MAJOR ARTICLE

Impact of Early Valve Surgery on Outcome of *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis: Analysis in the International Collaboration of Endocarditis–Prospective Cohort Study

Catherine Chirouze,[1,2] François Alla,[3,4,5] Vance G. Fowler Jr,[6] Daniel J. Sexton,[6] G. Ralph Corey,[6] Vivian H. Chu,[6] Andrew Wang,[6] Marie-Line Erpelding,[4,5] Emanuele Durante-Mangoni,[7] Nuria Fernández-Hidalgo,[8] Efthymia Giannitsioti,[9] Margaret M. Hannan,[10] Tatjana Lejko-Zupanc,[11] José M. Miró,[12] Patricia Muñoz,[13] David R. Murdoch,[14] Pierre Tattevin,[15] Christophe Tribouilloy,[16] and Bruno Hoen[1,2,17,18]; on behalf of the ICE Prospective Investigators[a]

[1]UMR CNRS 6249 Chrono-Environnement, Université de Franche-Comté, and [2]Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Régional Universitaire, Besançon, [3]Université de Lorraine, Université Paris Descartes, Apemac, EA4360, [4]INSERM, CIC-EC, CIE6, and [5]CHU Nancy, Pôle S2R, Epidémiologie et Evaluation Cliniques, Nancy, France; [6]Department of Medicine, Duke University Medical Center, Durham, North Carolina; [7]Department of Cardiothoracic Sciences, University of Naples S.U.N., Monaldi Hospital, Italy; [8]Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain; [9]Fourth Department of Internal Medicine, Attikon University General Hospital, Athens, Greece; [10]Department of Microbiology, Mater Misericordiae University Hospital, Dublin, Ireland; [11]Department of Infectious Diseases, Medical Centre Ljubljana, Slovenia; [12]Hospital Clinic–IDIBAPS, University of Barcelona, and [13]Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [14]Microbiology Unit, Canterbury Health Laboratories, Christchurch, New Zealand; [15]Maladies Infectieuses et Réanimation Médicale, Pontchaillou University Hospital, Rennes, [16]Département de Cardiologie, Hôpital Universitaire Sud, Amiens, [17]Université des Antilles et de la Guyane, Faculté de Médecine Hyacinthe Bastaraud, EA 4537, Pointe-à-Pitre, Guadeloupe, and [18]Service de Maladies Infectieuses et Tropicales, CIC 1424, Centre Hospitalier Universitaire, Pointe-à-Pitre, France

(See the Editorial Commentary by Karchmer and Bayer on pages 750–2.)

Background. The impact of early valve surgery (EVS) on the outcome of *Staphylococcus aureus* (SA) prosthetic valve infective endocarditis (PVIE) is unresolved. The objective of this study was to evaluate the association between EVS, performed within the first 60 days of hospitalization, and outcome of SA PVIE within the International Collaboration on Endocarditis–Prospective Cohort Study.

Methods. Participants were enrolled between June 2000 and December 2006. Cox proportional hazards modeling that included surgery as a time-dependent covariate and propensity adjustment for likelihood to receive cardiac surgery was used to evaluate the impact of EVS and 1-year all-cause mortality on patients with definite left-sided *S. aureus* PVIE and no history of injection drug use.

Results. EVS was performed in 74 of the 168 (44.3%) patients. One-year mortality was significantly higher among patients with *S. aureus* PVIE than in patients with non–*S. aureus* PVIE (48.2% vs 32.9%; $P = .003$). *Staphylococcus aureus* PVIE patients who underwent EVS had a significantly lower 1-year mortality rate (33.8% vs 59.1%; $P = .001$). In multivariate, propensity-adjusted models, EVS was not associated with 1-year mortality (risk ratio, 0.67 [95% confidence interval, .39–1.15]; $P = .15$).

Conclusions. In this prospective, multinational cohort of patients with *S. aureus* PVIE, EVS was not associated with reduced 1-year mortality. The decision to pursue EVS should be individualized for each patient, based upon infection-specific characteristics rather than solely upon the microbiology of the infection causing PVIE.

Keywords. endocarditis; prosthetic valve; surgery; 1-year mortality.

Received 19 February 2014; accepted 16 September 2014; electronically published 10 November 2014.

[a]The ICE Prospective Investigators are listed in the Appendix.

Correspondence: Catherine Chirouze, MD, PhD, Service de Maladies Infectieuses et Tropicales, Hôpital Jean Minjoz, Boulevard Fleming, 25030 Besançon Cedex, France (cchirouze@chu-besancon.fr).

Clinical Infectious Diseases® 2015;60(5):741–9

DOI: 10.1093/cid/ciu871

Staphylococcus aureus (SA) prosthetic valve infective endocarditis (PVIE) is associated with some of the highest mortality rates observed in bacterial infections, ranging from 40% to 80% [1–10]. In a number of reports, in-hospital mortality rates of SA PVIE were significantly higher in patients who had not undergone valve surgery [4–6, 8, 9, 11–13]. These observations have prompted some authors to conclude that early valve surgery (EVS) should be considered standard treatment for any patient with SA PVIE, especially those with early-onset (within 2 months of prosthetic valve insertion) infection [9]. For instance, after a comprehensive review of the literature, Attaran et al concluded recently that infection with *S. aureus* should be considered an indication for surgery in prosthetic valve endocarditis even without cardiac or valvular complications. They even suggested that these patients should undergo surgery as soon as possible before cerebral complications develop [14].

By contrast, the literature and the experience of the International Collaboration on Endocarditis (ICE) group indicate that decisions about EVS in patients with SA PVIE should be made on a careful, case-by-case basis [7, 15–17]. In this respect, a study performed by Hill et al is quite instructive [17]. Patients who received medical-only treatment were divided into 2 subgroups of patients: those with no indication for surgery and those in whom surgery was contraindicated. The highest survival rate was observed in the subgroup with no surgical indication. These results implied that selected patients with SA PVIE could actually be cured without valve surgery.

