increased early after the operation and that the constant-phase risk is similar for staphylococcal and streptococcal endocarditis.

Table IV. Risk factors for staphylococcal endocarditis after AVR (N = 2686; 36 events)

Risk factor	Hazard phase			
	Early		Constant	
	Coefficient	p	Coefficient	p
Demographic				
Age (younger)*			-0.9939	<0.007
Clinical history				
Diabetes	2.733	0.005		
Number of previous aortic valve operations	1.248	0.06		
Renal dysfunction			1.596	<0.001
Preoperative endocarditis with Staph. aureus (active or remote)			2.567	<0.0001
Intercept	-6.633	<0.0001	-8.136	<0.0001

Note: Age, in years, was transformed as: age' = (age/50)². Renal dysfunction was defined as creatine concentration greater than or equal to 0.2 mmol/L at last blood test before operation.

*Younger patients were at increased risk.

replacement) endocarditis are at increased risk for postoperative endocarditis,^{11,15} and this analysis further stratifies this risk by identifying two important characteristics of patients with preoperative endocarditis: the causative organism (*Staphylococcus aureus* or other) and the infection status at the time of valve replacement (active or remote). These characteristics lead to four possible risk categories

for those with preoperative infection: (1) active *Staphylococcus aureus* infection, (2) active infection with an organism other than *Staphylococcus aureus*, (3) remote *Staphylococcus aureus* infection, and (4) remote infection with an organism other than *Staphylococcus aureus* (see Fig. 3).

That active valve infection, but not remote, increases the early-phase risk of replacement valve

infection suggests that in some patients with active preoperative endocarditis the infection persists into the postoperative period. These findings support the concept that an allograft valve is indicated in the face of active endocarditis.²

Constant-phase risk of recurrent endocarditis was found to be increased in all patients with previous endocarditis, but the magnitude was dependent on the infecting organism. Preoperative *Staphylococcus aureus* infection increased the constant risk more than infection with other organisms. From a separate analysis of risk factors for staphylococcal endocarditis, we found that another staphylococcal infection tended to recur. This apparent predisposition to valve infection, most pronounced in those who had staphylococcal endocarditis, has been suggested previously.¹ Such a recurrence tendency might be expected in patients who are prone to recurrent bacteremias, such as persons who abuse intravenous drugs or those with chronic skin infections (e.g., carbuncles). Alternatively, this tendency to recurrence might reflect subtle difference in immunologic susceptibility,¹⁶ perhaps otherwise clinically insignificant, which predispose some patients to recurrent valve infections.

Patient-specific risk factors for replacement valve endocarditis. The identified increased risk of postoperative endocarditis in the younger valve recipient likely results from the broader environmental exposure to potential pathogens experienced by this group. In support of this hypothesis, we found a correlation between younger age and endocarditis with *Coxiella burnetii* (Q fever), an organism likely to infect workers in slaughter houses, usually young men. The association of renal dysfunction, commonly seen in patients with dysfunction of other organ systems, with increased constant-phase risk for endocarditis probably represents the reduced resistance to infection in this group of patients.

Operative risk factors for replacement valve endocarditis. Of particular interest to the surgeon is the possibility that choice of a valve replacement device can favorably modulate the effects of existing (patient-specific) risk factors. Our finding that those who received allograft valves had only a single constant-phase risk for replacement valve infection is consistent with previous reports.^{2, 11, 14} This negation of early-phase risk provides the greatest potential for benefit when early risk is expected to be the highest, as in the patient with active preoperative endocarditis or the patient who requires an aortic root replacement. However, in a patient with a

remote episode of endocarditis (elevated *constant* risk), the allograft valve is not predicted to prevent recurrent endocarditis, because its beneficial effects are confined to the early phase.

