Impact of Valve Surgery on 6-Month Mortality in Adults With Complicated, Left-Sided Native Valve Endocarditis

A Propensity Analysis

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Context Complicated, left-sided native valve endocarditis causes significant morbidity and mortality in adults. The presumed benefits of valve surgery remain unproven due to lack of randomized controlled trials.

Objective To determine whether valve surgery is associated with reduced mortality in adults with complicated, left-sided native valve endocarditis.

Design and Setting Retrospective, observational cohort study conducted from January 1990 to January 2000 at 7 Connecticut hospitals. Propensity analyses were used to control for bias in treatment assignment and prognostic imbalances.

Patients Of the 513 adults with complicated, left-sided native valve endocarditis, 230 (45%) underwent valve surgery and 283 (55%) received medical therapy alone.

Main Outcome Measure All-cause mortality at 6 months after baseline.

Results In the 6-month period after baseline, 131 patients (26%) died. In unadjusted analyses, valve surgery was associated with reduced mortality (16% vs 33%; hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.29-0.63; $P<.001$). After adjustment for baseline variables associated with mortality (including hospital site, comorbidity, congestive heart failure, microbial etiology, immunocompromised state, abnormal mental status, and refractory infection), valve surgery remained associated with reduced mortality (adjusted HR, 0.35; 95% CI, 0.23-0.54; $P<.02$). In further analyses of 218 patients matched by propensity scores, valve surgery remained associated with reduced mortality (15% vs 28%; HR, 0.45; 95% CI, 0.23-0.86; $P=.01$). After additional adjustment for variables that contribute to heterogeneity and confounding within the propensity-matched group, surgical therapy remained significantly associated with a lower mortality (HR, 0.40; 95% CI, 0.18-0.91; $P=.03$). In this propensity-matched group, patients with moderate to severe congestive heart failure showed the greatest reduction in mortality with valve surgery (14% vs 51%; HR, 0.22; 95% CI, 0.09-0.53; $P=.001$).

Conclusions Valve surgery for patients with complicated, left-sided native valve endocarditis was independently associated with reduced 6-month mortality after adjustment for both baseline variables associated with the propensity to undergo valve surgery and baseline variables associated with mortality. The reduced mortality was particularly evident among patients with moderate to severe congestive heart failure.

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The advent of surgical therapy for complicated native valve infective endocarditis has been associated with reduced mortality in published observational experiences.[1-3] Since the initial descriptions of valve replacement for active infective endocarditis,[4,5] valve surgery has been recommended for patients with native valve endocarditis who exhibit complications that adversely affect prognosis: congestive heart failure, new valvular regurgitation, systemic embolization to vital organs, refractory infection (eg, perivalvular abscess, persistent fever and bacteremia, or fungemia), and demonstration of a vegetation on echocardiography.[3,6-10] However, documentation of improved clinical outcome that results from valve surgery has been unproven due to the lack of controlled trials and the inherent biases of observational studies.

Recently, our group derived and externally validated a prognostic classification system in a large cohort of patients with complicated, left-sided native valve endocarditis.[2] In the present study, we sought to determine whether valve surgery reduced mortality in the same

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cohort of patients, controlling for the inherent biases in treatment selection and prognostic imbalances using propensity analyses and multivariable modeling.

METHODS

Patients

Research patients were identified through medical record review at the 7 Connecticut hospitals where valve surgery was performed from January 1990 to January 2000. Patients were identified as having infective endocarditis if they met the Duke criteria for definite or possible endocarditis.[11] Our patient cohort has been described in detail elsewhere.[2]

Patients were included if they had left-sided involvement of a native valve (ie, aortic valve, mitral valve, or both) and if they had exhibited a clinical complication for which valve surgery is considered in current clinical practice: congestive heart failure, new valvular regurgitation, refractory infection, systemic embolization to vital organs, or presence of a vegetation on echocardiography. For patients with multiple episodes of endocarditis, only the first episode was analyzed. Patients were excluded if they were comatose at baseline (n=26), if clinical outcome data were not available 6 months after baseline (n=8), or if the decision about surgery was not explicitly stated in the medical record (n=5). The study was approved by the Human Investigation Committee at Yale University School of Medicine and the institutional review boards of all 7 participating hospitals.