Although a randomized controlled trial could definitively establish the impact of valve surgery on the outcome of SA PVIE, such a trial would be difficult or impossible to complete [18, 19].

In the current investigation, we reevaluated the relationship between EVS and outcome of SA PVIE using appropriate analytical methods to examine data from the ICE Prospective Cohort Study (PCS).

METHODS

Study Population and Clinical Data

The ICE-PCS is a prospective, multicenter, international (64 sites from 28 countries) registry of patients with infective endocarditis (IE) [2]. Between January 2000 and December 2006, data were prospectively recorded using standard definitions during the index hospitalization and 1 year after through national death records, medicals records, and/or patient contact as available. Informed consent (oral/written) was obtained from all patients according to local institutional review boards or ethic committee guidelines at all sites. We extracted the data of patients with SA PVIE and a definite diagnosis of IE according to the modified Duke criteria from the ICE-PCS database, which contained 5668 cases by December 2006 (see sample acquisition in Figure 1) [20]. Cases with the following characteristics were excluded: native-valve IE, right-sided IE, intravenous drug use, as well as cases with missing values for any of the following variables: sex, receipt and/or date of surgery, length of initial hospitalization, and survival status at 1-year follow-up. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was used. When essential data were missing in the database, sites and their investigators were queried to complete data collection.

Definitions

The definitions used in the ICE-PCS cohort have been reported in detail previously [21]. EVS was defined as replacement of the infected prosthetic valve within the first 60 days after admission for PVIE. Chronic illness was defined as the presence of comorbidities such as diabetes mellitus, cancer, immunosuppression, hemodialysis dependence, chronic obstructive pulmonary disease, and cirrhosis. Severity of heart failure was categorized according to New York Heart Association (NYHA) functional classification. Paravalvular complication was defined as transthoracic or transesophageal echocardiographic evidence of intracardiac abscess or fistula and prosthetic valve complication as evidence of dehiscence or new moderate-to-severe paravalvular regurgitation by transthoracic or transesophageal echocardiography.

Systemic embolization included embolism to any major arterial vessel, excluding stroke defined by acute neurological deficit of vascular origin lasting >24 hours. Healthcare-associated endocarditis consisted of either nosocomial or nonnosocomial healthcare-associated infection, using prior definitions [22, 23].

Analytical Methods

The primary endpoint was all-cause mortality 1 year after discharge from the hospitalization for the treatment of IE. We used 1-year mortality as the primary endpoint because it has been shown that a period of at least 6 months is necessary to offset the early high postoperative mortality related to valve surgery [24] and because information on 1-year follow-up was systematically recorded in the ICE-PCS database. We also looked at all-cause in-hospital mortality as a secondary endpoint.

We first compared in a univariate analysis SA PVIE patients with patients with PVIE due to any other pathogens. We then compared outcomes of SA PVIE patients between those who had undergone EVS and those who had not. Baseline characteristics and outcomes of patients with SA PVIE who underwent EVS were compared to those receiving medical therapy alone, using both univariate and multivariate analyses. A nonparsimonious multivariable logistic regression model was constructed to search for independent predictors of EVS. Adjusted risk estimates for EVS were presented as odds ratios and 95% confidence intervals (CIs).

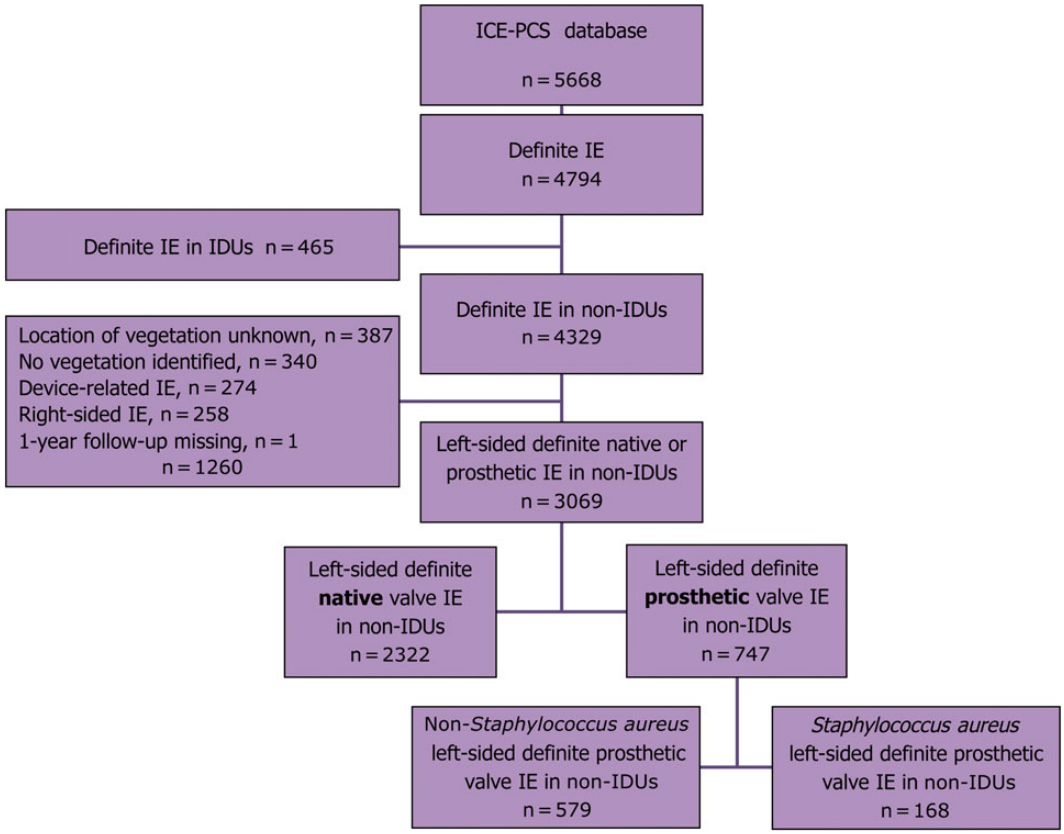

Figure 1. Sample acquisition. Abbreviations: ICE-PCS, International Collaboration on Endocarditis–Prospective Cohort Study; IDUs, intravenous drug users; IE, infective endocarditis.

