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Analysis of the Impact of Early Surgery on In-hospital Mortality of Native Valve Endocarditis: Use of Propensity Score and Instrumental Variable Methods to Adjust for Treatment Selection Bias

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Abstract

Background—The impact of early surgery on mortality in patients with native valve endocarditis (NVE) is unresolved. This study seeks to evaluate valve surgery compared to medical

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Dr. Fowler is a member of the Cubist 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, 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. No other potential conflicts of interest relevant to this article were reported.

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

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 using propensity-based matching adjusting for survivor bias, and 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 to medical therapy, early surgery was associated with a significant reduction in mortality in the overall cohort (12.1% [87/720] vs. 20.7% [172/832]) and after propensity-based matching and adjustment for survivor bias (absolute risk reduction (ARR) = -5.9 %; p<0.001). Using a combined instrument, the instrumental variable adjusted ARR in mortality associated with early surgery was -11.2% (p<0.001). In sub-group analysis, surgery was found to confer a survival benefit compared to medical therapy among patients with a higher propensity for surgery (ARR= -10.9% for quintiles 4 and 5; p=0.002); 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 with valve perforation or congestive heart failure.

Conclusions—Early surgery for NVE is associated with an in-hospital mortality benefit compared to medical therapy alone.

Keywords

early surgery; infective endocarditis; medical therapy; in hospital mortality

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Native valve endocarditis (NVE) is associated with mortality rates of 15 to30% 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 intra-cardiac damage, but there are insufficient data to support such recommendations.[6] Ethical, logistical and financial issues create major challenges for performing 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]

To date, six propensity analyses evaluating treatment strategies for NVE have been performed.[2-5,9,10] Two studies reported a significant reduction in six month and five 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 this study were 1) to assess whether early surgery is associated with lower in-hospital mortality compared to medical therapy; and 2) determine whether this association varied by propensity or specific indications for early surgery. We utilized a prospective, multinational cohort of patients with NVE, using statistical methods to control for treatment selection bias, survivor bias, and hidden bias.

Methods

Study population and clinical data

The cohort for this study was obtained from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) database, containing 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 prospectively collected between June 2000 and August 2005. The study was approved by the institutional review board or ethics committee at all participating sites.

Only patients who had definite left- or right-sided NVE, based on modified Duke criteria,[11] were included in this study. Patients with the following characteristics were excluded: injection drug use, prosthetic valves, non-native valve IE (e.g., pacemaker IE); receipt of surgery prior to 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 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 previously reported.[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. Health care associated IE consisted of either nosocomial or non-nosocomial health care associated infection.[14]

Analytical Plan

We utilized an observational cohort to estimate the impact of early surgery on mortality, using statistical methods to control for overt and hidden biases. Overt treatment bias, related to covariates measured in the study, was addressed using 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 *S aureus* infection.

Standardized differences between the two 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 two-sided p-value <0.05 was considered to be statistically significant. All analyses were performed using STATA software, version 10. [17]

Propensity Score Matching—A propensity score, which is the estimated probability that a patient would undergo early surgery, was calculated for each patient. The propensity score was computed using non-parsimonious multivariable logistic regression with early surgery as the dependent variable and incorporated 25 clinically relevant covariates, and three interaction terms as the independent variables (Supplementary Table 1).

Patients undergoing early surgery were matched 1-to-1 with patients treated medically on the basis of the following: 1) propensity score, using nearest neighbor matching with replacement (each medical therapy patient could be used more than once for matching, while 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—Our study utilized 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, i.e., 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: a) high correlation with early surgery; and b) no effect on mortality 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 one month prior to presentation, site specific rate of early surgery for NVE, transfer from another hospital, and transesophageal echocardiography performed. 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 is an exogenous variable in the mortality model, i.e., the effect of early surgery on mortality is independent of all measured and unmeasured covariates, we performed a chi square test of the null hypothesis that early surgery is exogenous.

Sub-group 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 p-values reflect this.

Results

The ICE-PCS cohort consisted of 2760 patients, including 1859 (69%) with NVE. Of these, 1552 (82%) qualified for our study (Supplementary Figure 1). Seven hundred and 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; to have transferred from another medical facility; and to have complications such as congestive heart failure, intracardiac abscess, and paravalvular complications. The median time from admission to surgery was 7 days (Q1-to-Q3: 2-17 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% vs. 20.7%; ARR = -8.6%; p <0.001) and after controlling for all other measured covariates using standard logistic regression analysis (ARR = -5.9%; p<0.001) (Supplementary Table 2). The latter model had a concordance index of 0.83, indicating a strong ability to discriminate between possible outcomes (i.e., in-hospital survival versus death).

