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Background—The impact of early surgery on mortality in patients with native valve endocarditis (NVE) is unresolved. This study sought to evaluate valve surgery compared with medical therapy for NVE and to identify characteristics of patients who are most likely to benefit from early surgery.

Methods and Results—Using a prospective, multinational cohort of patients with definite NVE, the effect of early surgery on in-hospital mortality was assessed by propensity-based matching adjustment for survivor bias and by instrumental variable analysis. Patients were stratified by propensity quintile, paravalvular complications, valve perforation, systemic embolization, stroke, *Staphylococcus aureus* infection, and congestive heart failure. Of the 1552 patients with NVE, 720 (46%) underwent early surgery and 832 (54%) were treated with medical therapy. Compared with medical therapy, early surgery was associated with a significant reduction in mortality in the overall cohort (12.1% [87/720] versus 20.7% [172/832]) and after propensity-based matching and adjustment for survivor bias (absolute risk reduction [ARR] −5.9%, $P<0.001$). With a combined instrument, the instrumental-variable–adjusted ARR in mortality associated with early surgery was −11.2% ($P<0.001$). In subgroup analysis, surgery was found to confer a survival benefit compared with medical therapy among patients with a higher propensity for surgery (ARR −10.9% for quintiles 4 and 5, $P=0.002$) and those with paravalvular complications (ARR −17.3%, $P<0.001$), systemic embolization (ARR −12.9%, $P=0.002$), *S aureus* NVE (ARR −20.1%, $P<0.001$), and stroke (ARR −13%, $P=0.02$) but not those with valve perforation or congestive heart failure.

Conclusions—Early surgery for NVE is associated with an in-hospital mortality benefit compared with medical therapy alone. **(*Circulation*. 2010;121:1005-1013.)**

Key Words: surgery ■ endocarditis ■ drug therapy ■ hospital mortality

Native valve endocarditis (NVE) is associated with mortality rates of 15% to 30%, and despite advances in diagnosis and treatment, mortality rates remain largely unchanged.[1–5] Consensus guidelines for the treatment of NVE advocate the use of early valve surgery for complications such as congestive heart failure, systemic embolization, or intracardiac damage, but there are insufficient data to support such recommendations.[6] Ethical, logistical, and financial

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All of the members of the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) are listed in the Appendix in the online-only Data Supplement.

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issues create major challenges to the performance of randomized controlled treatment trials for this relatively infrequent disease. Hence, investigators have focused on observational studies to compare outcomes in patients treated with surgery versus medical therapy for NVE using techniques such as propensity analyses to control for bias related to measured patient characteristics. However, these techniques do not adjust for survivor bias (patients who live longer are more likely to undergo surgery than patients who die early) or hidden bias (unmeasured patient characteristics that affect both the decision to treat and the outcome).[7,8]

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To date, 6 propensity analyses evaluating treatment strategies for NVE have been performed.[2–5,9,10] Two studies reported a significant reduction in 6-month and 5-year mortality associated with valve surgery.[2,3] A third study reported that the in-hospital mortality benefit of surgery was limited to patients with the highest propensity scores for surgery.[5] In contrast, other studies have demonstrated either no benefit or increased mortality associated with surgery.[4,9,10] This disparity in results is compounded by methodological limitations, including retrospective data collection, small sample sizes, and single-center studies. Finally, although the reported propensity-score analyses have controlled for overt or measured bias, none of these studies have adjusted for hidden bias.[7]

The objectives of the present study were to assess whether early surgery is associated with lower in-hospital mortality compared with medical therapy and to determine whether this association varied by propensity or specific indications for early surgery. We used a prospective, multinational cohort of patients with NVE and used statistical methods to control for treatment-selection bias, survivor bias, and hidden bias.

Methods

Study Population and Clinical Data

The cohort for the present study was obtained from the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) database, which contains 2760 patients with definite infective endocarditis (IE) as defined by the modified Duke criteria.[11] The background and inclusion criteria of this prospective, multicenter, international registry of IE have been reported previously.[1,12] Briefly, data on patients with IE from 61 centers in 28 countries were collected prospectively between June 2000 and August 2005. The study was approved by the institutional review board or ethics committee at all of the participating sites.

Only patients who had definite left- or right-sided NVE, based on modified Duke criteria,[11] were included in the present study. Patients with the following characteristics were excluded: injection drug use, prosthetic valves, non–native-valve IE (eg, pacemaker IE); receipt of surgery before admission; and missing values for gender, receipt of surgery, and in-hospital death. 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. All of the variables related to complications or outcomes of NVE had data collected for ≥97% of patients. Missing values for clinical outcomes were imputed with the negative category for categorical variables.

Definitions

Definitions of the variables have been reported elsewhere.[13] *Early surgery* was defined as replacement or repair of the affected valve during the initial hospitalization for IE. *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. *Systemic embolization* was defined as embolism to any major arterial vessel, excluding stroke. Healthcare-associated IE consisted of either nosocomial or nonnosocomial healthcare–associated infection.[14]

Analytical Plan

We used an observational cohort to estimate the impact of early surgery on mortality with statistical methods to control for overt and hidden biases. Overt treatment bias, related to covariates measured in the study, was addressed by use of propensity-score matching and multivariate regression analysis. To eliminate survivor bias, each patient in the medical therapy group was required to have survived at least as long as the time to surgery in the matched surgically treated patient. Instrumental variable analysis was used to control for all types of potential bias, including hidden or unmeasured bias. We also performed a subgroup analysis stratifying patients by propensity-score quintiles, paravalvular complications such as an abscess or fistula, valve perforation, systemic embolization, stroke, congestive heart failure, or *Staphylococcus aureus* infection.