In a next step, we identified factors associated with both in-hospital and 1-year mortality using both univariate and multivariate analyses through an adjusted Cox proportional hazards regression model, without entering the EVS variable into the models.

Finally we assessed EVS as a prognostic factor by evaluating the relationship between EVS and 1-year mortality through a Cox model adjusted to prognostic factors and predictors of EVS (propensity factors) identified in previous steps. Two Cox proportional hazard models that included all relevant covariates (to control for treatment selection bias) as well as EVS as a time-dependent variable (to control for survival bias) were constructed. In the second model, EVS was time-partitioned into 2 time-dependent covariates (because the proportional hazard assumption is not satisfied, related to a higher postoperative mortality in the surgery group than in the nonsurgery group that reversed after 7 days): the first indicated whether the patient had undergone EVS within the prior 7 days, which reflects the short-term effect of EVS; the second indicated whether the patient had had EVS >7 days before, which reflects the long-term effect of EVS. Thus, adjustment for short-term surgical effect can reveal long-term surgical effect. Results of prognosis analyses were expressed as risk ratios with 95% CIs; a 2-sided P value < .05 was considered significant. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

After exclusion of cases in intravenous drug users, cases of right-sided and native valve IE, and cases with missing data, a total of 747 patients with left-sided definite prosthetic valve IE, among whom 168 cases were due to *S. aureus* and 579 cases were due to other pathogens, were selected from the 5668 cases of IE in the ICE-PCS database (Figure 1). Susceptibility to methicillin was characterized in 149 patients (missing information for 19 patients); 48 strains were resistant to methicillin (32.2%). Patients with SA PVIE had a shorter time from onset to admission, were more often on hemodialysis, had more frequently healthcare-associated IE, and presented with or developed more often a stroke than patients with non-SA PVIE. Echocardiography evidenced more frequently a prosthetic valve dehiscence in SA PVIE than in non-SA PVIE. EVS was performed less frequently in patients with SA PVIE, although

the difference was not statistically significant (44.3% vs 51.5; $P = .1$). One-year mortality was significantly higher in patients with SA PVIE compared with patients with non-SA PVIE (48.2% vs 32.9%; $P = .003$).

Patients with SA PVIE who received EVS were younger, more often had paravalvular complications, prosthetic dehiscence, or an intracardiac abscess and had a significantly lower 1-year mortality rate (33.8% vs 59.1%; $P = .001$) than patients with SA PVIE who did not receive EVS (Table 1).

Table 2 shows the results of the propensity analysis of the factors associated with EVS. The existence of paravalvular complications was significantly associated with EVS both in univariate analysis and in the multivariate model (odds ratio, 4.1 [95% CI, 1.9–8.6]). We therefore decided to use "paravalvular complications" as an adjustment variable in the multivariate prognosis model discussed below.

Multivariate prognosis analysis in SA PVIE patients (without considering EVS as a potential prognostic factor) identified the following 3 variables to be associated with 1-year mortality: age, stroke, and congestive heart failure, defined by NYHA class III or IV, with the following adjusted hazard ratios [HRs]: age (per 1-year increment: HR, 1.03 [95% CI, 1.01–1.05]; $P = .002$); stroke (time-dependent: HR, 2.56 [95% CI, 1.62–4.05]; $P < .0001$); and congestive heart failure (HR, 2.06 [95% CI, 1.29–3.30]; $P = .002$).

Table 3 shows results of the intermediate model that indicated no impact of EVS on in-hospital mortality. The results of the final adjusted models are displayed in Tables 4 and 5. They show that, overall, EVS was not significantly associated with 1-year mortality. However, the time-partitioned coding revealed an interaction between HR of death and time: within 7 days following intervention, mortality was higher in the surgery group

Table 1. Compared Characteristics of *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis Patients by Performance of Early Valve Surgery

	No EVS (n = 93 [55.7%])			EVS (n = 74 [44.3%])			
Characteristic	No.	%	SD	No.	%	SD	*P* Value
Male sex	56	60.2		42	56.8		.65
Age, y, mean (SD)	93	64.0	14.9	74	59.2	14.8	.0434
Duration of symptoms >1 mo prior to presentation	5	5.4		12	16.7		.04
Associated conditions and comorbidities							
Hemodialysis dependence	12	13.5		3	4.1		.04
Diabetes mellitus	22	24.7		9	12.7		.06
Cancer	5	5.6		7	9.9		.30
Charlson index, mean (SD)	46	1.8	1.6	33	2.0	2.1	.58
Place of acquisition							.18
Community	40	43.0		33	44.6		
Healthcare: hospital	39	41.9		33	44.6		
Healthcare: nonhospital	11	11.8		3	4.1		
Unknown	2	2.2		5	6.8		
Prior history of IE	18	19.6		14	19.2		.95
Intracardiac device	18	19.4		9	12.3		.22
Echocardiographic findings							
Evidence of new regurgitation	37	40.2		36	48.6		.28
Paravalvular complications	18	19.6		36	48.6		<.0001
Prosthetic valve dehiscence	3	3.3		12	16.4		.004
Complications							
CHF (NYHA class III or IV)	26	28.0		17	23.0		.46
Stroke	30	33.0		27	37.0		.59
Embolic event	12	13.3		14	19.4		.29
Intracardiac abscess	15	16.7		29	40.3		.0008
Outcome							
Days to death, mean (SD)	55	46.0	81.5	25	229.6	560.9	.02
In-hospital death	45	48.4		18	24.3		.001
1-year mortality	55	59.1		25	33.8		.001

Abbreviations: CHF, congestive heart failure; EVS, early valve surgery; IE, infective endocarditis; NYHA, New York Heart Association; SD, standard deviation.

