In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis.

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Original Investigation

In-Hospital and 1-Year Mortality in Patients Undergoing Early Surgery for Prosthetic Valve Endocarditis

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IMPORTANCE There are limited prospective, controlled data evaluating survival in patients receiving early surgery vs medical therapy for prosthetic valve endocarditis (PVE).

OBJECTIVE To determine the in-hospital and 1-year mortality in patients with PVE who undergo valve replacement during index hospitalization compared with patients who receive medical therapy alone, after controlling for survival and treatment selection bias.

DESIGN, SETTING, AND PARTICIPANTS Participants were enrolled between June 2000 and December 2006 in the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), a prospective, multinational, observational cohort of patients with infective endocarditis. Patients hospitalized with definite right- or left-sided PVE were included in the analysis. We evaluated the effect of treatment assignment on mortality, after adjusting for biases using a Cox proportional hazards model that included inverse probability of treatment weighting and surgery as a time-dependent covariate. The cohort was stratified by probability (propensity) for surgery, and outcomes were compared between the treatment groups within each stratum.

INTERVENTIONS Valve replacement during index hospitalization (early surgery) vs medical therapy.

MAIN OUTCOMES AND MEASURES In-hospital and 1-year mortality.

RESULTS Of the 1025 patients with PVE, 490 patients (47.8%) underwent early surgery and 535 individuals (52.2%) received medical therapy alone. Compared with medical therapy, early surgery was associated with lower in-hospital mortality in the unadjusted analysis and after controlling for treatment selection bias (in-hospital mortality: hazard ratio [HR], 0.44 [95% CI, 0.38-0.52] and lower 1-year mortality: HR, 0.57 [95% CI, 0.49-0.67]). The lower mortality associated with surgery did not persist after adjustment for survivor bias (in-hospital mortality: HR, 0.90 [95% CI, 0.76-1.07] and 1-year mortality: HR, 1.04 [95% CI, 0.89-1.23]). Subgroup analysis indicated a lower in-hospital mortality with early surgery in the highest surgical propensity quintile (21.2% vs 37.5%; $P = .03$). At 1-year follow-up, the reduced mortality with surgery was observed in the fourth (24.8% vs 42.9%; $P = .007$) and fifth (27.9% vs 50.0%; $P = .007$) quintiles of surgical propensity.

CONCLUSIONS AND RELEVANCE Prosthetic valve endocarditis remains associated with a high 1-year mortality rate. After adjustment for differences in clinical characteristics and survival bias, early valve replacement was not associated with lower mortality compared with medical therapy in the overall cohort. Further studies are needed to define the effect and timing of surgery in patients with PVE who have indications for surgery.

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Prosthetic valve endocarditis (PVE) occurs in approximately 3% to 6% of patients within 5 years of valve implantation and is associated with significant morbidity and mortality.[1-4] Surgical intervention with debridement and valve replacement is recommended by consensus guidelines[5,6] for patients with complications such as valve dysfunction, dehiscence, heart failure, cardiac abscesses, or persistent bacteremia. These guidelines are based largely on expert opinion and limited observational data.[7] Studies[8-25] comparing survival between patients undergoing surgery vs medical therapy for PVE have reported conflicting results. In addition, retrospective data collection, single-center study design, and small sample sizes of these studies limit the ability to control for treatment selection and survivor bias.

Propensity score methods use an estimated probability of a treatment (ie, valve surgery) based on observed baseline characteristics to control for selection bias. This method has been used frequently in studies estimating treatment effects for patients with native valve endocarditis or including patients with either native valve endocarditis or PVE.[26-29] Important recommendations regarding performance of observational studies and use of propensity score–based methods were recently published.[30-33] The method of inverse probability of treatment weighting (IPTW) using the surgical propensity score in regression models for mortality is favored because of its superior performance in controlling for selection bias compared with stratification or propensity matching.[32] Survivor bias can profoundly affect outcome estimates, and this bias should be addressed by matching or including treatment (surgery) as a time-dependent covariate.[27,33]

Although a small randomized trial of early surgery for native valve infective endocarditis (IE) has recently been reported,[34] to our knowledge, no randomized studies of surgery for PVE have been performed. The objective of the present study was to assess in-hospital and 1-year mortality in patients with PVE who undergo valve replacement compared with patients who receive medical therapy alone using appropriate propensity score–based methods to provide adjusted estimates of treatment effect.

Methods

Study Population and Clinical Data

The International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) is a prospective, multicenter, international registry of patients with IE.[35,36] Data based on standard definitions were collected prospectively between January 1, 2000, and December 31, 2006, from 64 sites in 28 countries. The study was approved by the institutional review boards or ethics committees at all participating sites.

Inclusion criteria for this study cohort were patients diagnosed with definite PVE based on the modified Duke criteria.[37] Patients with the following characteristics were excluded: native and nonnative valve IE (eg, pacemaker IE), receipt of surgery before admission, and missing values for sex, receipt and/or date of surgery, length of initial hospitalization, in-hospital death, and death at 1-year follow-up. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was used. For missing data in ICE-PCS, sites and their investigators were queried to complete data collection.