Although several previous studies of replacement valve endocarditis have grouped different valves on the basis of the predominant material in their construction (i.e., mechanical, xenograft), in our analysis this approach would have masked valve-specific differences in risk, perhaps as a result of an insufficient number of observations. Indeed, the estimated constant-phase risk for valves grouped in this manner is not believably different. However, when the risk was entered into the analysis individually, we found, in addition to differences in now "historical" mechanical valves, that those receiving the St. Jude Medical valve ($n = 505$) were at lower risk and those receiving Carpentier-Edwards xenograft valves ($n = 1021$) were at a higher constant risk. The lower constant-phase risk in the St. Jude Medical recipients was unexpected and perhaps explains why, in a previous analysis of mortality (based on many of the same patients in this study group), AVR with a St. Jude Medical valve was found to result in a lower constant-phase risk of death.¹

That aortic root replacement with a synthetic graft was associated with a greatly increased early-phase risk, but aortic root replacement with tissue (allograft aortic root replacement) was not, suggests that it is the placement of the synthetic material, not progression of the disease process alone, which predisposes patients to postoperative valve infection. With this evidence, the need to replace the aortic root would favor the use of an allograft valve with contiguous replacement of the aortic root, especially in the setting of preoperative infection.

Longer bypass time, although identified previously as a correlate for postoperative endocarditis,^{1, 11} was found in this analysis to be associated with increased *constant-phase* risk for replacement valve endocarditis, whereas the relationship of bypass time to early risk of infection, the usual experience in surgery, was weak and not believable. Longer bypass time may be a surrogate for a group of individually weak associations that indicate poor patient condition or more extensive disease, such as concomitant procedures, preoperative and postoperative organ system dysfunction, number of previous aortic valve operations, and New York Heart Association class. The increase in risk expected for patients with longer bypass time probably represents the grouped influence of several individually weak risk factors.

Association of postoperative complications to replacement valve endocarditis. Although the association of major postoperative wound infections with subsequent endocarditis was strong (large coefficient) and believable ($p < 0.0001$), it is unclear whether this represents a causal relationship. Regardless, the patient with a wound infection is at a greatly increased risk for subsequent diagnosis of prosthetic valve endocarditis, and when it occurs, the valve infection is usually caused by the same organism. These findings indicate that a patient who has a postoperative wound infection after AVR should receive aggressive antimicrobial therapy selected on the basis of positive cultures from the infected wound.

Postoperative cardiac dysfunction was also associated with replacement valve endocarditis. This finding may reflect the decreased immunologic tolerance of these patients or the increased bacteriologic challenge imposed by invasive monitoring and frequent diagnostic procedures.

Summary

Overall, the risk of replacement aortic valve endocarditis was low. When the replacement device was an allograft valve the risk was constant; with other devices there was an initial peaking risk that gave way to a constant risk by about 6 months. Compared with the risk of replacement with an allograft valve, the constant risk of endocarditis was found to be lower when a St. Jude Medical (mechanical) valve was used and higher when replacement was with a Carpentier-Edwards (xenograft) valve. Active preoperative endocarditis increased both the early and the constant risk of recurrent infection, whereas remote endocarditis increased only the constant-phase risk. When preoperative endocarditis was caused by *Staphylococcus aureus*, patients were at greater risk of recurrent infection than when the preoperative infection was caused by other organisms. Patients receiving a concomitant aortic root replacement were at increased early risk of endocarditis when a synthetic graft was used. A culture-positive postoperative wound infection was associated with an increased risk of subsequent diagnosis of endocarditis; both infections were usually caused by the same organism.

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Discussion

Dr. Robert B. Karp (Chicago, Ill.). The large number of patients in this study allows the analysis to approach the concept of "truth." The incidence of replacement valve endocarditis over a 23-year period was 3.7%, with a mean of about 7 years' follow-up. This is a laudably low figure, and as the authors point out, it should not be taken as the exact figure because of statistical methods that allow censoring and reinclusion of patients.

Some of the concepts elaborated should be reiterated. The allograft neutralized the early risk factors for replacement valve endocarditis. However, what is abundantly clear is that the patient is a risk factor, particularly the patient with acute or even remote bacterial endocarditis. Constant risks were renal dysfunction, younger age, and, as noted, healed endocarditis. Disturbingly, the use of a synthetic valve conduit was a risk factor, along with the well-known factor of *Staphylococcus aureus* native valve endocarditis.