Standardized differences between the 2 treatment groups were calculated as the differences in the means divided by the pooled standard deviation and expressed as a percentage. The primary outcome was all-cause mortality during initial hospitalization. Differences in mortality between treatment groups are reported in terms of absolute risk reduction (ARR) and odds ratios, in accordance with recent recommendations.[15,16] A 2-sided probability value <0.05 was considered statistically significant. All analyses were performed with STATA software, version 10 (StataCorp, College Station, Tex).[17]

Propensity-Score Matching

A propensity score, which was the estimated probability that a patient would undergo early surgery, was calculated for each patient. The propensity score was computed with nonparsimonious multivariable logistic regression, with early surgery as the dependent variable; it incorporated 25 clinically relevant covariates and 3 interaction terms as the independent variables (Table I in the online-only Data Supplement).

Patients undergoing early surgery were matched on a 1-to-1 basis with patients treated medically on the basis of the following: (1) propensity score, by use of nearest-neighbor matching with replacement (each medical therapy patient could be used more than once for matching, whereas surgically treated patients were matched once only) and a matching tolerance (caliper) of 0.05; and (2) follow-up times, such that each patient in the medical group survived at least as long as the time to surgery in the surgical patient.

Instrumental Variable Analysis

The present study used an observational cohort, and therefore, assignment to early surgery or medical therapy depended on patient characteristics rather than randomization. Given the limitations of observational data collection, omission of covariates that influence treatment assignment and the associated outcome may have occurred. The conventional probit (or logit) approach assumes that after controlling for measured characteristics of the patient, there are no unmeasured characteristics that influence both the decision to treat and the outcome of treatment. Instrumental variable analysis is an econometric method used to control for the possible existence of hidden bias (ie, caused by the omission of relevant covariates).[7] We evaluated several candidate instrumental variables (separately and as a combined instrument) with the following key characteristics: (1) high correlation with early surgery and (2) no effect on mortality

Table 1. Characteristics of Patients With NVE Treated With Early Surgery Versus Medical Therapy

	Overall Cohort			Propensity-Matched Cohort With Adjustment for Survivor Bias		
Characteristics	Early Surgery (n=720)	Medical Therapy (n=832)	Standardized Difference*	Early Surgery (n=619)	Medical Therapy (n=619)	Standardized Difference*
Male gender	72.9	66.1	14.8	73.2	70.8	5.4
Age, mean, y	53	61	45.8	53.4	53.1	1.3
Chronic illness†	48.1	67.2	38.8	49.3	48.9	0.6
Duration of symptoms >1 mo before presentation	29.7	19.7	23.3	27.6	23.9	8.5
Transfer from another facility	59	29.3	60	59.9	61.6	3.3
Healthcare-associated infection	27.2	38	22.9	27.8	33.1	11.6
Transesophageal echocardiography performed	75.0	66.2	19.2	73.5	80.3	16.1
Transesophageal echocardiographic evidence of endocarditis	70.3	61.2	19.1	68.5	74.8	14.0
New valvular regurgitation	85.6	60.3	56.2	85.3	82.9	6.6
Aortic	54.2	22.4	65.8	53.2	48.1	10.0
Mitral	41.7	39.2	5.1	41.5	39.1	4.9
Tricuspid	5.4	7.3	7.8	6.0	4.8	5.0
New valvular vegetations‡	90.4	88.8	5.2	90.3	91.4	3.9
Aortic	52.1	34.5	35.6	51.9	53.3	2.9
Mitral	44.4	51.7	14.5	43.9	41.7	4.6
Tricuspid	6.1	9.5	12.5	6.3	3.7	11.8
Paravalvular complications§	23.8	4.3	57.1	22.1	17.8	10.9
Valve perforation‡	16.8	6.6	32.1	16.6	14.7	5.3
Stroke	16	19.6	9.4	16.3	16.2	0.4
Intracranial hemorrhage	3.5	4.7	6.1	3.6	1.9	9.9
Systemic embolization‖	25	21.5	8.3	25.0	28.1	6.9
Congestive heart failure	44.9	24.8	42.4	44.4	42.5	3.9
Pulmonary edema	28.2	14.7	33.2	29.4	31.8	5.3
Intracardiac abscess¶	20.7	4.6	49.5	20.5	14.4	16.2
Persistent bacteremia	6.7	9.7	11.1	7.1	8.2	4.2
Blood microorganism						
S aureus	19.7	34.6	33.3	20.2	19.5	1.6
Coagulase-negative staphylococcus	11.4	6	19.3	11.3	14.5	9.6
Viridans group streptococci	19.9	22.7	7	19.1	19.1	0.0
Enterococcus species	10.7	11.7	3.1	10.3	15.0	14.1
Culture negative	13.9	4.8	31.7	13.9	11.3	7.8
In-hospital death	12.1	20.7	23.0	11.8	17.4	16.0

Values are percentages unless otherwise indicated.

*Standardized difference is the mean difference divided by the pooled standard deviation, expressed as a percentage.

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

‡Based on transesophageal or transthoracic echocardiography.

§Transesophageal or transthoracic echocardiographic evidence of paravalvular abscess or fistula formation.

‖Includes embolism to any major arterial vessel, excluding stroke.