Definitions

The definitions used in the ICE-PCS cohort have been reported.[38] *Early surgery* was defined as replacement or repair of the infected prosthetic valve during the initial hospitalization for PVE. *Chronic illness* was defined as the presence of chronic comorbidities, such as diabetes mellitus, cancer, immunosuppression, hemodialysis dependence, chronic obstructive pulmonary disease, and cirrhosis. *Paravalvular complication* was defined as the presence of an intracardiac abscess or fistula by transthoracic or transesophageal echocardiography. *Prosthetic valvular complication* was defined as evidence of dehiscence or severe regurgitation by transthoracic or transesophageal echocardiography. *Systemic embolization* was defined as embolism to any major arterial vessel, excluding stroke. *Health care–associated endocarditis* consisted of either nosocomial or nonnosocomial health care–associated infection.[39]

Analytical Plan

The association between early surgery and mortality was evaluated in a prospective, observational cohort. The primary outcomes were all-cause mortality during initial hospitalization and at 1-year follow-up. Analyses were expressed as hazard ratios (HRs) with 95% CIs; a 2-sided P value <.05 was considered significant. The unadjusted effect of early surgery on survival time was estimated using a univariate Cox proportional hazards model. Next, adjustment for measured confounders was performed using a multivariable Cox proportional hazards model with IPTW to address treatment selection bias. The cohort was also stratified by propensity score, and outcomes were compared between the treatment groups within each stratum using the Fisher exact test. A final Cox proportional hazards model included all relevant covariates as well as surgery as a time-dependent variable and IPTW to control for survival and treatment selection bias. All analyses were performed using commercial software (SAS, version 9.2; SAS Institute Inc).

Standard Univariate and Multivariable Analysis

Baseline characteristics and outcomes of patients with PVE who received early surgery were compared with those receiving medical therapy alone using the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. Unadjusted HRs were computed using a univariate Cox proportional hazards model. A multivariable Cox proportional hazards model with IPTW was performed to identify independent predictors of in-hospital and 1-year mortality (see the IPTW and Adjustment for Survivor Bias subsection below). This model included 19 clinically relevant variables (Supplement [eTable]). All of the variables used in the multivariable model had data collected for 97% or more of patients. Missing values for clinical outcomes were imputed with the negative category for categorical variables.

Propensity Score Model

To account for treatment selection bias (ie, systematic differences in clinical characteristics between patients in the 2 treat-

Table 1. Characteristics of 1025 Patients With Prosthetic Valve Endocarditis Treated With Early Surgery vs Medical Therapy

Characteristic	No. (%)		*P* Value	OR for Early Surgery (95% CI)[a]
	Early Surgery (n = 490)	Medical Therapy (n = 535)		
Male sex	343 (70)	335 (63)	.01	1.24 (0.92-1.67)
Age, mean (range), y	59.4 (0.5-88)	63.8 (0.3-91)	<.001	0.98 (0.97-0.99)
Aortic valve prosthesis[b]	350 (71.0)	369 (68.9)	.80	
Mitral valve prosthesis[b]	221 (45.1)	252 (47.1)	.85	
Endocarditis within 1 y of implantation[c]	78/195 (40)	90/213 (42)	.64	
Chronic illness[d]	154 (31)	199 (37)	.05	0.86 (0.64-1.15)
Duration of symptoms >1 mo before presentation	367 (75)	451 (84)	<.001	0.60 (0.42-0.85)
Transfer from another facility	239 (49)	184 (34)	<.001	1.54 (1.16-2.04)
Health care–associated infection	143 (29)	170 (32)	.37	0.92 (0.67-1.27)
Transesophageal echocardiography performed	426 (87)	443 (83)	.07	1.42 (0.95-2.12)
Fever	387 (79)	472 (88)	<.001	0.54 (0.37-0.79)
Echocardiographic findings[e]				
Aortic regurgitation	161 (33)	103 (19)	<.001	1.33 (0.93-1.91)
Mitral regurgitation	141 (29)	105 (20)	<.001	1.64 (1.16-2.31)
Aortic valve vegetation	220 (45)	204 (38)	.03	1.53 (1.12-2.08)
Mitral valve vegetation	179 (37)	191 (36)	.78	1.57 (1.13-2.19)
Paravalvular complications	213 (44)	108 (20)	<.001	2.62 (1.92-3.58)
Prosthetic valve complications[f]	204 (42)	129 (24)	<.001	1.63 (1.17-2.27)
Causative microorganism				
Staphylococcus aureus	96 (20)	133 (25)	.04	0.82 (0.57-1.18)
Coagulase-negative staphylococci	98 (20)	61 (11)	<.001	1.63 (1.09-2.45)
Viridans group streptococci	56 (11)	68 (13)	.53	
Enterococcus species	45 (9)	91 (17)	<.001	0.55 (0.35-0.85)
Complications				
Congestive heart failure	176 (36)	157 (29)	.02	1.22 (0.90-1.66)
NYHA class III or IV heart failure[g]	123/447 (28)	110/507 (22)	.15	
Stroke	88 (18)	115 (22)	.16	0.74 (0.52-1.07)
Other systemic embolization[h]	72 (15)	90 (17)	.35	0.81 (0.55-1.19)
Persistent bacteremia	39 (8)	45 (8)	.79	1.04 (0.61-1.77)
Outcome				
Length of hospitalization, median (IQR)	33.5 (19-52)	28.0 (14-44)	.008	
In-hospital mortality	108 (22)	143 (27)	.08	
1-y Mortality	133 (27)	196 (37)	.001	

Abbreviations: IQR, interquartile range; NYHA, New York Heart Association; OR, odds ratio.

[a] Odds ratio and CI calculated from the logistic regression model used to determine the propensity score for surgery.

[b] Includes valve repair with prosthesis and/or replacement.

[c] Data missing for 295 patients in the surgery group and 322 patients in the medical therapy group.