Clinical Data

From medical records, baseline clinical information was recorded for sociodemographic data, comorbid conditions, previous heart disease, symptoms, physical findings, blood cultures, electrocardiogram, echocardiography, type of surgery performed, and operative findings; baseline was defined as the date of valve surgery or the date that the decision not to operate was noted in the medical record.[2] Comorbidity was assessed by using the Charlson comorbidity scale,[12] which assigns weights to specific comorbid disease states: 1 point for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, or diabetes; 2 points for hemiplegia, moderate to severe renal disease, diabetes with end-organ damage, any tumor, leukemia, or lymphoma; 3 points for moderate to severe liver disease; and 6 points for metastatic solid tumor or AIDS.

Outcomes

The primary outcome was all-cause mortality at 6 months after baseline. All patient episodes were followed up for the 6-month period after baseline for survival or death. For patients whose medical records lacked documentation of survival or death 6 months after baseline, the National Death Index was used to determine outcome.[13-15]

Statistical Analyses

Differences between patients undergoing valve surgery and those undergoing medical therapy alone were compared using the χ^2 or Fisher exact tests for categorical variables; the 2-tailed, unpaired *t* test or Wilcoxon rank sum test was used for continuous variables. The association of valve surgery with all-cause, 6-month mortality was determined using bivariate and multivariable Cox proportional hazard regression analyses[16] with consideration of clinically plausible interactions. Heterogeneity, defined as baseline features that were associated with mortality, was adjusted for in these Cox models. The proportional hazards assumption was confirmed by inspection of log (−log [survival]) curves and by examination of time-dependent covariates. Survival curves were constructed using Kaplan-Meier estimates with comparisons between curves based on the log-rank χ^2 statistic.

Since patients with endocarditis were not randomly assigned to medical therapy or valve surgery, potential confounding (ie, selection biases) was adjusted for by developing a propensity score for valve surgery treatment. The rationale and methods underlying the use of a propensity score for a proposed causal exposure variable have been previously described.[17,18] Stepwise logistic regression analyses were used to select baseline variables that were associated with valve surgery; clinically plausible interactions were included in these analyses. Variables that were clinically relevant but not significant in the initial logistic regression analyses were then added to derive a full nonparsimonious model. This model yielded a concordance index (*c* index) of 0.86 (95% confidence interval [CI], 0.82-0.89), indicating a strong ability to differentiate between patients receiving medical therapy and those undergoing surgery. Using these selected baseline variables, a propensity score for undergoing valve surgery for each patient was estimated by maximum likelihood logistic regression analysis.[19] This score ranged from 0.00 to 0.996 and reflected the probability that a patient would undergo valve surgery.

Using a macro previously described (available at http://www2.sas.com/proceedings/sugi26/p214-26.pdf), the propensity scores were used to match patients undergoing valve surgery to unique control patients.[20] Specifically, we sought to match each patient who had valve surgery to a patient who received medical therapy and had a propensity score that was identical to 5 digits. If this could not be done, we then proceeded to a 4-, 3-, 2-, or 1-digit match. If this threshold was exceeded, that patient who had valve surgery was excluded. Using this algorithm, we were able to match 109 patients who had valve surgery to 109 unique control patients treated with medical therapy alone. Further adjustments for confounding (using propensity scores) and heterogeneity (using baseline variables associated with mortality) were performed in additional Cox proportional hazards analyses.

Patient characteristics associated with the maximum mortality reduction from

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valve surgery were determined by subgroup analysis with a statistical test of interaction on the propensity-matched patients.[21] In these subgroup analyses, the only variables considered were those with clinical plausibility to affect the decision of whether to perform valve surgery.[21]

Appropriate regression diagnostics, including examination of residuals and testing for outliers, excessively influential observations, and multicollinearity, were performed to confirm the validity of these analyses. All analyses were conducted using SAS statistical software, version 8.02 (SAS Institute Inc, Cary, NC); $P<.05$ was considered statistically significant.