¶Based on echocardiographic evidence or intraoperative finding of intracardiac abscess.

independent of its effect through early surgery. A combined instrument consisting of the following variables fulfilled these criteria: evidence of NVE on transthoracic echocardiography, echocardiography performed at the referral hospital, duration of symptoms greater than 1 month before presentation, site-specific rate of early surgery for NVE, transfer from another hospital, and performance of transesophageal echocardiography. The specific instrumental variable estimation method we used is a STATA routine called BIPROBIT. This is a simultaneous maximum-likelihood procedure that estimates equations for mortality and treatment simultaneously, to enhance the efficiency (precision) of the estimates.[18,19] This bivariate probit (biprobit) model also explicitly takes into account the fact that both the outcome (mortality) and the treatment (surgery) are "0, 1" indicator variables. To evaluate whether early surgery was an exogenous variable in the mortality model (ie, the effect of early surgery on mortality was independent of all measured and unmeasured covariates), we performed a χ^2 test of the null hypothesis that early surgery is exogenous.

Table 2. Unadjusted and Adjusted ARRs and Odds Ratios for Mortality Associated With Early Surgery and Medical Therapy

Risk-Adjustment Method for In-Hospital Mortality	ARR, %*	*P*	Odds Ratio	95% Confidence Interval
Unadjusted	−8.6	<0.001	0.53	0.40–0.70
Logistic regression†	−5.9	<0.001	0.56	0.38–0.82
Propensity matched, survivor-bias adjusted‡	−5.9	<0.001	0.55	0.31–0.96
Instrumental-variable adjusted§	−11.2	<0.001	0.44	0.33–0.59

*A negative value represents the percent difference in mortality between patients undergoing early surgery and medical therapy, in favor of early surgery.

†Logistic regression of mortality against 27 measured covariates and 5 interaction terms (see Table II in the online-only Data Supplement).

‡Patients matched on the basis of the propensity for surgery (see Table I in the online-only Data Supplement for propensity-score model) and follow-up times such that each patient in the medical therapy group survived at least as long as the time to surgery in the surgically treated patient. Logistic regression was performed with clustered standard errors, to account for matching with replacement, and interaction terms.

§Using the combined instrument, 22 measured covariates, and 5 interaction terms as the independent variables and mortality and early surgery as the dependent variable. Independent variable analysis was performed with the bivariate probit (biprobit) method.

Subgroup Analysis

Clinically plausible variables known to affect the decision to perform valve surgery were used to perform subgroup analysis to determine characteristics associated with maximum mortality benefit. The propensity-matched, survivor-bias–adjusted cohort (n=1238 patients) was divided into quintiles based on the propensity scores for surgical patients, and the differential in-hospital mortality between matched surgical and medically treated patients in each quintile was then computed. Patients were also stratified by presence or absence of paravalvular complications, valve perforation, systemic embolization, stroke, *S aureus* infection, or congestive heart failure. The subgroup analysis was performed by adding interaction terms to the logistic regression model. In the propensity analysis of the effects of surgery, clustered standard errors were estimated to account for matching with replacement of controls, and the reported probability values reflect this.

Results

The ICE-PCS cohort consisted of 2760 patients, including 1859 (67%) with NVE. Of these, 1552 (83%) qualified for the present study (Figure I in the online-only Data Supplement). Seven hundred twenty (46%) patients underwent early surgery, and 832 (54%) were treated with medical therapy (Table 1). Patients who were treated with early surgery were younger; more likely to be male and to have transferred from another medical facility; and more likely to have complications such as congestive heart failure, intracardiac abscess, and paravalvular complications. The median time from admission to surgery was 7 days (quintile 1 to quintile 3: 2 to 17 days). *S aureus* was the most common pathogen in patients receiving medical therapy. Early surgery was associated with a significant reduction in mortality in an unadjusted univariate analysis (12.1% versus 20.7%; ARR −8.6%, $P<0.001$) and after controlling for all of the other measured covariates by standard logistic regression analysis (ARR −5.9%, $P<0.001$; Table II in the online-only Data Supplement). The latter model had a concordance index of 0.83, which indicates a strong ability to discriminate between possible outcomes (ie, in-hospital survival versus death).

To control for observed differences in patient characteristics, we estimated the probability of surgery (propensity

Table 3. Early Surgery Versus Medical Therapy for NVE: Effect on In-Hospital Mortality Across Subgroups

	Propensity-Matched Cohort With Adjustment for Survivor Bias			
	Early-Surgery Patients in Each Group, n	ARR,* %	*P*†	*P* for Difference‡
Total cohort	619	−5.9	<0.001	
Propensity quintile§				
1st	124	−5.3	0.142	
2nd	124	0.1	0.984	
3rd	124	0.1	0.964	
4th	124	−17.8	0.002	
5th	123	−4.8	0.214	
Paravalvular complications‖				0.009
No	482	−3.1	0.06	
Yes	137	−17.3	<0.001	
Valve perforation¶				0.55
No	516	−6.2	0.002	
Yes	103	−3.5	0.392	
Systemic embolization#				0.04
No	464	−3.4	0.052	
Yes	155	−12.9	0.002	
Stroke				0.15
No	518	−4.5	0.01	
Yes	101	−13.0	0.02	
S aureus infection				<0.001
No	494	−2.3	0.148	
Yes	125	−20.1	<0.001	
Congestive heart failure				0.17
No	344	−8.3	0.002	
Yes	275	−3.4	0.188	

*A negative value represents the percent point reduction in mortality for patients undergoing early surgery compared with those treated with medical therapy.

†*P* based on logistic regression using propensity-matched, survivor bias–adjusted cohort with clustered standard errors and interaction terms.

‡Indicates the difference across strata for the variable.

§Quintiles based on the propensity scores for surgical patients. Differential mortality benefit of surgery was observed in combined quintile 4 and 5 stratum (ARR −10.9%, $P=0.002$) versus stratum with quintiles 1 through 3 (ARR −2.4%, $P=0.2$; *P* for difference=0.029).