[d] Includes diabetes mellitus, cancer, immunosuppression, hemodialysis dependence, chronic obstructive pulmonary disease, cirrhosis, and other chronic comorbid conditions.

[e] Based on transesophageal or transthoracic echocardiography.

[f] Transesophageal or transthoracic echocardiographic evidence of dehiscence or severe regurgitation.

[g] Data missing for 43 patients in the surgery group and 28 patients in the medical therapy group.

[h] Includes embolism to any major arterial vessel, excluding stroke.

ment groups that may affect treatment selection), the propensity or probability for early surgery was calculated for each patient on the basis of a nonparsimonious multivariable logistic regression model. This model included 21 clinically relevant variables (**Table 1**) considered a priori by the investigators to contribute to surgical treatment. Odds ratios (ORs) and 95% CIs for early surgery were calculated for all predictors. The total cohort of 1025 patients was stratified into quintiles based on the probability of early surgery (and without regard to actual treatment received by the patient), and outcomes were estimated within each stratum.

IPTW and Adjustment for Survivor Bias

An additional Cox proportional hazards model was created to estimate the effect of surgery on mortality while controlling for treatment selection and survivor bias. Survivor bias was considered important, since the likelihood of receiving early surgery may be influenced by longer survival (or, in other words, patients who die early during hospitalization may be considered as deaths associated with medical therapy despite surgical indications). To adjust for treatment selection bias, each patient was assigned a "weight" or influence when estimating the effect of treatment on mortality, which was inversely proportional to the probability of receiving the treatment to which they were assigned in reality (IPTW). To reduce survivor bias, early surgery was included as a time-dependent covariate, that is, surgical patients were included in the medical therapy group until the date of surgery and in the surgical group thereafter.

Results

A total of 4166 patients with definite left- or right-sided IE were enrolled in the ICE-PCS cohort between January 1, 2000, and

Table 2. Cox Proportional Hazards Model Ratios for In-Hospital and 1-Year Mortality Associated With Early Surgery Compared With Medical Therapy

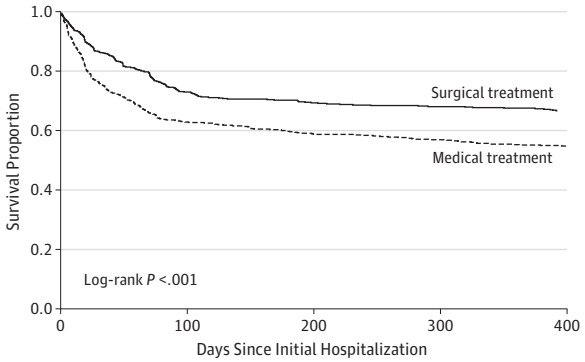
	Unadjusted		Multivariable Model With IPTW[a]		Multivariable Model With IPTW and Surgery as Time-Dependent Covariates[b]	
Characteristic	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
In-hospital mortality	0.68 (0.53-0.87)	.003	0.44 (0.38-0.52)	<.001	0.90 (0.76-1.07)	.24
1-y Mortality	0.68 (0.55-0.85)	<.001	0.57 (0.49-0.67)	<.001	1.04 (0.89-1.23)	.62

Abbreviations: HR, hazard ratio; IPTW, inverse probability of treatment weighting (using the propensity score for surgery).

[a] See the Supplement (eTable) for the full model.

[b] See Table 3 for the full model.

Figure 1. Kaplan-Meier Curves for the Cumulative Probability of Survival at 1 Year



No. at risk				
Surgery	490	287	255	239
Medical therapy	535	275	250	224

Cox proportional hazards model weighted by the inverse probability of treatment.

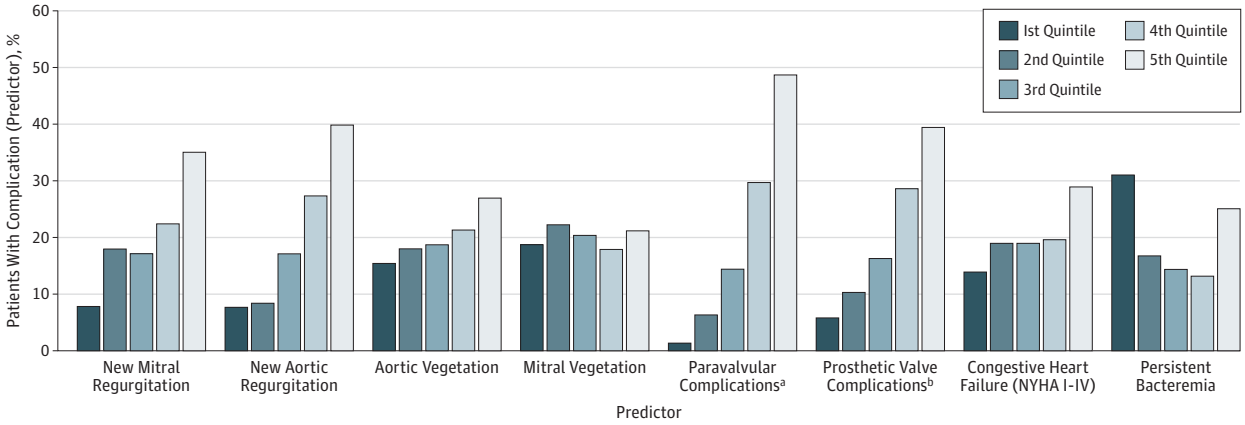
December 31, 2006. Of these, 1025 patients had definite PVE and met the eligibility criteria for this study (Supplement [eFigure]). A prosthetic aortic valve was present in 719 (70.1%) patients (mechanical valve: 349 [48.5%]; bioprosthetic valve: 353 [49.1%]; repair: 17 [2.4%]), and a prosthetic mitral valve or ring was present in 473 (46.1%) patients (mechanical valve: 303 [64.1%]; bioprosthetic valve: 86 [18.2%]; repair: 84 [17.8%]) patients. *Staphylococcus aureus* was the most common cause of PVE. Among the PVE cases, 490 of 1025 patients (47.8%) underwent early surgery and 535 patients (52.2%) received medical therapy alone during the index hospitalization (Table 1). There was no significant difference in the time interval between valve insertion and PVE diagnosis between the 2 treatment groups among the 408 patients for whom this variable was collected (the variable was removed from case report forms in August 2005). The median time from admission to surgery was 8 days (quintile 1 to quintile 3, 4-20 days).