Table 2. Factors Associated With the Performance of Early Valve Surgery in *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis Patients (Propensity Analysis)

	SA PVIE (n = 167)	EVS (n = 74)		Univariate Analysis			Multivariate Analysis	
Characteristic	No.	No.	%	OR	95% CI	*P* Value	OR	95% CI
Male sex	98	42	42.9	1		.65		
Female sex	69	32	46.4	1.2	.6–2.1			
Age ≤ 65 y	84	42	50.0	1		.14		
Age >65 y	83	32	38.6	0.6	.3–1.2			
Duration of symptoms >1 mo prior to presentation	17	12	70.6	3.3	1.1–9.8	.04		
Chronic hemodialysis	15	3	20.0	0.3	.1–1.0	.03		
Diabetes mellitus	31	9	29.0	0.4	.2–1.0	.05		
Cancer	12	7	58.3	1.9	.6–6.1	.30		
Charlson index, per 1 unit	79	33	41.8	1.1	.8–1.4	.58		
Nosocomial IE	72	33	45.8	1.2	.7–2.3	.53		
Prior history of IE	32	14	43.8	1.0	.4–2.1	.95		
Intracardiac device	27	9	33.3	0.6	.2–1.4	.22		
Evidence of new regurgitation	73	36	49.3	1.4	.8–2.6	.28		
Paravalvular complications	54	36	66.7	3.9	2.0–7.7	<.0001	4.1	1.9–8.6
Prosthetic valve dehiscence	15	12	80.0	5.8	1.6–21.3	.003		
CHF (NYHA class III or IV)	43	17	39.5	0.8	.4–1.6	.46		
Stroke	57	27	47.4	1.2	.6–2.3	.59		
Embolic event	26	14	53.8	1.6	.7–3.6	.29		
Intracardiac abscess	44	29	65.9	3.4	1.6–7.0	.0008		

Abbreviations: CHF, congestive heart failure; CI, confidence interval; EVS, early valve surgery; IE, infective endocarditis; NYHA, New York Heart Association; OR, odds ratio; PVIE, prosthetic valve infective endocarditis; SA, *Staphylococcus aureus*.

than in the nonsurgery group (nonsignificant statistical association); but thereafter, mortality was significantly lower in the surgery group than in the nonsurgery group (risk ratio, 0.53 [95% CI, .30–.97]; $P = .04$).

DISCUSSION

Although guidelines may help clinicians decide whether and when patients with IE should undergo surgery, such decisions can be extremely difficult in individual and unique patients, and particularly in patients with PVIE [25–28]. Patients with SA PVIE who undergo EVS are younger, have more severe cardiac complications, and appear to have significantly lower in-hospital and 1-year mortality rates than patients with SA PVIE who do not undergo EVS. However, EVS was not an independent predictor of better outcome, whether considering in-hospital or 1-year mortality, if appropriately designed prognostic models are utilized to examine outcomes.

Table 3. Prognostic Multivariate Model Adjusted on Age, Sex, Stroke, Heart Failure, Paravalvular Complications, and Early Valve Surgery—Endpoint: In-Hospital Mortality

Variable	RR	95% CI	*P* Value
Age (per 1-year increment)	1.03	1.01–1.05	.0075
Female sex	1.17	.68–2.01	.58
Stroke (time-dependent)	2.94	1.68–5.14	<.0002
Cardiac failure (NYHA class III or IV)	2.00	1.13–3.50	.0163
Early valve surgery (time-dependent)	0.82	.41–1.62	.5645

Model is based on 166 patients, after exclusion of 2 cases due to missing data.

Abbreviations: CI, confidence interval; NYHA, New York Heart Association; RR, risk ratio.

Table 4. Prognostic Multivariate Model Adjusted on Age, Sex, Stroke, Heart Failure, Paravalvular Complications, and Early Valve Surgery—Endpoint: 1-Year Mortality

Variable	RR	95% CI	*P* Value
Age (per 1-year increment)	1.03	1.01–1.05	.002
Female sex	1.43	.91–2.40	.12
Stroke (time-dependent)	2.54	1.58–4.09	<.0001
Cardiac failure (NYHA class III or IV)	2.02	1.25–3.26	.004
Paravalvular complications	1.20	.74–1.96	.46
Early valve surgery (time-dependent)	0.67	.39–1.15	.15

Model is based on 150 patients, after exclusion of 18 cases due to missing data.

Abbreviations: CI, confidence interval; NYHA, New York Heart Association; RR, risk ratio.

Table 5. Prognostic Multivariate Model Adjusted on Age, Sex, Stroke, Heart Failure, Paravalvular Complications, and Early Valve Surgery (Partitioned)—Endpoint: 1-Year Mortality

Variable	RR	95% CI	*P* Value
Age (per 1-year increment)	1.03	1.01–1.05	.002
Female sex	1.44	.92–2.26	.11
Stroke (time-dependent)	2.53	1.57–4.08	<.0001
Cardiac failure (NYHA class III or IV)	2.05	1.27–3.32	.003
Paravalvular complications	1.23	.75–2.01	.41
EVS (time-dependent, partitioned, D0–D7)	1.34	.59–3.02	.49
EVS (time-dependent, partitioned, D8–D365)	0.52	.28–.96	.04

Model is based on 150 patients, after exclusion of 18 cases due to missing data.

Abbreviations: CI, confidence interval; D0-D7, day 0 to day 7; D8-D365, day 8 to day 365; EVS, early valve surgery; NYHA, New York Heart Association; RR, risk ratio.