‖Transesophageal or transthoracic echocardiographic evidence of paravalvular abscess or fistula formation.

¶Based on transesophageal or transthoracic echocardiography.

#Includes embolism to any major arterial vessel, excluding stroke.

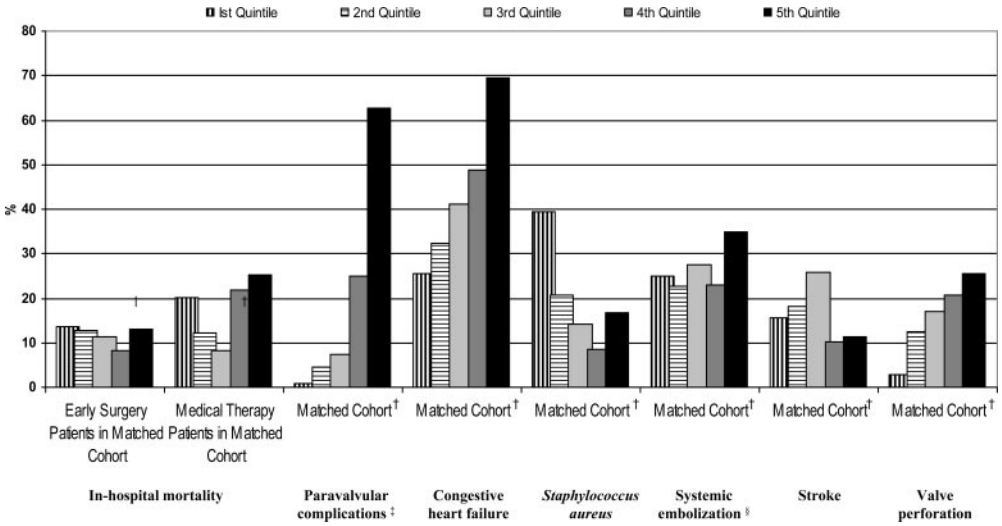

Figure. Distribution of key characteristics of the propensity-matched, survivor-bias–adjusted cohort of patients with NVE by surgical propensity-score quintiles. *Propensity-matched, survivor-bias–adjusted cohort (n=1238 or 169 matched pairs); quintiles based on propensity scores. †Frequency based on the propensity-matched, survivor-bias–adjusted surgery and medical therapy patients within each quintile. Percentages calculated as fraction of patients with outcome (eg, paravalvular complication) out of total number of patients in the quintile. ‡Transesophageal or transthoracic echocardiographic evidence of paravalvular abscess or fistula formation.

score) for each patient. After nearest-neighbor propensity-score matching with replacement and adjustment for survivor bias, 619 patients who underwent early surgery were each matched with a medical therapy patient to yield a quasi-randomized sample. Of the 619 medical therapy control subjects used for matching with replacement, 120 (19.4%) were selected more than once. Standardized differences between covariates in the 2 treatment groups decreased substantially after propensity matching and survivor bias adjustment (Table 1). The mortality benefit associated with early surgery persisted after propensity matching, adjustment for survivor bias, and controlling for confounders (ARR −5.9, $P<0.001$; Table 2).

Next, instrumental variable analysis (with the biprobit technique) was performed to adjust for hidden bias. Candidate variables for this composite instrumental variable were selected on the basis of clinical judgment that each would influence or increase the probability of surgical treatment without otherwise being associated with in-hospital mortality. The c-statistic for the surgery equation in the biprobit model was 0.86. The Hosmer-Lemeshow test statistic of 10.91 and associated probability value of 0.207 implied that we could not reject the null hypothesis of no difference between the observed values of surgery and the values predicted by the surgery equation. The instrumental-variable–adjusted mortality reduction with early surgery versus medical therapy was −11.2% ($P<0.001$). We were unable to reject the hypothesis that early surgery was an exogenous variable (ie, its effects on mortality were independent of all of the measured and unmeasured covariates) in the mortality model ($\chi^2=0.51$, $P=0.48$). A comparison of the adjusted odds ratios and ARRs associated with early surgery and medical therapy is shown in Table 2.

To determine the impact of early surgery on mortality across different strata, subgroup analyses were performed on the matched cohort (Table 3). For the quintile-stratification analysis, patients were divided into 5 subgroups based on the propensity scores of surgical patients. The distribution of key characteristics across the propensity score quintiles is depicted in the Figure. With 1238 patients, this yielded approximately 248 patients (about half surgical and half medical therapy patients) per quintile. A differential benefit of surgery that favored patients with a higher propensity for surgery compared with those with a lower propensity score was observed (ARR −10.9% [$P=0.002$] for patients in quintiles 4 and 5 versus −2.4% in patients in quintiles 1 to 3 [$P=0.2$]; P for difference=0.029). A mortality benefit associated with early surgery was also found in patients with paravalvular complications, systemic embolization, *S aureus* NVE, and stroke but not in those with valve perforation or congestive heart failure. Finally, a differential, greater benefit of surgery was observed in the presence of paravalvular complications, systemic embolization, and *S aureus* NVE than in NVE without these characteristics.

Discussion

Early surgery is performed in a high percentage of patients with NVE, generally in patients with a complicated clinical course for whom medical therapy is deemed inadequate. During the last 3 decades, observational studies have yielded conflicting conclusions regarding the use of early surgery for complicated NVE, and optimal patient selection has not been determined.[2–5,9,10] The results of the present study demonstrate that early surgery is associated with significant in-hospital mortality benefit compared with medical therapy, even after adjustment for important biases such as treatment selection, survivorship, and hidden biases.