Patients who received early surgery were significantly younger, had a shorter duration of symptoms, and were more likely to have been transferred from another facility. Prosthetic valve endocarditis caused by *S aureus* and enterococci was associated with receiving medical therapy, while coagulase-negative *Staphylococcus* was associated with higher use of surgery. As expected, a significantly higher proportion of the surgical group compared with the medical group had complications of PVE, such as mitral valve regurgitation (28.8% vs 19.60%; OR, 1.64 [95% CI, 1.16-2.31]), paravalvular complications (43.5% vs 20.2%; OR, 2.62 [95% CI, 1.92-3.58]), or prosthetic valve complications (41.6% vs 24.1%; OR, 1.63 [95% CI, 1.17-2.27]). Early surgery was associated with lower in-hospital mortality (22.0% vs 26.7%; HR, 0.68 [95% CI, 0.53-0.87]) and 1-year mortality (27.1% vs 36.6%; HR, 0.68 [95% CI, 0.55-0.85]) in the unadjusted Cox proportional hazards model.

To control for treatment selection bias, the probability of surgery by propensity score was calculated for each patient. The propensity score model had a concordance index of 0.74 and a Hosmer-Lemeshow test statistic of 7.78 (P = .45), indicating good discriminative and predictive ability. The predicted probability of surgery for the total cohort ranged from 5.2% to 98.2%. An adjusted Cox proportional hazards model, including IPTW and controlling for other measured covariates, was performed. Early surgery remained strongly associated with lower mortality after adjusting for treatment selection bias (in-hospital mortality: HR, 0.44 [95% CI, 0.38-0.52] and 1-year mortality: HR, 0.57 [95% CI, 0.49-0.67]) (**Table 2**, **Figure 1**, and Supplement [eTable]).

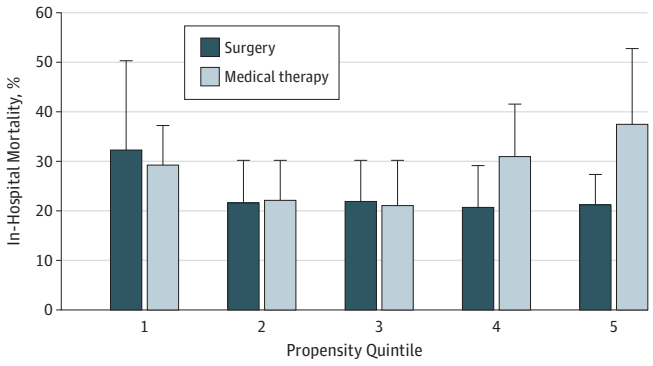
The cohort was then divided into 5 subgroups (ie, quintiles) based on the predicted probability of surgery (and without regard to actual treatment received by the patient). Thus, each quintile had 205 patients who were comparable in clinical characteristics and probability of surgery but differed by the treatment received (a process similar to randomization). In addition, patients in the fifth quintile had a higher predicted probability of surgery (range, 68.5%-98.2%) vs those in the first quintile (range, 5.2%-27.5%). **Figure 2** shows the frequency of PVE complications that may indicate a clinical indication for surgery across the quintiles of propensity. Patients in quintile 5 had a higher frequency of new mitral or aortic

Figure 2. Distribution of Key Predictors of Surgery Across the Propensity Quintiles in a Cohort of Patients With Prosthetic Valve Endocarditis



NYHA I-IV indicates New York Heart Association class I to IV heart failure.
[a]Transesophageal or transthoracic echocardiographic evidence of paravalvular abscess or fistula formation.
[b]Transesophageal or transthoracic echocardiographic evidence of dehiscence or severe regurgitation.

Figure 3. In-Hospital Mortality Rates for Patients With Prosthetic Valve Endocarditis by Propensity Quintile for Surgery



Propensity, mean (range)	0.20 (0.05-0.28)	0.34 (0.28-0.40)	0.46 (0.40-0.53)	0.61 (0.53-0.69)	0.79 (0.69-0.98)
No. of patients					
Medical therapy	171	131	109	84	40
Surgery	34	74	96	121	165
P value[a]	.72	.93	.89	.09	.03

Data are given as mortality point estimates; error bars indicate 95% CIs.
[a]Fisher exact *P* value.