RESULTS

Patient Characteristics

In the cohort of 513 patients with complicated, left-sided native valve endocarditis, 499 (97%) met Duke criteria for definite endocarditis. Valve surgery was performed in 230 patients (45%): 109 (47%) had undergone mechanical valve replacement, 102 (44%) had undergone bioprosthetic valve replacement, and 20 (9%) had undergone valve repair (1 patient had undergone >1 procedure).

Baseline characteristics of patients who had valve surgery or received medical therapy are given in TABLE 1. Valve surgery was performed more often during the second half of the study period (ie, 1995-2000), and there were significant differences among hospitals in the frequency of valve surgery for endocarditis. Patients who had undergone valve surgery were more likely to be younger, white, and immunocompetent; they were also more likely to have a vegetation, intracardiac abscess or valve regurgitation by echocardiography, moderate to severe congestive heart failure, and clinical evidence of refractory infection (ie, persistent fever, persistent bacteremia, or fungemia). Patients who underwent valve surgery were less likely to have human immunodeficiency virus or AIDS, comorbid illnesses, or an abnormal mental status.

Associations of Baseline Features With 6-Month Mortality

Unadjusted analyses examined the relationship between baseline features and 6-month mortality for the total cohort. In these analyses, female sex ($P<.001$), older age ($P=.002$), immunocompromised state ($P<.001$), fever ($P=.02$, intracardiac abscess visualized on echocardiography ($P=.01$), comorbidity ($P<.001$), moderate to severe congestive heart failure ($P<.001$), abnormal mental status ($P<.001$), bacterial etiologies other than viridans streptococci ($P<.001$), elevated serum creatinine level ($P<.001$), and refractory infection ($P=.004$) were all statistically associated with 6-month mortality. Valve surgery was associated with reduced 6-month mortality (16% vs 33%; hazard ratio, 0.43; 95% CI, 0.29-0.63; $P<.001$).

Creation of Propensity Scores and Cohort Matching

To create a propensity score and matched cohort using baseline variables listed in Table 1, a nonparsimonious model was developed. Variables in this model included hospital site, human immunodeficiency virus infection, comorbidity, congestive heart failure, abnormal mental status, symptomatic or disabling emboli, fever, refractory infection, intracardiac abscess or new valve regurgitation on echocardiography, microbial etiology, valve involved, and number of embolic events. A comparison between propensity-matched patients (n=218) at baseline is given in TABLE 2. In contrast to the entire cohort (n=513), the 2 propensity-matched groups revealed no significant differences in baseline variables.

Valve Surgery and Mortality

In the total cohort (n=513), 131 patients (26%) died during a 6-month follow-up. As shown in TABLE 3, valve surgery was associated with a significant reduction in mortality in unadjusted Cox proportional hazards analyses. The association of valve surgery with reduced mortality remained when adjusted for heterogeneity (ie, baseline variables associated with 6-month mortality). In the propensity-matched group (n=218), valve surgery remained associated with reduced mortality compared with medical therapy alone (15% vs 28%; $P=.01$; Table 2 and FIGURE 1). As shown in Table 3, valve surgery remained associated with reduced mortality in propensity-matched patients after adjustment for both confounding (using propensity scores) and heterogeneity. In a supplementary analysis, exclusion of patients with possible endocarditis by Duke criteria did not materially alter the findings.

Characteristics Predictive of Maximum Mortality Benefit From Valve Surgery

By using subgroup analyses with statistical test of interaction, patients with moderate to severe congestive heart failure showed the greatest reduction in mortality with valve surgery. Stratifying the data by congestive heart failure among propensity-matched patients undergoing surgery revealed that among patients with none to mild congestive heart failure, valve surgery was not associated with reduced mortality compared with medical therapy (HR, 1.04; 95% CI, 0.43-2.48; $P=.93$). However, among propensity-matched patients with moderate to severe congestive heart failure, valve surgery was associated with a significant reduction in mortality compared with medical therapy (HR, 0.22; 95% CI, 0.08-0.53; $P=.01$; FIGURE 2).