Table 4 summarizes the studies that have used propensity analysis to evaluate the effect of surgery for NVE. Although most studies have shown a mortality benefit associated with early surgery, others have demonstrated no benefit or possible harm. Tleyjeh et al[4] reported that surgery offered no signifi-

Table 4. Summary of Reported Propensity Analyses Evaluating the Impact of Surgery Compared With Medical Therapy in NVE

Reference (Year of Publication)	Years of Patient Accrual	Data Collection Method	No. Centers	Type of IE
Present study	2000–2005	Prospective	61 Centers, 28 countries	Left- and right-sided NVE
Sy et al[10] (2009)	1996–2006	Retrospective	2 Centers, Sydney, Australia	Left-sided NVE/PVE
Tleyjeh et al[4] (2007)	1980–1988	Retrospective	Single center, Minnesota	Left-sided NVE/PVE
Aksoy et al[2] (2007)	1996–2002	Prospective	Single center, North Carolina	Left-sided NVE/PVE
Cabell et al[5] (2005)	1984–1999	Retrospective	7 Centers, 5 countries	Left- and right-sided NVE
Mourvillier et al[9] (2004)	1993–2000	Retrospective	Single center, France	Left- and right-sided NVE/PVE
Vikram et al[3] (2003)	1990–2000	Retrospective	7 Centers, Connecticut	Left-sided NVE

CI indicates confidence interval; PVE, prosthetic valve endocarditis; and N/A, not applicable.

*No. of patients in surgery group:No. of patients in the medical therapy group. Propensity-score–based matching was performed in all studies except Sy et al[10] and Cabell et al.[5]

†Mortality rate in the matched cohort.

‡Adjustments as follows: treatment-selection bias=propensity-score–based method; survivor bias=patients in the medical therapy group survived at least as long as the time to surgery in the matched surgery patient, or with a time-dependent analysis that used proportional hazards; hidden bias=instrumental variable analysis.

§Not applicable: These studies did not use propensity matching. Sy et al[10] included propensity score as a covariate in the regression model for mortality; Cabell et al[5] compared mortality between surgical and medically treated groups within each propensity quintile.

||Mortality end point was defined as all-cause mortality during follow-up (median follow-up 5.2 years; interquartile range 2.5 to 8 years).

cant reduction in 6-month mortality (hazard ratio 0.92, 95% CI 0.48 to 1.76) after adjusting for treatment and survivor bias. There are several methodological differences in the design of the present study compared with these prior studies that may explain the disparate results. Prior investigations used retrospective, single-center data; included both NVE and prosthetic valve endocarditis in their analyses; and had different end points (eg, inpatient versus 6-month mortality).[3–5,9,10] Propensity-based matching reduces sample size (most studies have been limited to matched cohorts of ≤100 patients), thus reducing the power to detect small differences in mortality and to evaluate the efficacy of treatment strategies in the different propensity quintiles or other subgroups. In contrast, the present study used the largest contemporary, multinational cohort of prospectively enrolled patients and did not include patients with prosthetic valve endocarditis, for whom indications for surgery may differ from NVE. Even after matching on the basis of propensity scores and survival times, each treatment group had 619 patients. The present results indicate that early surgery was associated with an absolute reduction in mortality in the overall cohort of 5.9% to 11.2% compared with medical therapy; the number of patients needed to treat with early valve surgery to prevent 1 in-hospital death ranged from 9 to 17. This beneficial effect of early surgery is also discrepant from results reported recently by Bannay et al[20] of a study in which valve surgery was associated with an early increase in mortality within 14 days of surgery and the survival benefit of surgery was not evident until >6 months after surgery.

On a broader level, the present study used the technique of propensity modeling in a rigorous manner to evaluate nonrandomized treatment with surgery, which reflects the concerns raised by Austin[15] in his assessment of 44 cardiovascular studies. In addition to the large sample size and prospective nature of the present investigation, other advantages include (1) a thorough description of the matching method; (2) complete reporting of the balance in baseline variables between surgically treated and untreated patients; (3) appropriate statistical methods for estimating the effect of early surgery on in-hospital mortality, particularly adjustment for survival bias; and (4) appropriate statistical methods for subgroup analysis, including the use of interaction terms to account for any treatment differences in outcome that may be related to the patient subgroup and the use of clustered standard errors to account for matching with replacement of controls.[4]

Although surgery was shown to confer a mortality benefit over medical therapy alone for NVE in the overall cohort, important caveats are suggested from the subgroup analyses. Similar to results previously published by our group,[5] the benefit of early surgery was not distributed uniformly among all of the propensity quintiles. A differential benefit of surgery was observed in patients with strong indications for surgical intervention (ie, those in the combined fourth and

Table 4. Continued

No. NVE Patients/ Total Patients	No. Patients in Propensity Cohort*	Timing of Mortality End Point	Surgery/Medical Therapy Mortality Rate, %†	Biases Adjusted for in the Study‡	Hazard Ratio/Odds Ratio (95% CI)
1552/1552	634:634	In-hospital	11.8/17.4	Treatment-selection bias Survivor bias Hidden bias	0.44 (0.33–0.59)
169/223	62:161§	5 y‖	N/A§	Treatment-selection bias Survivor bias	0.77 (0.42–1.40)
356/512	93:93	6 mo	29/19.4	Treatment-selection bias Survivor bias	0.92 (0.48–1.76)
248/333	51:51	5 y	11.5/18	Treatment-selection bias	0.27 (0.13–0.55)
1516/1516	610:906§	In-hospital	N/A§	Treatment-selection bias	Quintiles§ 1: 2.38 (0.83–6.88) 2: 0.49 (0.19–1.22) 3: 0.52 (0.23–1.18) 4: 0.79 (0.46–1.35) 5: 0.21 (0.10–0.41)
146/228	27:27	In-hospital	Not reported	Treatment-selection bias	0.96 (CI not reported; $P=0.95$)
499/499	109:109	6 mo	15/28	Treatment-selection bias	0.40 (0.18–0.91)