Our findings and conclusions are similar to those by Lalani et al who addressed the same questions in all patients with prosthetic valve IE within the same ICE registry [29]. A specific finding of our analysis is that patients with SA PVIE who underwent EVS and survived the first 7 postoperative days had a better survival rate at 1 year. In our study, the long-term protection of ESV did not compensate for the early postoperative excess mortality. It must indeed require longer follow-up to offset the effect of postoperative mortality and to show an overall protective effect [24].

Our findings contradict conventional assumptions and suggest that EVS may not always improve outcome in patients with SA PVIE [14]. EVS is certainly beneficial to a selected group of SA PVIE patients, as those with clear indications for surgery [6]. But we currently do not have a way to specifically identify individual patients who would actually benefit from EVS, nor do we know the optimal timing of EVS. Our data as well as others' provide no evidence to support the routine performance of EVS in patients with PVIE, including SA PVIE. We can only confirm that, as in previous studies when there is a clear indication for valve surgery (cardiac failure, valve destruction, prosthesis dehiscence), patients' outcome is better when surgery is performed [17, 28, 29].

The major strength of this observational study is that every effort was made to minimize the impact of potential biases, especially treatment selection and survivor biases. Indeed, it has been shown that a proper analysis of the relationship between EVS and outcome in IE should fulfill at least the following criteria: using Cox models adjusted on both potentially prognostic variables and predictors of EVS (propensity factors), choosing long-term (1 year or more) mortality as the primary endpoint, and minimizing survivor selection bias by coding surgery as a time-dependent variable [24]. The latter point is critical as the likelihood of receiving EVS may be influenced by longer survival; that is, patients who die early during hospitalization may be considered as dying with medical therapy with indications for surgery.

Our study has several limitations. The study sample size might be too small to evidence a positive impact of EVS on mortality in IE even though the ICE-PCS database is the largest registry ever built in this field. Also ICE-PCS data have been collected between 2000 and 2006 and may reflect practices—especially surgical—that have changed in the recent years. Despite the efforts we made to minimize biases, we may have been unable to identify the confounding effect of some variables. In addition, we cannot exclude that referral bias may have played a role as most institutions participating in the ICE cohort are tertiary-care centers. More importantly, neither our study nor any other prior observational study has addressed the myriad of factors that affect surgical decision making in IE (and notably we could not analyze the well-validated indications of surgery), the impact of the expertise of the IE dedicated team, or the impact of surgeon skill on patient outcome. Likewise, we could not make an analysis of the attributable causes of death in each individual case. Although it would be useful to separate deaths due to complications of surgery vs endocarditis in patients who underwent EVS and to clearly identify the cause of death in nonoperated patients, this information was not available in the ICE database.

Although mortality associated with SA PVIE is among the highest observed in patients with IE, and although mortality rates are lower in patients who undergo EVS than in those who do not, our study showed that EVS is not an independent predictor of reduced mortality in patients with SA PVIE. Consequently, we believe that decisions about EVS in patients with SA PVIE should be individualized for each patient and be based on a careful clinical multidisciplinary evaluation, exactly as in any other patient with IE. Further research to define the effect and optimize the timing of surgery in patients with SA PVIE and more generally, PVIE, should in the future rely on well-designed multicenter interventional trials.

Notes

Financial support. This work was supported in part at Hospital Clinic of Barcelona (Spain) by grants from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III (Madrid, Spain); the Spanish Network for Research in Infectious Diseases (REIPI RD06/0008); Fondo de Investigaciones Sanitarias (Madrid, Spain) (grant FIS 1101131); and Fundación Máximo Soriano Jiménez (Barcelona, Spain).

Potential conflicts of interest. J. M. M. has received consulting honoraria and/or research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Cubist, Novartis, GlaxoSmithKline, Gilead Sciences, Pfizer, Roche, Theravance, and ViiV. N. F.-H. was supported by Ministerio de Economía y Competitividad, Instituto de Salud Carlos III, cofinanced by European Development Regional Fund "A way to achieve Europe," Spanish Network for the Research in Infectious Diseases (REIPI RD12/0015). V. G. F. was supported by the National Institutes of Health (grant number R01-AI068804). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