COMMENT

In our cohort of 513 patients with complicated, left-sided native valve endocarditis, valve surgery was associated with a significant reduction in 6-month mortality. The reduction of mortality associated with valve surgery persisted in analyses that controlled for cohort heterogeneity (ie, other baseline variables that were associated with mortality) and confounding variables that were associated with the performance of valve surgery (ie, using propensity analyses). In a subset of the cohort (n=218) that was propensity matched, valve surgery was

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Table 1. Patient Characteristics According to Treatment Assignment[a]

Variable	Surgery (n = 230)	Medical Therapy (n = 283)	*P* Value
Year of admission, No. (%)			
1990-1994	104 (45)	160 (57)	.01
1995-2000	126 (54)	123 (43)	
Hospital, No. (%)[b]			
A	60 (26)	64 (23)	<.001
B	11 (5)	16 (6)	
C	3 (1)	7 (2)	
D	8 (3)	46 (16)	
E	77 (33)	81 (29)	
F	59 (26)	37 (13)	
G	12 (5)	32 (11)	
Demographics			
Men, No. (%)	156 (68)	175 (62)	.16
Age, mean (SD), y	53.0 (16.3)	56.6 (18.6)	.02
Race, No. (%)			
White	179 (78)	193 (68)	.02
Nonwhite	51 (22)	90 (32)	
Temperature >38.0°C, No. (%)	50 (22)	83 (29)	.06
Comorbidities, No. (%)			
Immunocompromised state[c]	40 (17)	84 (30)	.001
HIV infection	9 (4)	41 (14)	<.001
AIDS	1 (<1)	22 (8)	<.001
History of injection drug use	48 (21)	79 (28)	.07
Charlson comorbidity score ≥2[d]	63 (27)	130 (46)	<.001
Congestive heart failure, No. (%)[e]			
None to mild	108 (47)	183 (65)	<.001
Moderate to severe	122 (53)	100 (35)	
Mental status, No. (%)			
Lethargic or disoriented	26 (12)	58 (21)	.01
Alert	189 (88)	219 (79)	
Organisms isolated in blood culture, No. (%)			
Staphylococcus aureus	53 (23)	90 (32)	.09
Viridans streptococci	86 (37)	96 (34)	
Others[f]	91 (40)	97 (34)	
Serum creatinine, mean (SD), mg/dL	2.0 (2.2)	1.8 (2.1)	.46
Echocardiographic findings[g]			
Ejection fraction, mean (SD)	57.1 (9.9)	57.3 (11.3)	.88
Vegetation, No. (%)	199 (87)	218 (77)	.006
Intracardiac abscess, No. (%)	34 (15)	7 (2)	<.001
New valvular regurgitation No. (%)[h]	170 (74)	150 (53)	<.001
Symptomatic or disabling emboli, No. (%)[i]	99 (43)	102 (36)	.11
Fungemia, No. (%)	3 (1)	2 (1)	.66
Refractory infection No. (%)[j]	65 (28)	39 (14)	<.001
6-Month mortality, No. (%)	37 (16)	94 (33)	<.001

Abbreviations: HIV, human immunodeficiency virus; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
SI conversion: To convert serum creatinine from mg/dL to mmol/L multiply by 88.4.
[a]Percentages may not sum to 100 due to rounding.
[b]*P* value refers to a comparison among hospitals of the proportion of patients who underwent valve surgery.
[c]Patients with HIV, AIDS, solid organ or bone marrow transplantation, receiving steroids (≥20 mg daily of prednisone or equivalent for >1 month), end-stage renal disease, or recent chemotherapy (<1 month).
[d]Scale assigned weights as specified in the "Methods" section.
[e]None to mild: (1) absence of rales on examination, (2) no shortness of breath at rest, and (3) no pulmonary edema on chest radiograph; moderate: presence of only 1 or 2; and severe: presence of all 3 symptoms.
[f]Others included: *Enterococcus,* other streptococci, coagulase-negative *Staphylococcus*, Enterobacteriaceae, other gram-negative rods, HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella*) group of organisms, fungi, and culture-negative endocarditis.
[g]Represents echocardiographic findings on TEE if patient underwent both TEE and TTE or TEE alone; otherwise, represents finding on TTE.
[h]Regurgitation demonstrated on echocardiography during current episode of endocarditis with no evidence of regurgitation on a prior echocardiogram. In the absence of a prior echocardiogram, regurgitation was seen for the first time during the current episode.
[i]Symptomatic: patients with symptoms as a direct consequence of embolic phenomenon that were not disabling (includes cerebrovascular, joint, major artery, eye, spleen, liver, kidney, and skin emboli); disabling: stroke syndrome, blindness, or major arterial emboli (emboli to extremities requiring amputation, mesenteric arterial emboli leading to intestinal infarction, or coronary emboli resulting in myocardial infarction).
[j]Persistent fever or recurrent bacteremia for more than 7 days after initiation of effective antibiotic therapy, or presence of myocardial abscess on TTE or TEE.