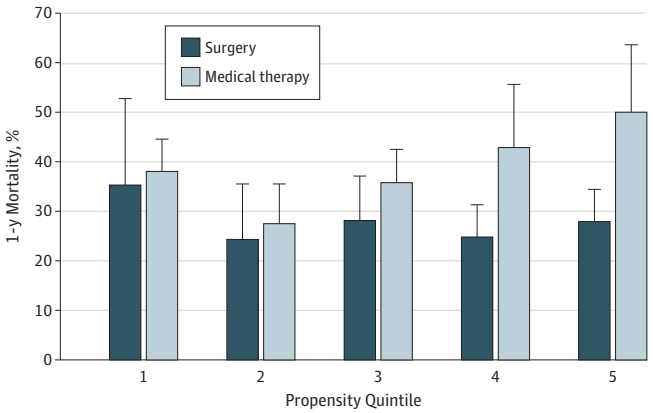
valve regurgitation, prosthetic valve/paravalvular complications, and New York Heart Association class I to IV congestive heart failure compared with patients in the lower quintiles and therefore had a higher probability of receiving surgical treatment. We then compared the outcomes between patients who underwent valve surgery with those who received medical therapy alone within each quintile. A lower in-hospital mortality incidence for surgery was observed only in the highest surgical propensity quintile (21.2% vs 37.5%, respectively; *P* = .03) (**Figure 3**). At the 1-year follow-up, lower mortality associated with surgery was observed in the fourth (24.8% vs 42.9%; *P* = .007) and fifth (28% vs 50%; *P* = .007) quintiles (**Figure 4**).

Next, we evaluated the effect of early surgery on mortality after controlling for treatment selection and survivor bias. The survival benefit was no longer evident after adjusting for survivor bias by including surgery as a time-dependent variable in the Cox proportional hazards model (in-hospital mortality: HR, 0.90 [95% CI, 0.76-1.07] and 1-year mortality: HR, 1.04 [0.89-1.23]). Variables independently associated with in-hospital and 1-year mortality in this model included chronic illness, *S aureus* infection, health care–associated infection, and PVE complications of stroke, congestive heart failure, intracardiac abscess, and paravalvular complications (**Table 3**).

Discussion

Our study compared the clinical characteristics and outcome of patients with PVE treated with early surgery or medical therapy during the index hospitalization. Our main findings were (1) a high percentage of patients with PVE (48%), par-

Figure 4. One-Year Mortality Rates for Patients With Prosthetic Valve Endocarditis by Propensity Quintile for Surgery



Propensity, mean (range)	0.20 (0.05-0.28)	0.34 (0.28-0.40)	0.46 (0.40-0.53)	0.61 (0.53-0.69)	0.79 (0.69-0.98)
No. of patients					
Medical therapy	171	131	109	84	40
Surgery	34	74	96	121	165
P value[a]	.77	.62	.24	.007	.007

Data are given as mortality point estimates; error bars indicate 95% CIs.
[a]Fisher exact *P* value.

ticularly those with complications related to endocarditis, underwent surgery during the index hospitalization; (2) although early surgery was associated with a mortality benefit in the unadjusted analysis and after controlling for treatment selection bias, this mortality benefit was neutralized after controlling for survivor bias in the overall cohort; (3) surgery in subgroups of patients who had strong indications for surgery (eg, valve regurgitation, vegetation, and dehiscence or paravalvular abscess/fistula) was associated with lower 1-year mortality. To our knowledge, this is the largest study of PVE in the medical literature with strengths of prospectively collected data from multinational centers with an expertise in IE and in a contemporary era of surgical therapy.

The rate of valve surgery in our cohort (48%) is similar to surgical rates for PVE reported in the literature.[8-25] This is a reflection of the guidelines from the American Heart Association/American College of Cardiology and the European Society of Cardiology that recommend consideration of surgery for all patients with PVE, particularly those with complications unlikely to be treated effectively by medical therapy alone, such as heart failure, prosthetic valve dysfunction, and intracardiac abscess.[5,6] Nevertheless, operative (in-hospital) mortality remains high for surgical patients and not less than the rates in previous eras,[25] and patients with complicated PVE in our cohort had similar in-hospital and longer-term mortality compared with patients with a lower-risk clinical profile treated with medical therapy alone. A recent study reported in the Society of Thoracic Surgery database[40] showed a low operative mortality in IE (8%), but the study did not specifically evaluate PVE, and surgery during the active stage of IE was associated with a 2-fold higher operative mortality.

In our study, early surgery was not associated with a mortality benefit in the overall cohort after adjusting for treatment selection and survivor bias. The findings of our subgroup analysis support the American Heart Association guidelines because patients with the highest predicted probability of surgery (ie, those with the surgical indications mentioned above) had lower mortality rates when they received surgery vs medical therapy. However, these findings should be interpreted cautiously as results of a post hoc subgroup analysis that did not adjust for survivor bias.

Previous studies of PVE have found conflicting results regarding the effect of surgery. In a previous study by the International Collaboration on Endocarditis Investigators[41] of retrospectively merged IE databases with propensity matching, surgery and medical therapy had similar in-hospital mortality rates, but longer-term outcome was not evaluated. In planning the present study, we had hypothesized that a survival benefit of surgery may not be apparent during the initial hospitalization given the higher operative risk of patients with PVE. However, after adjusting for selection and survivor bias in the surgical group, mortality rates remained similar even at 1 year after PVE for both treatment groups and were strongly related to host factors, pathogen, and particularly complications of PVE (heart failure, stroke, and paravalvular complications). Of note, heart failure was the strongest predictor of both in-hospital and 1-year mortality, confirming the significance of this complication even with a high rate of surgical intervention.[42] Several other factors reflecting changes in the epidemiology of PVE, such as the higher patient age, cause of *S aureus*, and health care–associated infection, may contribute to the persistently high in-hospital and 1-year mortality compared with earlier studies.[25,41]