To control for observed differences in patient characteristics, we estimated the probability of surgery (propensity score) for each patient. Using nearest-neighbor propensity score matching with replacement and adjusting 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 controls used for matching with replacement, 120 (19.4%) were selected more than once. Standardized differences between covariates in the two treatment groups were substantially decreased 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 (using the biprobit technique) was performed to adjust for hidden bias. Candidate variables for this composite instrumental variable were selected based on 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 is 0.86. The Hosmer-Lemeshow test statistic of 10.91 and associated p-value of 0.207 imply that we cannot 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 (i.e., its effects on mortality were independent of all measured and unmeasured covariates) in the mortality model ($\chi^2 = 0.51$; p=0.48). A comparison of the adjusted odds ratios and ARR 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 sub-groups based on the propensity scores of surgical patients. The distribution of key characteristics across the propensity score quintiles is depicted in Figure 1. With 1238 patients, this yielded approximately 248 patients (about half surgical and half medical therapy patients) per quintile. A differential benefit of surgery favoring patient with a higher propensity for surgery compared to those with a lower propensity score was observed (ARR=-10.9% [p=0.002] for patients in quintile 4 and 5 vs. -2.4% in patients in quintiles 1-3 [p=0.2]; p-value 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 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 three 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 current study demonstrate that early surgery is associated with significant in-hospital mortality benefit compared to medical therapy, even after adjustment for important biases such as treatment selection, survivorship, and hidden biases.

Table 4 summarizes the studies that have utilized propensity analysis to evaluate the effect of surgery for NVE. While most studies have shown mortality benefit associated with early surgery, others have demonstrated no benefit or possible harm. Tleyjeh et al reported that surgery offered no significant reduction in six-month mortality (hazard ratio 0.92; 95% CI 0.48-1.76) after adjusting for treatment and survivor bias.[4] There are several methodological differences in the design of our study compared to these prior studies that may explain the disparate results. Prior investigations utilized retrospective, single center data; included both native and prosthetic valve endocarditis in their analyses; and had different end-points (e.g., inpatient vs. 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 sub-groups. In contrast, our study utilized the largest, contemporary, multi-national 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 based on propensity scores and survival times, each treatment group had 619 patients. Our results indicate that early surgery is associated with an absolute reduction in mortality in the overall cohort compared to medical therapy of 5.9% to 11.2%; the number of patients needed to treat with early valve surgery to prevent 1 in-hospital death ranges from 9 to 17. This beneficial effect of early surgery is also discrepant from those reported recently by Bannay et al., 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. [20] On a broader level, our study has utilized the technique of propensity modeling in a rigorous manner to evaluate non-randomized treatment with surgery that reflects the concerns raised by Austin in his assessment of 44 cardiovascular studies.[15] In addition to the large sample size and prospective nature of the current 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 patients 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 for NVE in the overall cohort, important caveats must be recognized from the sub-group analyses. Similar to results previously published by our group,[5] the benefit of early surgery was not uniformly distributed among all propensity quintiles. A differential benefit of surgery was observed in patients with strong indications for surgical intervention (i.e., those in the combined fourth and fifth quintile). Surgery was also found to confer a survival benefit among patients with paravalvular complications, systemic embolization and stroke but not 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, due to health care-associated infection and multiple co-morbid 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 as compared to patients who received medical therapy (number needed to treat = 5).