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Table 2. Selected Patient Characteristics According to Treatment Assignment in Propensity-Matched Patients[a]

Variable	Surgery (n = 109)	Medical Therapy (n = 109)	*P* Value
Year of admission, No. (%)			
1990-1994	46 (42)	58 (53)	.10
1995-2000	63 (58)	51 (47)	
Hospital, No. (%)			
A	27 (25)	35 (32)	.06
B	5 (5)	9 (8)	
C	1 (1)	5 (5)	
D	6 (6)	6 (6)	
E	42 (39)	30 (28)	
F	19 (17)	17 (16)	
G	9 (8)	7 (6)	
Demographics			
Men, No. (%)	75 (69)	73 (67)	.77
Age, mean (SD), y	53 (15)	55 (19)	.34
Race, No. (%)			
White	87 (80)	82 (75)	.42
Nonwhite	22 (20)	27 (25)	
Temperature >38.0°C, No. (%)	25 (23)	26 (24)	.87
Comorbidities, No. (%)			
Immunocompromised state[b]	20 (18)	23 (21)	.61
HIV infection	6 (6)	6 (6)	.99
AIDS infection	1 (1)	3 (3)	.31
History of injection drug use	20 (18)	28 (26)	.19
Charlson comorbidity score ≥2[c]	36 (33)	42 (39)	.40
Congestive heart failure, No. (%)[d]			
None to mild	67 (61)	68 (62)	.89
Moderate to severe	42 (39)	41 (38)	
Mental status, No. (%)			
Lethargic or disoriented	13 (12)	14 (13)	.84
Alert	96 (88)	95 (87)	
Organisms isolated in blood culture, No. (%)[e]			
Staphylococcus aureus	27 (25)	30 (28)	.69
Viridans streptococci	36 (33)	37 (34)	
Others[f]	46 (42)	42 (39)	
Serum creatinine, mean (SD), mg/dL	2.0 (2.3)	1.8 (1.9)	.50
Echocardiographic findings			
Ejection fraction, mean (SD), %	58.0 (9.0)	57.2 (11.3)	.59
Vegetation, No. (%)	89 (82)	90 (83)	.86
Intracardiac abscess, No. (%)	2 (2)	5 (5)	.25
New valvular regurgitation, No. (%)[g]	72 (66)	69 (63)	.67
Symptomatic or disabling emboli, No. (%)[h]	41 (38)	45 (41)	.58
Fungemia, No. (%)	1 (1)	1 (1)	.99
Refractory infection, No. (%)[i]	16 (15)	20 (18)	.47
6-Month mortality, No. (%)	16 (15)	31 (28)	.02