APPENDIX

ICE investigators: Argentina: Liliana Clara, MD, Marisa Sanchez, MD (Hospital Italiano). Francisco Nacinovich, MD, Pablo Fernandez Oses, MD, Ricardo Ronderos, MD, Adriana Sucari, MD, Jorge Thierer, MD (Instituto Cardiovascular). José Casabé, MD, PhD, Claudia Cortes, MD (Hospital Universitario de la Fundaciòn Favaloro), Javier Altclas, MD, Silvia Kogan, MD (Sanatorio de la Trinidad Mitre). Australia: Denis Spelman, MD (Alfred Hospital). Eugene Athan, MD, Owen Harris, MBBS, (Barwon Health). Karina Kennedy, MBBS, Ren Tan, MBBS (Canberra Hospital). David Gordon, MBBS, PhD, Lito Papanicolas, MBBS (Flinders Medical Centre). Damon Eisen, MBBS, MD, Leeanne Grigg, MBBS, Alan Street, MBBS (Royal Melbourne Hospital). Tony Korman, MD, Despina Kotsanas, BSc (Hons) (Southern Health). Robyn Dever, MD, Phillip Jones, MD, Pam Konecny, MD, Richard Lawrence, MD, David Rees, MD, Suzanne Ryan, MHSc (St George Hospital). Michael P. Feneley, MD, John Harkness, MD, Phillip Jones, MD, Suzanne Ryan, MHSc (St Vincent's). Austria: Phillip Jones, MD, Suzanne Ryan, MHSc (Sutherland). Phillip Jones, MD, Jeffrey Post, MD, Porl Reinbott, Suzanne Ryan, MHSc (University of New South Wales). Rainer Gattringer, MD, Franz Wiesbauer, MD (Vienna General Hospital). Brazil: Adriana Ribas Andrade, Ana Cláudia Passos de Brito, Armenio Costa Guimarães, MD (Ana Neri Hospital). Max Grinberg, MD, PhD, Alfredo José Mansur, MD, PhD, Rinaldo Focaccia Siciliano, MD, Tania Mara Varejao Strabelli, MD, Marcelo Luiz Campos Vieira, MD (Heart Institute [Incor], University of Sao Paulo Medical School). Regina Aparecida de Medeiros Tranchesi, MD, Marcelo Goulart Paiva, MD (Hospital 9 de Julho). Claudio Querido Fortes, MD (Hospital Universitario Clementino Fraga Filho/UFRJ). Auristela de Oliveira Ramos, MD (Instituto Dante Pazzanese de Cardiologia). Giovanna Ferraiuoli, MD, Wilma Golebiovski, MD, Cristiane Lamas, MD, PhD, Marisa Santos, MD, PhD, Clara Weksler, MD (Instituto Nacional de Cardiologi). Canada: James A. Karlowsky, MD, Yoav Keynan, MD, Andrew M. Morris, MD, Ethan Rubinstein, MD, LL.B (University of Manitoba). Chile: Sandra Braun Jones, MD, Patricia Garcia, MD (Hospital Clínico Pont. Universidad Católica de Chile). M. Cereceda, MD, Alberto Fica, Rodrigo Montagna Mella, MD (Hospital Clinico Universidad de Chile). Croatia: Bruno Barsic, MD, PhD, Suzana Bukovski, MD, PhD Vladimir Krajinovic, MD, Ana Pangercic, MD, Igor Rudez, MD, Josip Vincelj, MD, PhD (University Hospital for Infectious Diseases). Czech Republic: Tomas Freiberger, MD, PhD, Jiri Pol, MD, Barbora Zaloudikova, MSc (Centre for Cardiovascular Surgery and Transplantation). Egypt: Zainab Ashour, MD, Amani El Kholy, MD, Marwa Mishaal, MD, Hussien Rizk, MD (Cairo University Medical School). France: Neijla Aissa, MD, Corentine Alauzet, MD, Francois Alla, MD, PhD, CHU Catherine Campagnac, RN, Thanh Doco-Lecompte, MD, Christine Selton-Suty, MD (CHU Nancy-Brabois). Jean-Paul Casalta, MD, Pierre-Edouard Fournier, MD, Gilbert Habib, MD, Didier Raoult, MD, PhD, Franck Thuny, MD (Faculté de Médecine de Marseille). François Delahaye, MD, PhD, Armelle Delahaye, Francois Vandenesch, MD (Hospital Louis Pradel). Erwan Donal, MD, Pierre Yves Donnio, PhD, Christian Michelet, MD, PhD, Matthieu Revest, MD, Pierre Tattevin, MD, PhD, Jérémie Violette, MD (Pontchaillou University). Florent Chevalier, MD, Antoine Jeu, MD, Dan MD Rusinaru, MD, Claire Sorel, MD, Christophe Tribouilloy, MD, PhD (South Hospital Amiens). Yvette Bernard, MD, Catherine Chirouze, MD, PhD, Bruno Hoen, MD, PhD, Joel Leroy, MD, Patrick Plesiat, MD (University Medical Center of Besançon). Germany: Christoph Naber, MD, PhD, Carl Neuerburg (Universitaetskliniken Bergmannsheil Bochum). Bahram Mazaheri, PhD, Christoph Naber, MD, PhD, Carl Neuerburg (University Essen). Greece: Sofia Athanasia, MD, Ioannis Deliolanis, Helen Giamarellou, MD, PhD, Thomas Tsaganos, MD, Efthymia Giannitsioti, MD (Attikon University General Hospital). Elena Mylona MD, Olga Paniara, MD, PhD, Konstantinos Papanicolaou, MD, John Pyros, MD, Athanasios Skoutelis, MD, PhD (Evangelismos General Hospital of Athens) India: Gautam Sharma, MD (All India Institute of Medical Sciences). Johnson Francis, MD, DM, Lathi Nair, MD, DM, Vinod Thomas, MD, DM, Krishnan Venugopal, MD, DM (Medical College Calicut). Ireland: Margaret M. Hannan, MB, BCh, BAO, MSc, John Hurley, MB, BCh (Mater Hospitals). Israel: Dan Gilon, MD, Sarah Israel, MD, Maya Korem, MD, Jacob Strahilevitz, MD (Hadassah-Hebrew University). Ethan Rubinstein, MD, LL.B, Jacob Strahilevitz, MD (Tel Aviv University School of Medicine). Italy: Roberta Casillo, MD, PhD, Susanna Cuccurullo, MSc, Giovanni Dialetto, MD, Emanuele Durante-Mangoni, MD, PhD, Mattucci Irene, MD, Enrico Ragone, MD, PhD, Marie Françoise Tripodi, MD, Riccardo Utili, MD, PhD (II Università di Napoli). Enrico Cecchi,MD, Francesco De Rosa, MD, Davide Forno,MD, Massimo Imazio, MD, Rita Trinchero, MD (Maria Vittoria Hospital). Alessandro Tebini, MD, Paolo Grossi, MD, PhD, Mariangela Lattanzio, MD, Antonio Toniolo, MD (Ospedale di Circolo Varese). Antonio Goglio, MD, Annibale Raglio, MD, DTM&H, Veronica Ravasio, MD, Marco Rizzi, MD, Fredy Suter, MD (Ospedali Riuniti di Bergamo). Giampiero Carosi, MD, Silvia Magri, MD, Liana Signorini, MD (Spedali Civili – Università di Brescia). Lebanon: Tania Baban, MD, Zeina Kanafani, MD, MS, Souha S. Kanj, MD, Mohamad Yasmine, MD (American University of Beirut Medical Center). Malaysia: Imran Abidin, MD (University of