The authors found that wound infection was associated with replacement valve endocarditis. This poses one question: What comes first—a bacteremia caused by the mediastinitis that infects the replacement device or a bacteremia from other sources that seeds both the wound and the replacement device? As noted by the authors, one third of patients having bacterial endocarditis as a risk factor for replacement device endocarditis had active bacterial endocarditis. However, importantly, the remaining two thirds had remote or inactive endocarditis. Thus this prompts a second question. What are the rules and inferences for dealing with patients with remote endocarditis as to the most effective replacement device?

Young age was a risk factor for replacement valve endocarditis. Drug abuse occurs in the younger age groups, but this was not an issue in the Brisbane experience. There was, however, an association with young age and *Coxiella burnetii* or Q fever. For the North American surgeon, who is not dealing with endemic Q fever, do the authors believe young age would remain a risk factor?

These data suggest again that young patients should receive a homograft aortic valve both for the well-known advantage of anticoagulation-free, thromboembolism-free existence, but also to negate the early risk of replacement valve endocarditis.

Finally, many surgeons are not homograft enthusiasts. Can the authors speculate on the reason for the superiority of the St. Jude Medical prosthesis over the various porcine xenografts with regard to freedom from replacement valve endocarditis?

Dr. Agnihotri. Thank you, Dr. Karp, for your questions. I will address your comments sequentially.

We did do a separate multivariable analysis in which we included some postoperative variables. Many of you may be familiar with the statistical pitfalls of including covariates that occur after time zero, which in our case was the time of AVR. When these variables are identified as risk factors, the question of causality will typically arise, as it does in the identified association of postoperative wound infection and replacement valve endocarditis. I cannot say whether the wound infection led to the valve infection or whether they were both a result of bacteremia from some third source. Nevertheless, we believe that the observation does have clinical significance. If a major wound infection develops in a valve recipient, our data do indicate an important increase in risk for a subsequent diagnosis of endocarditis, and we would take aggressive steps to prevent the appearance of valve infection.

The distinction between active and remote endocarditis as patient-specific risk factors is important. Patients with active preoperative endocarditis, defined as culture-positive valve infection at operation, were at high risk for recurrence early after operation. Patients with healed endocarditis did not have evidence of this early increase in risk. These findings, in addition to the valve-specific difference in risk, lead us to the inference that patients with active preoperative endocarditis should receive an allograft replacement device. In the patient with remote infection, early risk is not increased, and I think that factors other than risk of recurrent infection determine appropriate valve selection.

As Dr. Karp points out, one of the interesting aspects of this data set, which originated in Australia, was that there was a higher prevalence of *Coxiella* than one would have found in a similar American data set. *Coxiella* is the organism responsible for Q fever, a public health problem in Australia that is primarily seen in young men, typically workers in slaughter houses. The number of patients in our study group with preoperative *Coxiella* endocarditis was 21, or roughly 8% of the total group of preoperative valve infections. Among these 21 patients there were only three recurrences. These numbers are sufficiently low that I do not believe they influenced our results or conclusions.

The last question regarding why we found modern mechanical valves to have a lower long-term resistance to infection in some patients than did the allograft valve is a fascinating one. We have discussed this issue among ourselves at length. What we do know from previous work is that the allograft valve is not static over time. There are structural changes, and one could hypothesize that these could lead to disturbances of flow and surfaces properties that could increase the likelihood of bacterial adherence, an essential step in the conversion of a bacteremia into a localized valve infection. These changes do not occur in mechanical valves, a fact that may explain the observed differences in late risk.

Appendixes

Appendix I. Variables entered into the multivariate analysis

Demographic variables. Demographic variables were age at operation and gender.