Abbreviations: HIV, human immunodeficiency virus; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
SI conversion: To convert serum creatinine from mg/dL to mmol/L multiply by 88.4.
[a]Percentages may not sum to 100 due to rounding.
[b]Patients with HIV, AIDS, solid organ or bone marrow transplantation, receiving steroids (≥20 mg of prednisone or equivalent for >1 month), end-stage renal disease, or recent chemotherapy (<1 month).
[c]Scale assigned weights as specified in the "Methods" section.
[d]None to mild: (1) absence of rales on examination, (2) no shortness of breath at rest, and (3) no pulmonary edema on chest radiograph; moderate: presence of only 1 or 2; and severe: presence of all 3 symptoms.
[e]Any others include: *Enterococcus,* other streptococci, Coagulase negative *Staphylococcus*, Enterobacteriaceae, other gram-negative rods, HACEK (see Table 1 footnote for definition) group of organisms, fungi, and culture negative endocarditis.
[f]Represents echocardiographic findings on TEE if patient underwent both TEE and TTE or TEE alone; otherwise, represents finding on TTE.
[g]Regurgitation demonstrated on echocardiography during current episode of endocarditis with no evidence of regurgitation on a prior echocardiogram. In the absence of a prior echocardiogram, regurgitation was seen for the first time during the current episode.
[h]Symptomatic: patients with symptoms as a direct consequence of embolic phenomenon that were not disabling (includes cerebrovascular, joint, major artery, eye, spleen, liver, kidney, and skin emboli); disabling: stroke syndrome, blindness, or major arterial emboli (emboli to extremities requiring amputation, mesenteric arterial emboli leading to intestinal infarction, or coronary emboli resulting in myocardial infarction).
[i]Persistent fever or recurrent bacteremia for more than 7 days after initiation of effective antibiotic therapy, or presence of myocardial abscess on TTE or TEE.

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associated with the greatest reduction in mortality for patients with moderate to severe congestive heart failure and not observed in patients with none to mild heart failure.

Since the advent of surgical therapy for infective endocarditis, decisions about surgery are often problematic due to the lack of evidence from prospective randomized controlled trials. Uncontrolled observational studies have suggested benefit of surgical therapy compared with medical therapy alone for patients with native valve endocarditis complicated by congestive heart failure, myocardial abscess, and acute valvular dysfunction.[22-28] However, controversy remains despite the suggestions of these observations and the clinical plausibility of the benefits of valve surgery for these clinical complications and others (eg, visible vegetations on echocardiography, major organ emboli, fungal endocarditis).[3,7-10,29-31] Given the potential ethical and logistical constraints of conducting a randomized controlled trial of surgery vs medical therapy for patients with native valve endocarditis, uncontrolled observational data and clinical experience have fostered current recommendations.

In this study, a large cohort of adults with complicated, left-sided native valve endocarditis was analyzed to evaluate the impact of valve surgery on mortality. To control for the inherent biases of treatment selection and baseline prognostic heterogeneity, propensity analyses and multivariable Cox modeling were performed. Recent studies[32,33] have shown that, if these inherent biases are rigorously controlled for, observational studies can achieve estimates of the effects of therapeutic interventions that are remarkably similar to randomized controlled trials.

Using this rigorously identified cohort to study the association of valve surgery with 6-month mortality, several observations emerged. First, in an unadjusted bivariate analysis of the entire cohort of 513 adults, valve surgery was associated with reduced mortality. This was expected and corroborated findings in other cohorts in which there was no adjustment for bias in treatment selection or baseline prognostic imbalances among patients. However, when multivariable Cox modeling was used to adjust for heterogeneity in baseline prognostic features, valve surgery remained associated with reduced mortality (Table 3). Second, when propensity analyses were used to match patients and adjust for confounding factors that affect treatment selection, valve surgery remained associated with reduced mortality (Figure 1). This association of valve surgery with reduced mortality persisted in the propensity-matched group (n=218) when adjusting for both confounding factors and heterogeneity in baseline prognosis (Table 3). Third, among propensity-matched patients, the association between valve surgery and reduced mortality was strongest for those with moderate to severe congestive heart failure (Figure 2). These observations corroborate recent uncontrolled studies of patients with native valve endocarditis complicated by congestive heart failure in which mortality was reduced by valve surgery.[34-39]