Propensity adjustment may be influenced by unmeasured variables, necessitating 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 chi-squared test for exogeneity, we were unable to reject the null hypothesis that surgery was exogenous. This finding implies that, in our sample, the effect of early surgery on mortality is independent of all measured and unmeasured covariates. The estimated effects of surgery before correcting 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, supporting our conclusion that early surgery is an independent predictor of in-hospital mortality and is associated with a mortality benefit when compared to medical therapy. Our 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 this 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, stroke etc, the timing of such events is not recorded, potentially affecting the reliability of the surgical propensity model. However, 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 our cohort due 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 endpoint 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, based on results of previous studies.[3] Randomized, controlled trials of surgery in NVE are lacking, but potentially would reduce differences in patient characteristics and treatment biases between groups. Two randomized trials evaluating the use of surgery in patients with NVE are reportedly underway.[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 for evaluating 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 as compared to 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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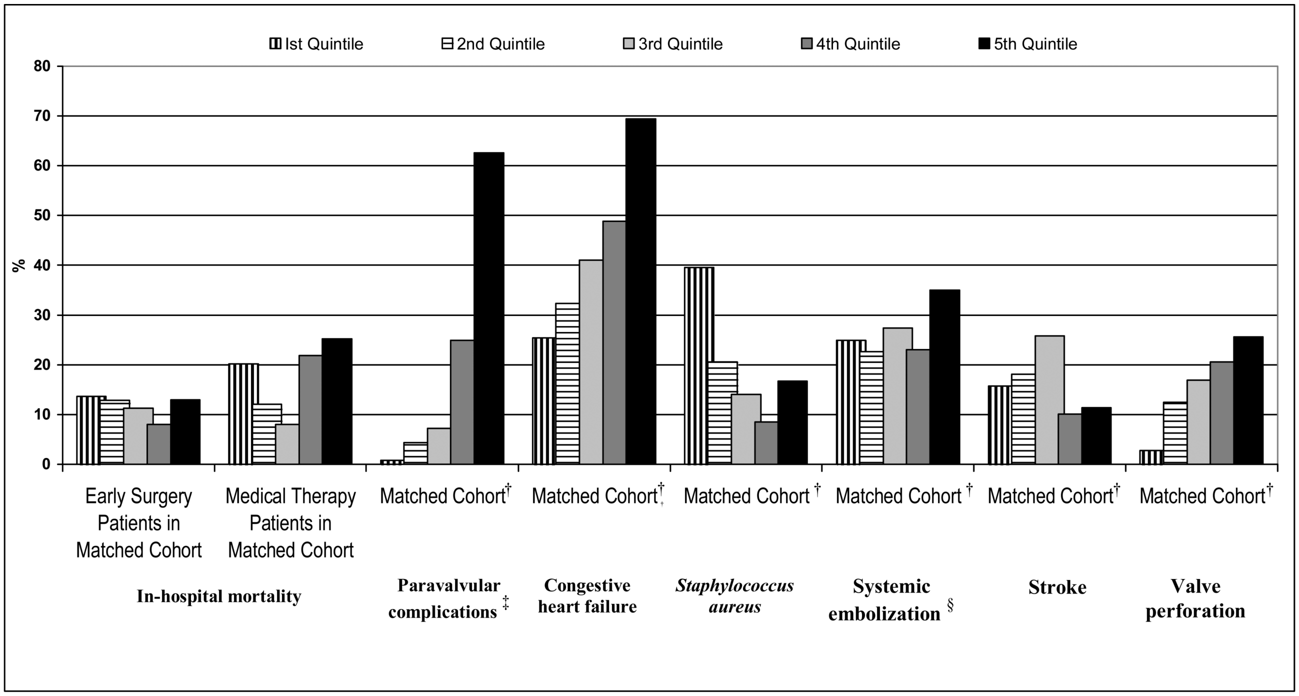

* Propensity matched survivor bias adjusted cohort (n=1238 or 619 matched pairs); quintiles based on surgical propensity scores.

† 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 (e.g., paravalvular complication) out of total number of patients in the quintile.

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

§ Includes embolism to any major arterial vessel, excluding stroke

Figure 1.

Distribution of key characteristics of the propensity matched survivor bias adjusted cohort of patients with native valve endocarditis by surgical propensity score quintiles.*

Table 1

Characteristics of patients with native valve endocarditis treated with early surgery versus medical therapy.

Characteristics	Overall Cohort			Propensity Matched Cohort with Adjustment for Survivor Bias		
	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 – years	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 month prior to 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
Health care 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

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Characteristics	Overall Cohort			Propensity Matched Cohort with Adjustment for Survivor Bias		
	Early Surgery (n=720) %	**Medical Therapy (n=832)%**	**Standardized Difference***	**Early Surgery (n=619)%**	**Medical Therapy (n=619) %**	**Standardized Difference***
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
Intra-cranial 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						
Staphylococcus 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

*Standardized difference is the mean difference divided by the pooled SD, expressed as a percentage

†Includes diabetes mellitus, cancer, immunosuppression, hemodialysis dependence, chronic obstructive pulmonary disease, cirrhosis and other chronic co-morbid conditions

‡Based on transesophageal or transthoracic echocardiography

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[§]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 intra-operative finding of intracardiac abscess

Table 2

Unadjusted and adjusted absolute risk reduction and odds ratios for mortality associated with early surgery and medical therapy.

Risk-adjustment method for in-hospital mortality	Absolute Risk Reduction (%)*	p-value	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 (Supplementary Table 2)

‡Patients matched based on the propensity for surgery (see Supplementary Table 1 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 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. IV analysis performed using the bivariate probit (biprobit) method.