Clinical variables. Clinical variables included the following: preoperative endocarditis status (yes/no; if yes, native valve or prosthetic valve endocarditis), causative organisms in patients with preoperative endocarditis, New York Heart Association functional class immediately before operation, organ system dysfunction before operation (hepatic, pulmonary, cardiac, renal), and number of previous AVRs.

Surgical variables. Surgical variables were as follows: date of operation, surgeon, valve replacement device, size of replacement valve, concomitant procedures, and duration of cardiopulmonary bypass.

Postoperative variables. Postoperative variables were as follows: wound infection (with fever, pain, discharge, inflammation, and positive results of cultures), postoperative organ system dysfunction (cardiac, renal, hepatic, pulmonary), returns to the operating room for postoperative bleeding, and any postoperative urinary tract infection.

Note: *Hepatic dysfunction* was defined as a bilirubin level greater than or equal to 35 mmol/L, and *renal dysfunction* was defined as a creatinine level greater than or equal to 0.3 mmol/L or a urea concentration greater than or equal to 15 mmol/L (or both). Pulmonary dysfunction

refers to the need for ventilation in the preoperative period or the inability to normally discontinue (wean from) ventilatory support in the postoperative period.

Appendix II. Parameter estimates from multivariable analyses. In the multivariable analysis for replacement valve endocarditis in which demographic, clinical history, and surgical variables were entered, shaping parameters for the hazard function were as follows: $\rho = 2.7025$, $\delta = 0$, $\nu = 0.2010$, $m = 1$ (corresponding risk factor estimates are provided in Table I). In an independent analysis for the event replacement valve endocarditis, in which demographic, clinical history, surgical, and postoperative variables were entered, shaping parameters were as follows: $\rho = 2.7025$, $\delta = 0$, $\nu = 0.2010$, $m = 1$ (corresponding risk factor estimates are provided in Table II). In a multivariable analysis for the event staphylococcal endocarditis, in which demographic and clinical history variables were entered, shaping parameters were as follows: $\rho = 1.951$, $\delta = 0$, $\nu = 1.042$, $m = 0$ (corresponding risk factor estimates are provided in Table IV). Standard errors of estimates and variance-covariance estimates are available from us on request.

Appendix Table 1. Concomitant procedures and non-risk-adjusted prevalence of endocarditis (920 procedures performed in 856 operations)

Concomitant procedure	n	Endocarditis		
		No.	%	CL (%)
Coronary surgery	515	6	1.2	0.7-1.9
Aortic surgery				
Root replacement with graft	53	4	7.5	3.9-13.3
Root replacement with tissue	81	2	2.4	0.082-5.7
Wall repair or reduction	25	2	8.0	2.6-17.9
Arch repair with graft	24	0	0	0-7.7
Root enlargement	13	0	0	0-13.7
False aneurysm, closure	15	5	33	19.4-50
Valve surgery				
Mitral repair	99	8	8.1	5.2-11.9
Tricuspid repair	5	0	0	0-32
Myectomy	39	0	0	0-4.9
Closure of VSD	14	0	0	0-12.8
Closure of abscess cavity	8	0	0	0-21
Closure of PDA	5	0	0	0-32
Repair of LV aneurysm	2	0	0	0-61
Other cardiac procedure	5	0	0	0-32
Noncardiac procedure	5	0	0	0-32
$P(\chi^2) = 0.003$				
Total	920	23*	2.8	2.2-3.5

CL, 70% confidence limits; VSD, ventricular septal defect; PDA, patent ductus arteriosus; LV, left ventricular.

*Note: Because some patients underwent more than one concomitant procedure, the sum of preceding rows (27) is greater than the actual number of events (23).