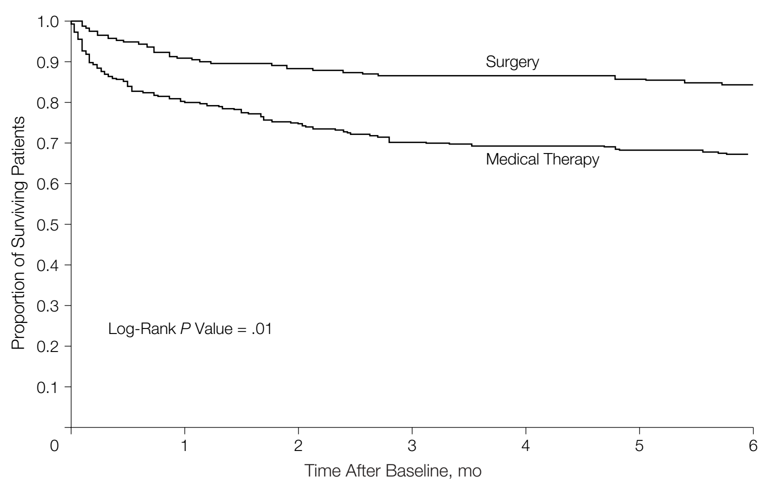
There were several advantages to the design of our cohort study, and we avoided the methodological limitations of previous work. First, the cohort itself had several advantages as previously described.[2] Among the ad-

Table 3. Cox Proportional Hazards Analyses of Time to Death Among Patients Undergoing Valve Surgery

Model	Hazard Ratio (95% CI)	*P* Value
Total cohort (n = 513)		
Unadjusted	0.43 (0.29-0.63)	<.001
Heterogeneity adjusted*	0.35 (0.23-0.54)	<.001
Propensity-matched group (n = 218)†		
Unadjusted	0.45 (0.23-0.86)	.02
Adjusted for confounding‡	0.45 (0.24-0.88)	.02
Adjusted for confounding and heterogeneity	0.40 (0.18-0.91)	.03

*Heterogeneity represents baseline variables associated with mortality. Factors included hospital site, Charlson comorbidity score, congestive heart failure, microbiology, immunocompromised state, abnormal mental status, and refractory infection.
†Propensity-matched group includes patients undergoing surgery vs medical therapy that are matched one to one based on their propensity score.
‡Confounding represents patient selection bias due to nonrandomized assignment of treatment. Propensity score derived from logistic equation for each patient is incorporated as a continuous variable into outcomes analysis to adjust for possible confounding.

Figure 1. Kaplan-Meier Curve Relating Valve Surgery to Time to Death Among Propensity-Matched Patients



No. at Risk							
Surgery	109	98	96	94	94	93	92
Medical Therapy	109	89	86	81	81	80	77

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vantages were its large size (513 adults), the explicit definition of baseline state, the minimization of bias in outcome detection using the National Death Index to supplement medical record information, the use of a validated index of comorbidity,[12] and the restriction to patients with endocarditis on left-sided native valves who exhibited complications at baseline for which valve surgery is considered in current practice (ie, congestive heart failure, new valvular regurgitation, systemic embolization to major organs, refractory infection, or the presence of an echocardiographically identifiable vegetation). Our strict inclusion criteria are evident by the fact that 97% of our cohort met Duke criteria for definite endocarditis and 94% had organisms isolated in blood culture.[2] The selected study period (1990-2000) was representative of contemporary practice in which transesophageal echocardiography is used in the diagnosis of endocarditis and its complications.[40,41]

Second, our explicit definition of baseline (ie, the date of surgery or the date that the decision not to operate was noted in the medical record) fostered reproducibility in assessment of baseline variables that affect mortality in our multivariable Cox modeling (ie, adjustment for heterogeneity) as observed in a previous study.[2] This definition resulted in the same median duration of time from hospital admission to baseline for patients who underwent valve surgery and those who did not (6 days; comparing medically and surgically treated patients, $P = .97$).