Recently, a small, randomized study[34] of surgery for native valve endocarditis was reported. In that study, patients treated with surgery within 48 hours of diagnosis had a lower rate of embolic events but similar survival at 6 months compared with patients treated with usual care (yet 77% of patients receiving usual care underwent surgery).[34]

Table 3. Cox Proportional Hazards Model Weighted by the Inverse Probability of Early Surgery and Using Early Surgery and a Time-Dependent Variable: Predictors of In-Hospital and 1-Year Mortality

Characteristic	HR (95% CI)	
	In-Hospital Mortality	1-y Mortality
Early surgery, as a time-dependent covariate	0.90 (0.76-1.07)	1.04 (0.89-1.23)
Age	1.02 (1.02-1.03)	1.02 (1.02-1.03)
Male sex	1.20 (1.03-1.39)	1.06 (0.90-1.23)
Chronic illness[a]	1.36 (1.17-1.58)	1.34 (1.15-1.57)
History of CHF before IE episode	0.59 (0.46-0.74)	0.66 (0.52-0.83)
Health care–associated infection	1.27 (1.08-1.48)	1.39 (1.18-1.64)
Coagulase-negative staphylococcal infection	0.91 (0.73-1.13)	0.99 (0.78-1.24)
Staphylococcus aureus infection	1.26 (1.05-1.52)	1.45 (1.19-1.76)
Viridans group streptococcal infection	0.57 (0.40-0.80)	0.92 (0.67-1.23)
Enterococcal infection	0.79 (0.62-1.00)	1.03 (0.80-1.31)
Transesophageal echocardiography performed	0.42 (0.35-0.51)	0.48 (0.40-0.59)
Intracardiac vegetation	1.75 (1.45-2.13)	1.58 (1.30-1.92)
Intracardiac abscess[b]	1.38 (1.11-1.72)	1.41 (1.13-1.76)
Paravalvular complications[c]	1.54 (1.24-1.90)	1.40 (1.13-1.73)
Prosthetic valve complication[d]	0.95 (0.81-1.12)	1.07 (0.90-1.26)
Systemic embolization[e]	1.11 (0.92-1.34)	1.10 (0.90-1.33)
Stroke	1.38 (1.17-1.63)	1.64 (1.37-1.95)
Persistent bacteremia	1.05 (0.84-1.31)	1.41 (1.12-1.75)
CHF	2.05 (1.76-2.38)	1.84 (1.58-2.16)

Abbreviations: CHF, congestive heart failure; HR, hazard ratio; IE, infective endocarditis.

[a] Includes diabetes mellitus, cancer, immunosuppression, hemodialysis dependence, chronic obstructive pulmonary disease, cirrhosis, and other chronic comorbid conditions.

[b] Based on transesophageal or transthoracic echocardiography.

[c] Transesophageal or transthoracic echocardiographic evidence of paravalvular abscess or fistula formation.

[d] Transesophageal or transthoracic echocardiographic evidence of dehiscence or severe regurgitation.

[e] Includes embolism to any major arterial vessel, excluding stroke.

No randomized studies of surgery for PVE have been performed. Based on the differing survival estimates between the propensity-adjusted and Cox proportional hazards model, our results emphasize that survival bias and timing of surgery should be considered when evaluating the treatment effect on mortality. Although patients underwent surgery at a median of 8 days after admission, the potential benefit of earlier intervention was not evaluated and may influence outcome.

This study had several other limitations. The ICE cohort may be influenced by referral bias because most institutions are tertiary care centers with voluntary participation. Thus, the results of the present study may not be generalizable to the global epidemiology, treatment, and outcomes of PVE. Despite the use of propensity score adjustment to reduce selection bias for surgical treatment and Cox proportional hazards modeling to reduce survival bias, other variables not evaluated may confound the results of this analysis. The timing of PVE diagnosis relative to the date of prosthetic valve implantation was not evaluated because of missing data. Data regarding the presence of surgical indications in medically treated patients and the reason for not undergoing valve surgery were also unavailable for most patients in the cohort. However, other variables included in these analyses, such as health care–associated infection and causative organism (staphylococcal), correlate with early PVE characteristics. Data regarding surgery after hospital discharge were not routinely collected; among 252 of 392 patients (64%) who received medical therapy and survived to hospital discharge, only 24 of 252 patients (10%) had undergone surgery at 1-year follow-up.

In conclusion, approximately one-third of patients with PVE die within 1 year after diagnosis, with mortality strongly associated with other chronic illness, health care–associated infection, *S aureus*, and complications of PVE. Surgical treatment was not associated with a lower mortality at 1-year in the overall PVE cohort after controlling for treatment selection and survivor bias. Further studies are needed to define the effect and timing of surgery in patients with PVE who have indications for surgery.

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REFERENCES

1. Agnihotri AK, McGiffin DC, Galbraith AJ, O'Brien MF. The prevalence of infective endocarditis after aortic valve replacement. *J Thorac Cardiovasc Surg*. 1995;110(6):1708-1724.

2. Calderwood SB, Swinski LA, Waternaux CM, Karchmer AW, Buckley MJ. Risk factors for the development of prosthetic valve endocarditis. *Circulation*. 1985;72(1):31-37.

3. Arvay A, Lengyel M. Incidence and risk factors of prosthetic valve endocarditis. *Eur J Cardiothorac Surg*. 1988;2(5):340-346.