fifth quintiles). Surgery was also found to confer a survival benefit among patients with paravalvular complications, systemic embolization, and stroke but not among those with valve perforation or congestive heart failure. In addition, a significant differential benefit of early surgery was observed in patients with *S aureus* NVE, yet our unadjusted analysis and prior reports show that patients with *S aureus* NVE are less likely to undergo early surgery because of healthcare-associated infection and multiple comorbid conditions.[2,3,5] Even after adjustment for treatment and survivor bias, patients with *S aureus* NVE who underwent early surgery had a 20.1% ARR in mortality compared with patients who received medical therapy (number needed to treat=5).

Propensity adjustment may be influenced by unmeasured variables, which necessitates the use of instrumental variable analysis to adjust for hidden biases. With the use of a single-instrument approach, it is less likely that the variable is inadvertently associated with mortality except via its effect on the intervention.[7,21] Even in a relatively large cohort of NVE patients, we were unable to predict the instrumented values of early surgery with adequate precision using a single variable. With the use of a combined instrument, the adjusted ARR in mortality associated with early surgery was 11.2% ($P<0.001$). Using the χ^2 test for exogeneity, we were unable to reject the null hypothesis that surgery was exogenous. This finding implies that in the present sample, the effect of early surgery on mortality was independent of all measured and unmeasured covariates. The estimated effects of surgery before correction for propensity score and survivor bias thus should be similar to the estimated effects after these corrections. Indeed, the estimated effects of surgery were consistent across techniques, which supports our conclusion that early surgery is an independent predictor of in-hospital mortality and is associated with a mortality benefit compared with medical therapy.

The present study has several limitations. The ICE cohort may be influenced by referral bias, because most centers 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 NVE. Limitations associated with data collection were also present. Although the ICE-PCS case report form captures the occurrence of events such as congestive heart failure and stroke, the timing of such events is not recorded, which potentially affects the reliability of the surgical propensity model. Such complications are more likely to occur soon after hospitalization and determine whether surgical intervention is indicated. Surgery was not found to confer a survival benefit for patients with heart failure. Evaluation of the effect of surgery as a function of heart failure severity, previously reported to be limited to patients with moderate or severe heart failure,[3] was not feasible in the present cohort owing to incomplete collection of this variable (based on New York Heart Association classification). Although early surgery was associated

with mortality reduction in NVE complicated by stroke, the effect of timing of surgery on outcome could not be evaluated. The end point of in-hospital mortality does not reflect long-term outcome, yet this early benefit may extrapolate to a significant survival benefit in longer follow-up, on the basis of the results of previous studies.[3]

Randomized controlled trials of surgery in NVE are lacking but may reduce differences in patient characteristics and treatment biases between groups. Two randomized trials evaluating the use of surgery in patients with NVE are reportedly under way.[22,23] It may be challenging, however, to define an intermediate-risk group for whom surgery is not required for complications of NVE yet the benefit of surgery is uncertain, and studies such as the present investigation may help to define these criteria. Furthermore, the results of the observational studies are important to evaluate the effectiveness of early surgery for NVE in clinical practice.

In conclusion, early surgery for NVE is associated with a significantly lower in-hospital mortality rate than medical therapy. The mortality benefit associated with surgery was observed in patients with a high propensity for surgery and specifically those with paravalvular complications, systemic embolization, stroke, or *S aureus* infection. Careful assessment for these complications and prompt surgical intervention may improve the outcome of this serious disease. In addition, given the high and increasing prevalence of *S aureus* NVE in the contemporary era, additional studies are needed to evaluate the use and outcome of surgery in these patients.

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Disclosures

Dr Fowler is a member of the Cubist Pharmaceuticals advisory committee; has served as a consultant for Astellas, Biosynexus, Cubist, Inhibitex, Merck, Johnson & Johnson, and Leo Pharmaceuticals; received research support from Cerexa, Cubist, Inhibitex, Theravance, and Merck; participated as a speaker for Cubist; and received honoraria from Arpida, Astellas, Biosynexus, Cubist, Inhibitex, Merck, Nabi, Pfizer, Theravance, and Ortho-McNeil. Dr Corey is a consultant for Theravance, Cubist, Implicit, Inimex, Arpida, Pfizer, Targanta, AstraZeneca, Merck, and Cerexa. He is on the advisory board for Pfizer, Cubist, Inhibitex, Merck, Vicuron, and Johnson & Johnson and has received grants or research support from Theravance, Innocoll, Cerexa, and Cempra. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

A challenging clinical dilemma in the treatment of patients with native valve endocarditis (NVE) is selection for valve surgery during the acute period of hospitalization. Although consensus guidelines provide recommendations for surgery in endocarditis, such recommendations are based on observational retrospective studies. Some previous studies have shown a mortality benefit associated with early surgery, whereas others have found that surgery offers no survival benefit or even potential harm. This discrepancy is due in part to methodological limitations, including lack of adjustment for survivor bias (ie, patients who live longer are more likely to undergo surgery) or hidden bias (factors associated with mortality and probability of receiving surgical treatment that are not measured in the data set). The present study used the largest prospective cohort of patients with NVE and evaluated the effect of early surgery (during initial hospitalization) versus medical therapy alone on in-hospital mortality. In a cohort of 1552 patients with NVE, by use of the methods to reduce biases mentioned previously, valve surgery was associated with a significant in-hospital survival benefit compared to medical therapy alone. In subgroup analysis, surgery was found to confer a survival benefit among patients with a high propensity (or indications) for surgery and those with paravalvular complications, systemic embolization, and stroke. The survival benefit of surgery was evident in patients with NVE caused by *Staphylococcus aureus*, despite the lower use of surgery among patients with *S aureus* endocarditis. These findings support current guidelines recommending early surgery for NVE in patients with paravalvular complications or systemic embolization and suggest a beneficial effect of surgery in controversial settings such as stroke or *S aureus* NVE.