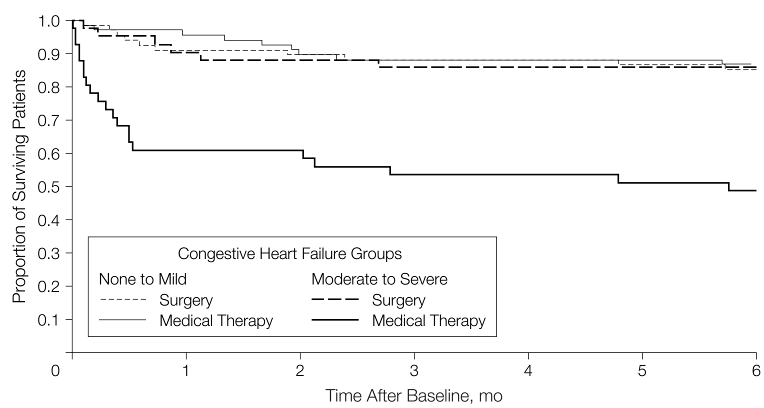
Third, our propensity analysis allowed us to control for unavoidable biases in treatment selection among observational cohorts and to develop a propensity-matched cohort to evaluate the association of valve surgery and 6-month mortality.[17-19] Other investigations have demonstrated the value of propensity analyses to evaluate effects of treatment interventions and clinical outcome in observational cohorts.[20,42,43]

Despite these advantages, our study had limitations. First, our cohort was assembled retrospectively, raising the possibility of bias in detection of baseline clinical features and clinical outcome 6 months later. However, our rigorous definitions of baseline state and use of 6-month mortality as the study end point reduced this potential bias as previously observed.[2] Second, although 6-month mortality had methodological advantages as a clinical outcome, it limited the assessment of the impact of valve surgery. The association of valve surgery with other clinically relevant outcomes (recurrent organ embolization, stroke, recurrent hospitalization, and other measures of quality of life) would be important to investigate and could not be determined in our study. Third, although the propensity-matched cohort demonstrated that the association of valve surgery with reduced mortality was limited to the subgroup of patients with moderate to severe congestive heart failure, the propensity matching process reduced this analysis to only 218 patients of the total cohort. This compromised our ability to optimally analyze the subgroup with intracardiac abscess, which included only 7 patients in the matched cohort. Fourth, our definition of baseline as the date of surgery (or the date of the decision not to operate) had methodological advantages, but its disadvantage was that it prevented an analysis of the association of timing of valve surgery on clinical outcome; future investigation is needed for this difficult but clinically important issue.

The major limitation of this study is that valve surgery was not based on a prospective randomized assignment and therefore susceptible to bias. Although our use of propensity analyses to adjust for confounding in treatment selection was intended to control for this bias, they cannot completely control the effect of confounding. The propensity analyses can only adjust for the factors that were measured in the cohort and are only as accurate as the data collection.

Despite these limitations, the association between valve surgery and reduced mortality from complicated, left-sided native valve endocarditis fulfilled several criteria of causality.[44] The association was strong, with close to 50% reduction in mortality in the propensity-matched group, a temporal pattern was evident, and biological plau-

Figure 2. Kaplan-Meier Curve Relating the Effect of Congestive Heart Failure to Time to Death Among Propensity-Matched Patients Receiving Medical Therapy or Surgery



No. at Risk							
None to Mild CHF Group							
Surgery	67	60	59	58	58	57	56
Medical Therapy	68	64	61	59	59	59	57
Moderate to Severe CHF Group							
Surgery	42	37	36	35	35	35	35
Medical Therapy	41	24	24	21	21	20	19

CHF indicates congestive heart failure.

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sibility exists given that the source of infection was physically excised and the valvular dysfunction repaired. Our results provide the strongest observational evidence to date of the potential value of valve surgery in adults with complicated, left-sided native valve endocarditis, particularly those with moderate to severe congestive heart failure. Although corroborating evidence from a randomized controlled trial would be desirable, in their absence our findings can provide assistance to the decision of whether to perform valve surgery in adults with native valve endocarditis.

Author Contributions: Dr Vikram had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Vikram, Hasbun, Quagliarello.
Acquisition of data: Vikram, Hasbun.
Analysis and interpretation of data: Vikram, Buenconsejo, Quagliarello.
Drafting of the manuscript: Vikram, Buenconsejo, Hasbun, Quagliarello.
Critical revision of the manuscript for important intellectual content: Vikram, Buenconsejo, Quagliarello.
Statistical expertise: Buenconsejo, Quagliarello.
Obtained funding: Quagliarello.
Administrative, technical, or material support: Vikram, Hasbun.
Study supervision: Quagliarello.
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