Appendix Table 2. Causative organisms in pre-replacement endocarditis

Organism	n	Recurrent endocarditis: No.
<i>Actinobacillus</i>	2	1
<i>Bacillus subtilis</i>	1	0
<i>Brucella</i> sp.	1	0
<i>Cardiobacterium hominis</i>	1	0
<i>Corynebacterium</i> sp.	6	1
<i>C. bovis</i>	1	0
<i>C. diphtheriae</i>	2	1
<i>C. xerosis</i>	1	0
Unspecified	2	0
<i>Coxiella burnetii</i>	21	3
<i>Diphtheroid</i> sp.	1	0
<i>Eikenella corrodens</i>	1	0
<i>Haemophilus</i> sp.	2	1
<i>Klebsiella pneumoniae</i>	2	0
<i>Micrococcus</i> sp.	2	0
<i>Moraxella lacunata</i>	1	0
<i>Mucor</i> sp.	1	1
<i>Neisseria gonorrhoeae</i>	1	0
<i>Pseudomonas</i> sp.	2	0

Appendix Table 2. Cont'd.

Organism	n	Recurrent endocarditis: No.
<i>Staphylococcus</i> sp.	69	15
<i>Staph. aureus</i>	52	13
<i>Staph. epidermidis</i>	12	1
Unspecified	5	1
<i>Streptococcus</i> sp.	96	4
<i>S. agalactiae</i>	2	0
<i>S. bovis</i>	6	0
<i>S. faecalis</i>	4	0
<i>S. milleri</i>	3	0
<i>S. mitis</i>	4	0
<i>S. pneumoniae</i>	1	0
<i>S. salivarius</i>	3	0
<i>S. sanguis</i>	16	0
<i>S. viridans</i>	38	3
Unspecified	19	1
Total	211*	26

*Some patients had polymicrobial infections, resulting in 211 organisms in 206 patients.

Appendix Table 3. Patient characteristics and non-risk-adjusted prevalence of replacement valve endocarditis (N = 2696 operations; 95 events)

Characteristic	n	% of 2686	Endocarditis			$P(\chi^2)$
			No.	%	CL (%)	
Gender						
Male	1982	74	79	4.0	3.5-4.5	0.04
Female	704	26	16	2.3	1.7-3.0	0.04
Diabetic	114	4.2	3	2.6	1.5-5.2	0.6
Preoperative organ system dysfunction						
Cardiac (NYHA III-V)	681	25.4	31	4.5	3.7-5.5	0.1
Renal	123	5.6	9	7.3	4.9-10.6	0.02
Pulmonary	77	2.9	3	3.9	1.7-7.7	0.9
Hepatic	59	2.2	4	6.8	3.5-12.0	0.2
Number of previous AVR						
None	2352	88	79	3.4	3.0-3.8	$p(\text{logistic}) = 0.2$
One	290	10.8	13	4.5	3.2-6.1	
Two	43	1.6	3	7.0	3.1-13.5	
Three	1	0.04	0	0	0-85	
Preoperative endocarditis						
Active	91	3.4	12	13.2	9.5-17.9	<0.001
Remote	152	5.7	18	11.8	9.1-15.2	<0.001

CL, 70% confidence limits; NYHA, New York Heart Association.

Appendix Table 4. Valve replacement device and non-risk-adjusted prevalence of endocarditis

Replacement device	n	% of 2686	Endocarditis		
			No.	%	CL (%)
Autograft	11	0.4	0	0	0-16.0
Allograft					
Cryopreserved	428	15	11	2.6	1.8-3.6
Stored at 4° C	134	5	6	4.5	2.7-7.2
Pulmonary	8	0.2	0	0	0-21
Allovital	1	<0.1	0	0	0-85
Subtotal	571	21	17	3.0	2.3-4.0
Mechanical					
St. Jude Medical*	505	18.8	3	0.6	0.2-1.2
Lillehei-Kaster†	265	9.9	13	4.9	3.5-6.7
Brunwald-Cutter‡	69	2.6	5	7.3	4.1-12.0
Björk-Shiley§	34	1.3	0	0	0-5.5
Hall-Kaster	4	0.1	3	75	37-97
Omniscience†	2	<0.1	0	0	0-9.6
Hemex¶	1	<0.1	0	0	0-85
Subtotal	880	36	24	2.4	2.2-3.4
Xenograft					
Carpentier-Edwards#	1021	30	38	3.7	3.1-4.4
Hancock**	71	2.6	2	2.8	0.9-6.5
Medtronic Intact	43	1.6	2	4.6	1.5-10.7
Xenotech††	16	0.6	0	0	0-11.3
Ionescu-Shiley§	1	<0.1	0	0	0-85
Subtotal	1,152	43	42	3.6	3.1-4.3
Facia lata	72	2.7	12	16.7	12.0-22.5
Total	2686	100	95	3.5	3.1-3.9

CL, 70% confidence limits.