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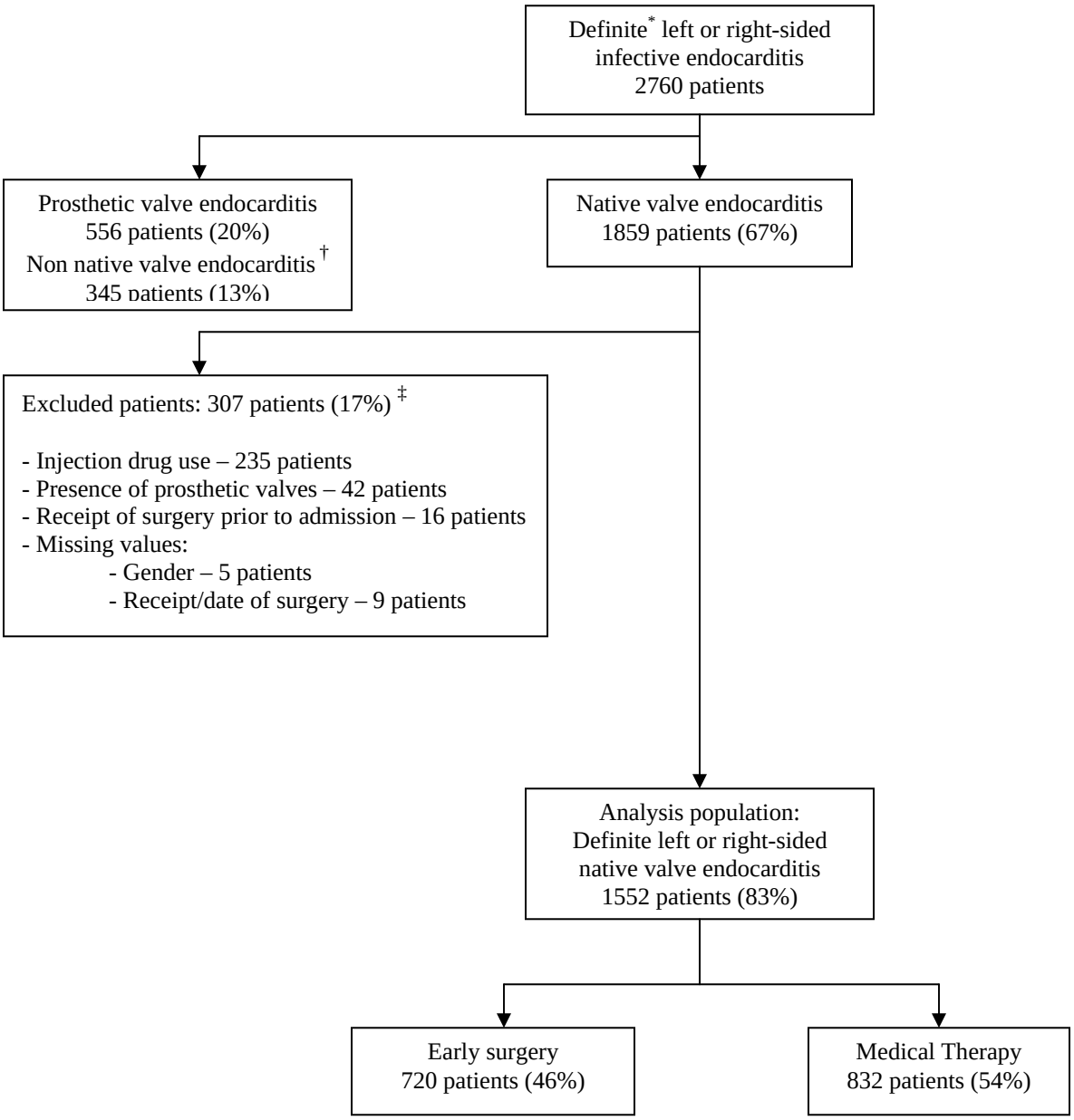
SUPPLEMENTARY MATERIAL

Supplementary Figure 1: Flow diagram of study patients from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) database.



* based on modified Duke criteria (10)
† includes device related endocarditis (e.g., pacemaker endocarditis)
‡ each patient counted once in a hierarchical manner

Supplementary Table 1. Logistic regression model: predictors of early surgery for native valve endocarditis