Malaya Medical Center). Syahidah Syed Tamin, MD (National Heart Institute). Mexico: Eduardo Rivera Martínez, MD, Gabriel Israel Soto Nieto, MD (Instituto Nacional de Cardiología Ignacio Chávez). Netherlands: Jan T. M. van der Meer, MD, PhD (University of Amsterdam). New Zealand: Stephen Chambers, MD, MSc (University of Otago), David Holland, MB, ChB, PhD (Middlemore Hospital), Arthur Morris, MD (Diagnostic Medlab), Nigel Raymond, MB, ChB (Wellington Hospital), Kerry Read, MB, ChB (North Shore Hospital). David R. Murdoch, MD, MSc, DTM&H (University of Otago). Romania: Stefan Dragulescu, MD, PhD, Adina Ionac, MD, PhD, Cristian Mornos, MD (Victor Babes University of Medicine and Pharmacy). Russia: O. M. Butkevich, PhD (Learning-Scientific Centre of Medical Centre of Russian Presidential Affairs Government Medical Centre of Russian). Natalia Chipigina, PhD, Ozerecky Kirill, MD, Kulichenko Vadim, Tatiana Vinogradova, MD, PhD (Russian Medical State University). Saudi Arabia: Jameela Edathodu, MBBS, Magid Halim, MBBS (King Faisal Specialist Hospital & Research Center). Singapore: Luh-Nah Lum, BSN, Ru-San Tan, MBBS (National Heart Centre). Slovenia: Tatjana Lejko-Zupanc, MD, PhD, Mateja Logar, MD, PhD, Manica Mueller-Premru, MD, PhD (Medical Center Ljubljana). South Africa: Patrick Commerford, MD, Anita Commerford, MD, Eduan Deetlefs, MD, Cass Hansa, MD, Mpiko Ntsekhe, MD (University of Cape Town and Groote Schuur Hospital). Spain: Manuel Almela, MD, Yolanda Armero, MD, Manuel Azqueta, MD, Ximena Castañeda, MD, Carlos Cervera, MD, Ana del Rio, MD, PhD, Carlos Falces, MD, Cristina Garcia-de-la-Maria, PhD, Guillermina Fita, MD, Jose M. Gatell, MD, PhD, Francesc Marco, MD, PhD, Carlos A. Mestres, MD, PhD, José M. Miró, MD, PhD, Asuncion Moreno, MD, PhD, Salvador Ninot, MD, Carlos Paré, MD, PhD, Joan Pericas, MD, Jose Ramirez, MD, PhD, Irene Rovira, MD, Marta Sitges, MD (Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona, Spain). Ignasi Anguera, MD, PhD, Bernat Font, MD, Joan Raimon Guma, MD (Hospitál de Sabadell). Javier Bermejo, Emilio Bouza, MD, PhD, Miguel Angel Garcia Fernández, MD, Victor Gonzalez-Ramallo, MD, Mercedes Marín, MD, Patricia Muñoz, MD, PhD, Miguel Pedromingo, MD, Jorge Roda, Marta Rodríguez-Créixems, MD, PhD, Jorge Solis, MD (Hospital General Universitario Gregorio Marañón). Benito Almirante, MD, Nuria Fernandez-Hidalgo, MD, Pilar Tornos, MD (Hospital Universitari Vall d'Hebron). Arístides de Alarcón, Ricardo Parra (Hospital Universitario Virgen del Rocío). Sweden: Eric Alestig, MD, Magnus Johansson, MD, PhD, Lars Olaison, MD, PhD, Ulrika Snygg-Martin, MD (Sahlgrenska Universitetssjukhuset/Östra). Thailand: Orathai Pachirat, MD, Pimchitra Pachirat, MD, Burabha Pussadhamma, MD, Vichai Senthong, MD (Khon Kaen University). United Kingdom: Anna Casey, MBBS, Tom Elliott, PhD, DSc, Peter Lambert, BSc, PhD, DSc, Richard Watkin, MBBS (Queen Elizabeth Hospital). Christina Eyton, John L. Klein, MD (St Thomas' Hospital). United States: Suzanne Bradley, MD, Carol Kauffman, MD (Ann Arbor VA Medical Center). Roger Bedimo, MD, MS (Dallas VA Medical Center). Vivian H. Chu, MD, MHS, G. Ralph Corey, MD, Anna Lisa Crowley, MD, MHS, Pamela Douglas, MD, Laura Drew, RN, BSN, Vance G. Fowler, MD, MHS, Thomas Holland, MD, Tahaniyat Lalani, MBBS, MHS, Daniel Mudrick, MD, Zaniab Samad, MD, MHS, Daniel J. Sexton, MD, Martin Stryjewski, MD, MHS, Andrew Wang, MD, Christopher W. Woods, MD, MPH (Duke University Medical Center). Stamatios Lerakis, MD (Emory University). Robert Cantey, MD, Lisa Steed, PhD, Dannah Wray, MD, MHS (Medical University of South Carolina). Stuart A. Dickerman, MD (New York University Medical Center). Hector Bonilla, MD, Joseph DiPersio, MD, PhD, Sara-Jane Salstrom, RN (Summa Health System). John Baddley, MD, Mukesh Patel, MD (University of Alabama at Birmingham). Gail Peterson, MD, Amy Stancoven, MD (UT-Southwestern Medical Center). Luis Afonso, MD, Theresa Kulman, RN, Donald Levine, MD, Michael Rybak, PharmD, MPH (Wayne State University). Christopher H. Cabell, MD, MHS (Quintiles).