*St. Jude Medical, Inc., St. Paul, Minn.

†Medical, Inc., Inver Grove Heights, Minn.

‡Cutter Biological, Berkeley, Calif.

§Shiley, Inc., Irvine, Calif.

||Medtronic, Inc., Minneapolis, Minn.

¶Hemex Scientific, Inc., Austin, Tex.

#Baxter Healthcare Corp., Edwards Division, Santa Ana, Calif.

**Johnson & Johnson Cardiovascular, King of Prussia, Pa.

††Medtronic Heart Valve Division, Irvine, Calif.

Appendix Table 5. Validation of multivariable equation: comparison of predicted to actual number of cases of replacement valve endocarditis

Patient characteristic	Replacement valve endocarditis		P
	Actual	Predicted*	
All	95	95	1.0
Gender			
Male	79	75.5	0.7
Female	16	19.5	0.4
Age (yr)			
<50	54	51.1	0.7
>50	41	43.9	0.7
No. of previous AVRs			
0 (primary)	79	78.5	0.9
1 (first re-replacement)	13	12.1	0.8
2 (second re-replacement)	3	4.3	0.5
Preoperative endocarditis			
Yes	65	65.6	0.9
No	30	29.4	0.9
Valve replacement device			
Mechanical	24	22.8	0.8
Xenograft	17	18.7	0.7
Allograft	42	41.2	0.9

*Predictions from multivariable equation depicted in Table I.

Appendix Table 6. Redo operation and prevalence of risk factors

Risk factor from multivariable analysis	Operation				P(χ^2)*
	Primary (n = 2352)		Redo (n = 334)		
	n	% of 2352	n	% of 334	
Preoperative endocarditis	183	7.8	60	18	<0.0001
Active at operation	63	2.7	29	8.7	<0.0001
Staph. aureus endocarditis	39	1.7	14	4.2	0.002
Renal dysfunction	96	4.1	27	8.1	0.001
Aortic root replacement with graft	45	1.9	9	2.7	0.3
Replacement device					
Allograft	534	22.7	48	14.4	<0.0001
Medtronic Intact†	37	1.6	6	1.8	0.8
Carpentier-Edwards‡	953	41	58	17.4	<0.0001
St. Jude Medical§	389	16.5	116	35	<0.0001
Fascia lata	54	2.3	18	5.4	0.001

*p Value is for difference in occurrence of variable between the primary and redo operations.

†Medtronic, Inc., Minneapolis, Minn.

‡Baxter Healthcare Corp., Edwards Division, Santa Ana, Calif.

§St. Jude Medical, Inc., St. Paul, Minn.

Appendix Table 7. Postoperative complications and non-risk-adjusted prevalence of endocarditis

Complication	n	% of 2686	Endocarditis			$P(\chi^2)$
			No.	%	CL (%)	
Re-entry for bleeding	129	5	7	5.4	3.4-8.3	0.2
Wound infection*	53	2	7	13.25	8.3-19.8	<0.001
Organ system dysfunction						
Cardiac	118	4.4	9	7.6	5.1-11.0	0.05
Hepatic	51	1.9	6	11.8	7.0-18.4	0.001
Pulmonary	94	3.5	6	6.4	3.8-10.1	0.13
Renal	47	1.8	2	4.3	1.4-9.8	0.8

CL, 70% confidence limits.

*Includes only those wound infections with positive cultures that were accompanied by fever, wound pain, discharge, and inflammation.