ADULT CARDIAC

Long-Term Outcome and Valve Surgery for Infective Endocarditis in the Systematic Analysis of a Community Study

Lauriane Pericart, MD, Laurent Fauchier, MD, Thierry Bourguignon, MD, Louis Bernard, MD, Denis Angoulvant, MD, François Delahaye, MD, Dominique Babuty, MD, and Anne Bernard, MD

Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Tours, France; Faculté de Médecine, Université François Rabelais, Tours, France; Service de Chirurgie Cardiaque et Thoracique, Centre Hospitalier Universitaire Trousseau, Tours, France; Service de Maladies Infectieuses, Centre Hospitalier Universitaire Bretonneau, Tours, France; and Service de Cardiologie, Hospices Civils de Lyon, Université Claude-Bernard Lyon I, Lyon, France

Background. **Information on the long-term prognosis of patients with infective endocarditis (IE) and valve surgical procedures is scarce, and most analyses are based on registries. This study described outcomes and predictors of mortality in a cohort of consecutive patients with IE with a long-term follow-up.**

Methods. **A total of 616 of patients with IE seen in an academic institution between 1990 and 2012 were identified and followed. The mean follow-up period was 4.8 ± 5.7 years (median, 2.6 years).**

Results. **Cardiac surgical procedures were performed in 47% of the patients, among whom 77% had surgical procedures in the first 6 months. Six-month and long-term (≥6 month) mortality rates were 15% and 40%, respectively. Older age, male sex, infection in a mechanical valve, *Staphylococcus aureus* infection, presence of vegetation, stroke, and atrioventricular block were independent predictors of mortality, whereas *Streptococcus* infection was independently associated with a better prognosis. Valve surgical procedures were independently associated with a decrease in mortality: hazard ratio (HR): 0.38; 95% confidence interval (CI): 0.26 to 0.56 for surgical treatment within 45 days; HR 0.36; 95% CI: 0.22 to 0.61 for surgical treatment between 45 and 180 days; and HR: 0.42; 95% CI: 0.25 to 0.73 for surgical treatment beyond 6 months. Decrease in mortality with valve surgical procedures was found in the two subgroups of patients with definite IE (adjusted HR: 0.36; 95% CI: 0.24 to 0.54; $p < 0.0001$) and in those with possible IE (HR: 0.40; 95% CI: 0.24 to 0.67; $p = 0.0005$).**

Conclusions. **In unselected patients with IE, prognostic factors for long-term mortality were consistent with those identified in previous studies for short-term mortality. These results confirm the apparent benefit associated with valve surgical procedures on long-term prognosis.**

(Ann Thorac Surg 2016;102:496–504)
© 2016 by The Society of Thoracic Surgeons

Despite advances in diagnosis, medical therapy, and surgical treatment, the in-hospital mortality rate for patients with infective endocarditis (IE) ranges from 15% to 20%, with 6-month mortality rates approaching 35%; mortality rates have not changed substantially in recent years [1–6]. Whereas the short-term prognosis of IE is well known, information on the long-term prognosis of IE and possible benefit associated with valve surgical treatment is scarce. Moreover, many studies on the prognosis of IE have their basis in data from registries [1–6]. The benefit of valve surgical procedures on the short-term prognosis of IE may also extend to the longer term and may be different in patients with severe associated comorbidities seen in daily clinical practice. The objective of this study was to describe the characteristics and outcomes of patients with IE, by using data from a large, unselected, consecutive cohort.

Patients and Methods

The Centre Hospitalier Régional et Universitaire of Tours serves approximately 400,000 inhabitants and it is the only public institution in an area of approximately 4,000 km^2. It includes four hospitals at four sites and covers all specialties in medicine and surgery (with a

Dr Pericart discloses a financial relationship with Boehringer Ingelheim; Dr Fauchier with Bayer, Medtronic, Sanofi Aventis, and Boehringer Ingelheim; Dr Bernard with Sanofi Aventis; Dr Angoulvant with Astra Zeneca, Eli Lilly, Novartis, Bayer, MSD, Amgen, and Pfizer; and Dr Babuty with Boston Scientific, Boehringer Ingelheim, and Medtronic.