Predictor	Odds Ratio (95% CI)	z score	p-value
Age	0.97 (0.97 - 0.98)	-6.99	<0.001
Congestive Heart Failure	2.02 (1.51 - 2.70)	4.76	<0.001
Chronic illness [*]	0.52 (0.39 – 0.69)	-4.51	<0.001
Coagulase negative staphylococcus infection	1.90 (0.98 - 3.70)	1.89	0.058
Systemic embolization [†]	1.24 (0.88 – 1.74)	1.22	0.223
Health care associated infection	1.05 (0.73 – 1.54)	0.30	0.768
Duration of symptoms >1 month prior to presentation	1.63 (1.21 – 2.21)	3.19	0.001
Paravalvular complications [‡]	5.26 (3.36 – 8.23)	7.27	<0.001
Valve perforation [§]	1.96 (1.32 – 2.92)	3.33	0.001
Staphylococcus aureus infection	0.62 (0.41 - 0.93)	-2.28	0.023
Male gender	1.07 (0.81 - 1.41)	0.49	0.627
Stroke	0.63 (0.41 - 0.95)	-2.18	0.029
Viridans group streptococcus infection	0.55 (0.39 - 0.77)	-3.45	0.001
Transfer from another facility	2.54 (1.95 - 3.30)	6.95	<0.001
Mitral or aortic valve regurgitation [§]	2.47 (1.84 - 3.32)	5.98	<0.001
Transesophageal echocardiography performed	2.05 (1.21 - 3.48)	2.68	0.007
Evidence of endocarditis on transesophageal echocardiogram	0.84 (0.51 - 1.39)	-0.67	0.503
Intracranial hemorrhage	0.64 (0.34 - 1.19)	-1.41	0.159
Persistent bacteremia	0.86 (0.53 - 1.40)	-0.62	0.538
Aortic valve vegetation [§]	1.21 (0.89 - 1.64)	1.20	0.231
Mitral valve vegetation [§]	0.87 (0.64 - 1.18)	-0.91	0.361
Pulmonary edema	1.52 (1.09 - 2.14)	2.43	0.015
Echocardiogram performed at referral hospital	0.61 (0.43 - 0.85)	-2.91	0.004
Evidence of endocarditis on transthoracic echocardiogram	1.25 (0.95 – 1.64)	1.62	0.105
New conduction abnormality	2.70 (1.61 - 4.55)	3.75	<0.001
Interaction Terms			
Stroke x systemic embolization	1.11 (0.57 – 2.20)	0.31	0.755
Health care associated infection x *S aureus*	0.84 (0.45 - 1.56)	-0.54	0.587
Health care associated infection x coagulase negative staphylococcus infection	0.79 (0.31 – 2.01)	-0.50	0.615

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

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

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

[§] Based on transesophageal or transthoracic echocardiography

Supplementary Table 2. Logistic regression model: predictors of mortality for native valve endocarditis

Predictor	Odds Ratio (95% CI)	z score	p-value
Early Surgery	0.56 (0.38 – 0.82)	-2.95	0.003
Age	1.03 (1.02 – 1.04)	5.26	<0.001
Congestive Heart Failure	2.33 (1.65 – 3.28)	4.83	<0.001
Chronic illness [*]	1.80 (1.23 - 2.64)	3.02	0.003
Coagulase negative staphylococcus infection	2.29 (1.12 - 4.68)	2.27	0.023
Systemic embolization [†]	1.63 (1.06 – 2.52)	2.22	0.026
Health care associated infection	1.32 (0.82 – 2.13)	1.13	0.257
Duration of symptoms >1 month prior to presentation	0.69 (0.44 - 1.09)	-1.60	0.110
Intra-cardiac abscess [‡]	2.37 (1.16 - 4.86)	2.36	0.018
Paravalvular complications [§]	2.50 (1.23 – 5.07)	2.55	0.011
Valve perforation [‖]	1.30 (0.76 - 2.23)	0.95	0.342
Staphylococcus aureus infection	2.10 (1.29 - 3.42)	3.00	0.003
Male gender	0.93 (0.67 - 1.30)	-0.41	0.682
Stroke	3.18 (2.03 - 5.00)	5.04	<0.001
Viridans group streptococcus infection	0.63 (0.37 - 1.07)	-1.71	0.088
Transfer from another facility	1.01 (0.72 - 1.42)	0.06	0.952
Mitral or aortic valve regurgitation [‖]	1.15 (0.81 - 1.67)	0.80	0.424
Transesophageal echocardiography performed	0.28 (0.14 – 0.56)	-3.56	<0.001
Evidence of endocarditis on transesophageal echocardiogram	1.31 (0.65 - 2.63)	0.76	0.450
Intracranial hemorrhage	1.61 (0.80 - 3.22)	1.35	0.179
Persistent bacteremia	2.23 (1.40 - 3.55)	3.38	0.001
Aortic valve vegetation [‖]	1.15 (0.79 – 1.68)	0.74	0.460
Mitral valve vegetation [‖]	1.04 (0.72 – 1.51)	0.22	0.829
Pulmonary edema	1.51 (1.04 – 2.18)	2.18	0.029
Echocardiogram performed at referral hospital	1.53 (0.99 - 2.36)	1.93	0.054
Evidence of endocarditis on transthoracic echocardiogram	0.74 (0.52 - 1.05)	-1.68	0.094
New conduction abnormality	1.63 (0.93 - 2.85)	1.72	0.085
Interaction Terms			
Paravalvular complications [§] x intra-cardiac abscess	0.27 (0.09 – 0.79)	-2.40	0.016
Valve perforation [‖] x intra-cardiac abscess	0.70 (0.21 – 2.34)	-0.57	0.567
Stroke x systemic embolization	0.55 (0.26 - 1.16)	-1.57	0.118
Health care associated infection x *S aureus* infection	0.65 (0.33 – 1.31)	- 1.20	0.229
Health care associated infection x coagulase negative staphylococcus infection	0.48 (0.17 – 1.36)	-1.38	0.167

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

† Includes embolism to any major arterial vessel, excluding stroke

[‡] Based on echocardiographic evidence or intra-operative finding of intracardiac abscess

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

[‖] Based on transesophageal or transthoracic echocardiography

Appendix:

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