4. Wang A, Athan E, Pappas PA, et al; International Collaboration on Endocarditis-Prospective Cohort Study Investigators. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297(12):1354-1361.

5. Bonow RO, Carabello BA, Chatterjee K, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease); Society of Cardiovascular Anesthesiologists. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2006;48(3):e1-e148. doi:10.1016/j.jacc.2006.05.021.

6. Habib G, Hoen B, Tornos P, et al; ESC Committee for Practice Guidelines; endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J*. 2009;30(19):2369-2413.

7. Attaran S, Chukwuemeka A, Punjabi PP, Anderson J. Do all patients with prosthetic valve endocarditis need surgery? *Interact Cardiovasc Thorac Surg*. 2012;15(6):1057-1061.

8. Calderwood SB, Swinski LA, Karchmer AW, Waternaux CM, Buckley MJ. Prosthetic valve endocarditis: analysis of factors affecting outcome of therapy. *J Thorac Cardiovasc Surg*. 1986;92(4):776-783.

9. Yu VL, Fang GD, Keys TF, et al. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy only. *Ann Thorac Surg*. 1994;58(4):1073-1077.

10. Otaki M. Prosthetic valve endocarditis: surgical procedures and clinical outcome. *Cardiovasc Surg*. 1994;2(2):212-215.

11. Wolff M, Witchitz S, Chastang C, Régnier B, Vachon F. Prosthetic valve endocarditis in the ICU: prognostic factors of overall survival in a series of 122 cases and consequences for treatment decision. *Chest*. 1995;108(3):688-694.

12. Ho HH, Siu CW, Yiu KH, Tse HF, Chui WH, Chow WH. Prosthetic valve endocarditis in a multicenter registry of Chinese patients. *Asian Cardiovasc Thorac Ann*. 2010;18(5):430-434.

13. John MD, Hibberd PL, Karchmer AW, Sleeper LA, Calderwood SB. *Staphylococcus aureus* prosthetic valve endocarditis: optimal management and risk factors for death. *Clin Infect Dis*. 1998;26(6):1302-1309.

14. Sohail MR, Martin KR, Wilson WR, Baddour LM, Harmsen WS, Steckelberg JM. Medical versus surgical management of *Staphylococcus aureus* prosthetic valve endocarditis. *Am J Med*. 2006;119(2):147-154.

15. Gordon SM, Serkey JM, Longworth DL, Lytle BW, Cosgrove DM III. Early onset prosthetic valve endocarditis: the Cleveland Clinic experience 1992-1997. *Ann Thorac Surg*. 2000;69(5):1388-1392.

16. Akowuah EF, Davies W, Oliver S, et al. Prosthetic valve endocarditis: early and late outcome following medical or surgical treatment. *Heart*. 2003;89(3):269-272.

17. Alonso-Valle H, Fariñas-Alvarez C, García-Palomo JD, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. *J Thorac Cardiovasc Surg*. 2010;139(4):887-893.

18. Habib G, Tribouilloy C, Thuny F, et al. Prosthetic valve endocarditis: who needs surgery? a multicentre study of 104 cases. *Heart*. 2005;91(7):954-959.

19. Kuyvenhoven JP, van Rijk-Zwikker GL, Hermans J, Thompson J, Huysmans HA. Prosthetic valve endocarditis: analysis of risk factors for mortality. *Eur J Cardiothorac Surg*. 1994;8(8):420-424.

20. López J, Revilla A, Vilacosta I, et al. Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis. *Eur Heart J*. 2007;28(6):760-765.

21. Chirouze C, Cabell CH, Fowler VG Jr, et al; International Collaboration on Endocarditis Study Group. Prognostic factors in 61 cases of *Staphylococcus aureus* prosthetic valve infective endocarditis from the International Collaboration on Endocarditis merged database. *Clin Infect Dis*. 2004;38(9):1323-1327.

22. Tornos P, Almirante B, Olona M, et al. Clinical outcome and long-term prognosis of late prosthetic valve endocarditis: a 20-year experience. *Clin Infect Dis*. 1997;24(3):381-386.

23. Truninger K, Attenhofer Jost CH, Seifert B, et al. Long term follow up of prosthetic valve endocarditis: what characteristics identify patients who were treated successfully with antibiotics alone? *Heart*. 1999;82(6):714-720.

24. Rekik S, Trabelsi I, Maaloul I, et al. Short- and long-term outcomes of surgery for active infective endocarditis: a Tunisian experience. *Interact Cardiovasc Thorac Surg*. 2009;9(2):241-245.

25. Edwards MB, Ratnatunga CP, Dore CJ, Taylor KM. Thirty-day mortality and long-term survival following surgery for prosthetic endocarditis: a study from the UK heart valve registry. *Eur J Cardiothorac Surg*. 1998;14(2):156-164.

26. Aksoy O, Sexton DJ, Wang A, et al. Early surgery in patients with infective endocarditis: a propensity score analysis. *Clin Infect Dis*. 2007;44(3):364-372.

27. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, et al. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. *Circulation*. 2007;115(13):1721-1728.

28. Tleyjeh IM, Steckelberg JM, Georgescu G, et al. The association between the timing of valve surgery and 6-month mortality in left-sided infective endocarditis. *Heart*. 2008;94(7):892-896.

29. Thuny F, Beurtheret S, Mancini J, et al. The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. *Eur Heart J*. 2011;32(16):2027-2033.

30. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-577.

31. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J*. 2009;51(1):171-184.

32. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med*. 2010;29(20):2137-2148.