The Appendix can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2016.02.010] on http://www.annalsthoracicsurgery.org.

Accepted for publication Feb 2, 2016.

Address correspondence to Dr Fauchier, Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, 37044 Tours, France; email: lfau@med.univ-tours.fr.

© 2016 by The Society of Thoracic Surgeons
Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.02.010

unique cardiac surgery department for an area of 39,151 km^2). We conducted a retrospective cohort analysis in all patients with IE seen in all departments since January 1990, identified through a systematic search of the hospital discharge records. All clinical reports were examined to validate the diagnosis of IE according to the Modified Duke IE Criteria [7]. Patients with definite and possible IE, both of which require similar management, were included in the study [8], and only the first episode of IE was taken into account. There were no other exclusion criteria for the analysis. Valve surgical treatment was defined by surgical procedures performed during initial hospitalization, during the initial antibiotic therapy, and within 12 months after admission.

Data on patient characteristics were obtained from the hospital medical records; diagnoses were made on the basis of the criteria of the tenth revision of the International Classification of Diseases (ICD-10). Follow-up was conducted by telephone and by using a search tool from the website of the main regional newspaper of the Région Centre, *La Nouvelle République* (http://nrco.lanouvellerepublique.fr/dossiers/necro/index.php). Patients with less than 1 year of follow-up were considered lost to follow-up.

For the incidence of IE, we referred to national and locoregional demographic information provided by the National Institute of Statistics and Economic Studies (www.insee.fr). Multivariable analysis with a proportional hazards model with adjustment for possible confounders presented in Table 1 was used to identify characteristics associated with the occurrence of events during follow-up until October 31, 2014. Deaths were classified as cardiovascular or noncardiovascular. Cardiovascular deaths were further subclassified as cardiac (sudden death and death from progressive heart failure), vascular (stroke or peripheral embolism, pulmonary embolism, or hemorrhage), and others (which included other cardiovascular causes and those cardiovascular deaths with insufficient information to assign a subclassification definitively). Noncardiovascular deaths included those resulting from malignant disease, trauma, or infection. If the cause of death could not be determined from the available evidence, the death was classified as undetermined. The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). A p value <0.05 was considered statistically significant. Statistical analysis was carried out with Statview 5.0 software (Abacus Concepts, Berkeley, CA).

The study was approved by The Institutional Review Board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) and registered as a clinical audit. Ethical review was therefore not required.

Results

We confirmed recent IE (possible or definite) in 616 patients. The annual incidence of IE in our population was 36 cases per million inhabitants, with a predominance of male over female patients (3:1), an increasing incidence in patients older than 50 years of age, and a peak incidence at approximately 220 cases per million population in patients between 70 and 80 years of age (Fig 1).

Patient-related characteristics are shown in Table 1. IE occurred preferentially in left-sided heart valves (533 patients; 87%). Cardiac surgical procedures were performed in 249 of the patients (47% of the patients with left-sided IE), among whom 78% had surgical procedures in the first 6 months. The mean age at diagnosis was lower in patients who underwent surgical treatment; these patients less frequently had comorbidities *and Staphylococcus* infections, but they more frequently had infections on native valves and abscesses. Surgical indications were as follows: heart failure or severe valvular regurgitation in 226 patients (91%); embolism in 50 patients (20%); large vegetations in 30 patients (12%); and perivalvular complications or persistent signs of infection in 52 patients (21%); 101 patients (41%) had two or more indications. For most patients, valve surgical procedures were performed between 10 and 45 days after IE diagnosis (16% of all patients and 39% of the patients undergoing surgical treatment). Among patients with surgical procedures between 45 and 180 days or beyond 180 days after diagnosis, there were respectively 1 of 59 (2%) and 1 of 51 (2%) patients who underwent surgical treatment while IE was still active. Among the 249 patients with surgical treatment, a total of 170 valve bioprostheses (mitral in 39 and aortic in 131), 53 mechanical valves (mitral in 17 and aortic in 36), and 4 aortic homografts were implanted. The valve, after excision of the vegetations, was repaired in 51 patients (mitral in 45 and aortic in 6). There were 9 patients with aortic root replacement. The type of surgery remained unknown for 1 patient.