ICE Coordinating Center: Khaula Baloch, MPH, Vivian H. Chu, MD, MHS, G. Ralph Corey, MD, Christy C. Dixon, Vance G. Fowler Jr, MD, MHS, Tina Harding, RN, BSN, Marian Jones-Richmond, Paul Pappas, MS, Lawrence P. Park, PhD, Thomas Redick, MPH, Judy Stafford, MS.

ICE Publications Committee: Kevin Anstrom, PhD, Eugene Athan, MD, Arnold S. Bayer, MD, Christopher H. Cabell, MD, MHS, Vivian H. Chu, MD, MHS, G. Ralph Corey, MD, Vance G. Fowler Jr, MD, MHS, Bruno Hoen, MD, PhD, A. W. Karchmer, MD, José M. Miró, MD, PhD, David R. Murdoch, MD, MSc, DTM&H, Daniel J. Sexton, MD, Andrew Wang, MD.

ICE Steering Committee: Arnold S. Bayer, MD, Christopher H. Cabell, MD, MHS, Vivian H. Chu, MD, MHS, G. Ralph Corey, MD, David T. Durack, MD, DPhil, Susannah Eykyn, MD, Vance G. Fowler Jr, MD, MHS, Bruno Hoen, MD, PhD, José M. Miró, MD, PhD, Phillipe Moreillon, MD, PhD, Lars Olaison, MD, PhD, Didier Raoult, MD, PhD, Ethan Rubinstein MD, LLB, Daniel J. Sexton, MD.

References

1. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA **2007**; 297: 1354–61.
2. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century. Arch Intern Med **2009**; 169:463–73.
3. Selton-Suty C, Célard M, Le Moing V, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. Clin Infect Dis **2012**; 54:1230–9.
4. Wolff M, Witchitz S, Chastang C, Régnier B, Vachon F. Prosthetic valve endocarditis in the ICU: prognostic factors of overall survival in a series of 122 cases and consequences for treatment decisions. Chest **1995**; 108:688–94.

5. Yu V, Fang G, Keys T, et al. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy only. Ann Thorac Surg **1994**; 58:1073–7.
6. John MD, Hibberd PL, Karchmer AW, Sleeper LA, Calderwood SB. *Staphylococcus aureus* prosthetic valve endocarditis: optimal management and risk factors for death. Clin Infect Dis **1998**; 26:1302–9.
7. Chirouze C, Cabell CH, Fowler VG, et al. Prognostic factors in 61 cases of *Staphylococcus aureus* prosthetic valve infective endocarditis from the international collaboration on endocarditis merged database. Clin Infect Dis **2004**; 38:1323–7.
8. Wang A, Pappas P, Anstrom KJ, et al. The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort. Am Hear J **2005**; 150:1086–91.
9. Habib G, Tribouilloy C, Thuny F, et al. Prosthetic valve endocarditis: who needs surgery? A multicentre study of 104 cases. Heart **2005**; 91:954–9.
10. Sy R, Chawantanpipat C, Richmond D, Kritharides L. Development and validation of a time-dependent risk model for predicting mortality in infective endocarditis. Eur Hear J **2011**; 32:2016–26.
11. Tornos P, Almirante B, Olona M, et al. Clinical outcome and long-term prognosis of late prosthetic valve endocarditis: a 20-year experience. Clin Infect Dis **1997**; 24:381–6.
12. Alonso-Valle H, Fariñas-Alvarez C, Garcia-Palomo J, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. J Thorac Cardiovasc Surg **2010**; 139:887–93.
13. Fernández-Guerrero M, González López J, Goyenechea A, Fraile J, de Górgolas M. Endocarditis caused by *Staphylococcus aureus*: a reappraisal of the epidemiologic, clinical, and pathologic manifestations with analysis of factors determining outcome. Medicine (Baltimore) **2009**; 88:1–22.
14. Attaran S, Chukwuemeka A, Punjabi P, Anderson J. Do all patients with prosthetic valve endocarditis need surgery? Interact Cardiovasc Thorac Surg **2012**; 15:1057–61.
15. Fowler V Jr, Sexton D. Editorial response: The role of valve replacement in the treatment of prosthetic valve endocarditis. Clin Infect Dis **1998**; 26:1310–1.
16. Sohail MR, Martin KR, Wilson WR, Baddour LM, Harmsen WS, Steckelberg JM. Medical versus surgical management of *Staphylococcus aureus* prosthetic valve endocarditis. Am J Med **2006**; 119:147–54.
17. Hill EE, Herregods M-C, Vanderschueren S, Claus P, Peetermans WE, Herijgers P. Management of prosthetic valve infective endocarditis. Am J Cardiol **2008**; 101:1174–8.
18. Kang D-H, Kim Y-J, Kim S-H, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med **2012**; 366: 2466–73.
19. San Román J, López J, Revilla A, et al. Rationale, design, and methods for the early surgery in infective endocarditis study (ENDOVAL 1): a multicenter, prospective, randomized trial comparing the state-of-the-art therapeutic strategy versus early surgery strategy in infective endocarditis. Am Heart J **2008**; 156:431–6.
20. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–8.
21. Fowler VGJ, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. JAMA **2005**; 293:3012–21.
22. Friedman N, Kaye K, Stout J, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med **2002**; 137:791–7.
23. Benito N, Miro J, de Llazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. Ann Intern Med **2009**; 150:586–94.
24. Bannay A, Hoen B, Duval X, et al. The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? Eur Hear J **2011**; 32:2003–15.
25. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. Circulation **2005**; 111:3167–84.
26. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J **2009**; 30:2369–413.
27. Hoen B, Duval X. Clinical practice. Infective endocarditis. N Engl J Med **2013**; 368:1425–33.
28. Bolger A. Challenges in treating prosthetic valve endocarditis. JAMA Intern Med **2013**; 173:1504–5.
29. Lalani T, Chu V, Park L, et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis early surgery for prosthetic valve endocarditis early surgery for prosthetic valve endocarditis. JAMA Intern Med **2013**; 173:1495–504.