33. Tleyjeh IM, Kashour T, Zimmerman V, Steckelberg JM, Wilson WR, Baddour LM. The role of valve surgery in infective endocarditis management: a systematic review of observational studies that included propensity score analysis. *Am Heart J*. 2008;156(5):901-909.

34. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366(26):2466-2473.

35. Cabell CH, Abrutyn E; lessons from the International Collaboration on Endocarditis. Progress toward a global understanding of infective endocarditis. *Cardiol Clin*. 2003;21(2):147-158.

36. Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis: early lessons from the International Collaboration on Endocarditis investigation. *Infect Dis Clin North Am*. 2002;16(2):255-272; vii.

37. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633-638.

38. Fowler VG Jr, Miro JM, Hoen B, et al; ICE Investigators. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA*. 2005;293(24):3012-3021.

39. Benito N, Miró JM, de Lazzari E, et al; ICE-PCS (International Collaboration on Endocarditis Prospective Cohort Study) Investigators. Health care–associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med*. 2009;150(9):586-594.

40. Gaca JG, Sheng S, Daneshmand MA, et al. Outcomes for endocarditis surgery in North America: a simplified risk scoring system. *J Thorac Cardiovasc Surg*. 2011;141(1):98-106; e101-e102. doi:10.1016/j.jtcvs.2010.09.016.

41. Wang A, Pappas P, Anstrom KJ, et al; International Collaboration on Endocarditis Investigators. The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort. *Am Heart J*. 2005;150(5):1086-1091.

42. Kiefer T, Park L, Tribouilloy C, et al. Association between valvular surgery and mortality among patients with infective endocarditis complicated by heart failure. *JAMA*. 2011;306(20):2239-2247.

Invited Commentary

Challenges in Treating Prosthetic Valve Endocarditis

Ann F. Bolger, MD

Which patients with endocarditis will benefit from early surgery is vigorously debated. Prospective randomized trials have demonstrated that patients with infections of native mitral and aortic valves associated with large vegetations and severe valvular regurgitation benefit from early surgery in terms of longer survival and fewer embolic complications[1]; several observational studies[2,3] using propensity score analysis have also supported early surgery in high-risk patients.

But what about patients with prosthetic valve infection? Such patients fill us with dread. Their outcomes are indisputably poor. Would early surgery make a difference in this group? Lalani and colleagues[4] provide us with data on 1025 patients with prosthetic valve endocarditis (PVE), approximately half of whom underwent early surgery during their initial hospitalization. Overall, nearly one-third of these patients died within a year after diagnosis. This mortality is within the range published over the past 20 years. Despite technical improvements in diagnosis and surgery, we clearly have not made significant improvements in the treatment of PVE. The numbers of patients with prosthetic valves and therefore at risk for these infections continue to expand, underscoring the need to find more effective treatment.

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The hypothesis of Lalani and colleagues was that early surgery within the index hospitalization would improve 1-year outcomes in patients with high-risk features. In keeping with their previously used statistical methods accounting for treatment selection bias, it appeared that early surgery did indeed improve early outcomes in patients in the highest quintile for propensity for surgery, and both early and 1-year outcomes in the fourth and fifth quintiles. These quintiles were assigned according to predictors of poor outcomes familiar from European Society of Cardiology and American Heart Association guidelines.[5,6] However, after accounting for survivor bias, the startling conclusion was that early surgery did not improve early or 1-year outcomes in the overall cohort. These results are surprising and will need broader confirmation. As they stand, they represent an opportunity for us to challenge ourselves as clinicians to consider how we weigh the various host-, bacteriologic-, and prosthesis-related aspects of this complex clinical scenario.

The echographic findings of prosthetic valve infections are often impressive. The anatomic distortions of abscesses, fistulae, and prosthetic dehiscence are dramatic and intuitively seem important to treat given that they are unlikely to improve with antibiotic therapy alone. Debriding the infection, removing the source of potential emboli and ongoing sepsis, and eliminating fistulous shunting or paravalvular leak would seem an appealing "root cause" solution.

Impressive as these visible anatomic and functional features of PVE may be, perhaps we overvalue them in our overall assessment of patient risk. Guidelines have consistently emphasized these features as indicators of a need for surgery. However, their presence does not guarantee poor immediate outcomes. It is important, as we discuss treatment options with the patient and care team, that we be nuanced in our assessment of the patient's comorbidities, as well as the individual patient's ability to tolerate some of the functional sequelae of prosthetic infection.

Fistulae, paravalvular leak, or transprosthetic leak create functional challenges to the heart via abnormal load and turbulence. In some situations, they are associated with heart failure and are harbingers of poor outcome, such as ventricular arrhythmia. For some patients, however, the functional impact of these lesions may be medically tolerable and/or nonprogressive in the short term. By definition, patients with PVE have had a prior reason to undergo valve surgery. It is reasonable to anticipate that their ventricles are no strangers to volume or pressure overload and might be more capable of handling the incremental load imposed by these abnormalities by virtue of prior compensatory remodeling. This may provide some tolerance for valvular regurgitation that would not be true of the patient with de novo native valvular infection and regurgitation. In that sense, flow-related lesions in a patient with PVE may not carry the same risk for decompensation as in a patient with native valve infection, for whom we fear delaying surgery in the setting of acute, de novo regurgitation. It is interesting to observe that, in the International Collaboration on Endocarditis data, a diagnosis of heart failure that preceded endocarditis was not associated with short- or long-term mortality in multivariate analysis in this study. Volume lesions may present a spectrum of cause, severity, and prognostic implication influenced by individual response. The in-