The mean follow-up period was 4.8 ± 5.7 years (median, 2.6 years; interquartile range, 6.8 years), and 16 patients (3%) were lost to follow-up (mean duration of follow-up, 92 ± 95 days). Complications were recorded for 266 (43%) patients during the course of IE (Table 2).

The outcomes of patients with IE and comparisons between valve surgical treatment and no valve surgical treatment are given in Table 2. The rates of cardiogenic shock, pulmonary embolism, secondary septic location (including osteoarticular infections), and neurologic complication events were higher in patients who did not undergo surgical treatment, whereas patients who underwent surgical treatment had a higher rate of atrioventricular block.

Death was recorded in 245 patients (40%). Among 249 patients who had surgical procedures, 12 patients (5%) died intraoperatively. Causes of in-hospital deaths and deaths during follow-up are described in Table 3. Predictors of all-cause and cardiovascular mortality are shown in Table 4 and in Appendix Table 1. Valve surgical treatment was independently associated with a decrease in mortality, whether the procedure was performed within 45 days, between 45 and 180 days, or beyond 6 months (Fig 2). Valve surgical treatment was independently associated with a decrease in mortality

Ann Thorac Surg
2016;102:496–504

Table 1. Characteristics of 616 Patients With Infective Endocarditis and Valve Surgical Treatment or No Valve Surgical Treatment

Variable	Total (n = 616)	No Valve Surgical Treatment (n = 367)	Valve Surgical Treatment (n = 249)	*p* Value
Age (years), mean(standard deviation)	64 (16)	67 (16)	61 (15)	<0.0001
≥75 years	119 (19%)	83 (23%)	36 (15%)	0.01
Men	464 (75%)	266 (72%)	198 (80%)	0.05
Comorbidities				
Renal failure	67 (11%)	53 (14%)	14 (6%)	0.0006
Hypertension	237 (38%)	161 (44%)	76 (31%)	0.0008
Diabetes	105 (17%)	62 (17%)	43 (17%)	0.90
Chronic pulmonary disease	49 (8%)	35 (10%)	14 (6%)	0.08
Coronary artery disease	172 (28%)	108 (29%)	64 (26%)	0.31
Alcohol misuse	101 (16%)	51 (14%)	50 (20%)	0.04
Atrial fibrillation	81 (13%)	61 (17%)	20 (8%)	0.002
Type of valve infected[a]				
Native	448 (73%)	245 (67%)	203 (82%)	<0.0001
Prosthetic	116 (19%)	74 (20%)	42 (17%)	0.30
Biologic	90 (15%)	58 (16%)	32 (13%)	0.31
Mechanical	26 (4%)	16 (4%)	10 (4%)	0.84
Native and prosthetic	8 (1%)	4 (1%)	4 (2%)	0.58
Location				
Aortic only	291 (47%)	155 (43%)	136 (55%)	0.004
Mitral only	165 (27%)	97 (27%)	68 (27%)	0.87
Tricuspid only	33 (5%)	33 (9%)	0 (0%)	<0.0001
Pulmonic only	1 (0%)	1 (0%)	0 (0%)	0.41
Multiple locations	78 (13%)	33 (9%)	45 (18%)	0.001
Bivalvular infective endocarditis	73 (12%)	31 (9%)	42 (17%)	0.002
Aortic and mitral	66 (11%)	27 (7%)	39 (16%)	0.001
Trivalvular infective endocarditis	5 (1%)	2 (1%)	3 (1%)	0.38
Pacemaker or implantable cardioverter defibrillator (alone)	44 (7%)	44 (12%)	0 (0%)	<0.0001
Undetermined	4 (1%)	4 (1%)	0 (0%)	0.10
Causative microorganism				
Streptococcus	223 (36%)	118 (32%)	105 (42%)	0.01
Staphylococcus	187 (30%)	136 (37%)	51 (20%)	<0.0001
Staphylococcus aureus	149 (24%)	106 (29%)	43 (17%)	0.001
Methicillin-sensitive *S. aureus*	120 (19%)	83 (23%)	37 (15%)	0.02
Methicillin-resistant *S. aureus*	29 (5%)	23 (6%)	6 (2%)	0.03
Coagulase-negative *Staphylococcus*	47 (8%)	34 (9%)	13 (5%)	0.06
Enterococcus	53 (9%)	30 (8%)	23 (9%)	0.64
Other	52 (9%)	29 (8%)	23 (9%)	0.56
Intracellular bacteria	11 (2%)	3 (1%)	8 (3%)	0.03
≥2 microorganisms	12 (2%)	6 (2%)	6 (2%)	0.49
Unknown	89 (14%)	48 (13%)	41 (16%)	0.24
Echocardiography (n = 498)				
Vegetation	359 (72%)	213 (71%)	146 (74%)	0.60
≥15 mm (n = 170)	66 (13%)	36 (12%)	30 (15%)	0.33
Abscess	87 (17%)	36 (12%)	51 (26%)	<0.0001
Prosthetic dehiscence	15 (3%)	4 (1%)	11 (6%)	0.007