Table 3

Early surgery versus medical therapy for native valve endocarditis – effect on in-hospital mortality across subgroups.

	Propensity matched cohort with adjustment for survivor bias			
	Early Surgery patients in each group	**Absolute Risk Reduction[*] (%)**	**p-value[†]**	**p-value for difference[‡]**
Total cohort	619	- 5.9	<0.001	
Propensity quintile[§]				
1st quintile	124	- 5.3	0.142	
2nd quintile	124	0.1	0.984	
3rd quintile	124	0.1	0.964	
4th quintile	124	- 17.8	0.002	
5th quintile	123	- 4.8	0.214	
Paravalvular complications[//]				0.009
No	482	- 3.1	0.060	
Yes	137	- 17.3	<0.001	
Valve perforation[#]				0.550
No	516	- 6.2	0.002	
Yes	103	- 3.5	0.392	
Systemic embolization[**]				0.040
No	464	- 3.4	0.052	
Yes	155	- 12.9	0.002	
Stroke				0.150
No	518	- 4.5	0.010	
Yes	101	- 13.0	0.020	
S aureus infection				<0.001
No	494	- 2.3	0.148	
Yes	125	- 20.1	<0.001	
Congestive heart failure				0.170
No	344	- 8.3	0.002	

	Propensity matched cohort with adjustment for survivor bias			
	Early Surgery patients in each group	**Absolute Risk Reduction * (%)**	**p-value†**	**p-value for difference‡**
Yes	275	- 3.4	0.188	

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

†p-value based on logistic regression using propensity matched, survivor bias adjusted cohort with clustered standard errors and interaction terms. SE for the ARR where derived using the delta method.

‡Indicates the difference across strata for the variable

§Quintiles based on the propensity scores for surgical patients. Differential mortality benefit of surgery observed in combined quintile 4 and 5 stratum (ARR= -10.9%; p=0.002) vs. stratum with quintiles 1-3 (ARR= -2.4%; p=0.2); p-value 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

Table 4

Summary of reported propensity analyses evaluating the impact of surgery compared to medical therapy in native valve endocarditis

Reference - Year of Publication	Years of patient accrual	Data Collection Method	Number of centers	Type of IE	Number of NVE patients/ Total patients	Number of patients in propensity cohort*	Timing of mortality endpoint	Surgery / Medical Therapy mortality rate†	Biases adjusted for in the study‡	Hazard ratio/ Odds ratio (95% CI)
Present Study	2000-05	Prospective	61 centers - 28 countries	Left and right sided NVE	1552/1552	634 : 634	In-hospital	11.8% / 17.4%	Treatment selection bias Survivor bias Hidden bias	0.44 (0.33 – 0.59)
Sy et al [10] - 2009	1996-06	Retrospective	2 centers – Sydney, Australia	Left sided NVE/PVE	169/223	62:161§	5 years‖	N/A§	Treatment selection bias Survivor bias	0.77 (0.42-1.40)
Tleyjeh et al.[4] -2007	1980-88	Retrospective	Single Center - Minnesota	Left sided NVE/PVE	356 / 512	93 : 93	6 months	29% / 19.4%	Treatment selection bias Survivor bias	0.92 (0.48 to1.76)
Aksoy et al.[2] - 2007	1996-02	Prospective	Single Center - North Carolina	Left sided NVE/PVE	248 / 333	51 : 51	5 years	11.5% / 18%	Treatment selection bias	0.27 (0.13-0.55)
Cabell et al. [5] – 2005	1984-99	Retrospective	7 Centers - 5 countries	Left and right sided NVE	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)
Mourvillier et al.[9]- 2004	1993-00	Retrospective	Single Center - France	Left and right sided NVE/PVE	146 / 228	27 : 27	In-hospital	Not Reported	Treatment selection bias	0.96 (CI not reported; p=0.95)
Vikram et al.[3] - 2003	1990-00	Retrospective	7 Centers - Connecticut	Left-sided NVE	499 / 499	109 : 109	6 months	15% / 28%	Treatment selection bias	0.40 (0.18-0.91)

*Number of patients in surgery group: Number of patient in the medical therapy group. Propensity score based matching was performed in all studies except Sy et al and Cabell et al.

†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 using proportional hazards; Hidden bias=Instrumental variable analysis

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

‖Mortality endpoint was defined as all cause mortality during follow up (median follow up: 5.2 years; interquartile range 2.5 to 8 years)