[a] Without pacemaker or implantable cardioverter defibrillator infective endocarditis (n = 44).

in the two subgroups of patients with definite IE (adjusted HR: 0.36; 95% CI: 0.24 to 0.54; $p < 0.0001$) and in those with possible IE (HR: 0.40; 95% CI: 0.24 to 0.67; $p = 0.0005$).

Comment

Our contemporary cohort is a large series of consecutive patients with IE, with systematic identification of patients,

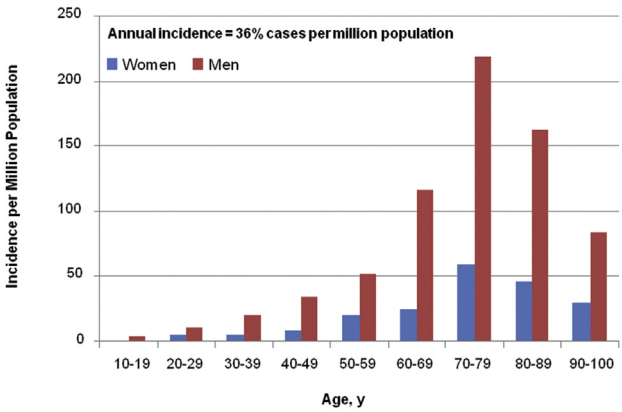

Fig 1. Incidence of infective endocarditis by age and sex in the study population.

with a long period of follow-up, and with a comparison of prognosis in patients with and without valve surgical treatment. Consequently, our population may be more representative of patients with IE treated in everyday clinical practice than patients in declarative surveys or registries.

The annual incidence of IE in our study was 36 cases per million, in line with other French or international studies (30 to 90 cases per million inhabitants) [1, 4, 5, 9–12]. Although many of the patients' characteristics in our study were similar to those found in previous studies, the mean age of our population was slightly higher (64 vs. 60 years) [9, 13–18], and it probably reflects the unselected nature of our cohort.

Many studies have shown the association between *Staphylococcus* IE and worse short-term and long-term prognoses [5, 13, 17, 19–22]. We found a rate of *Staphylococcus* IE of 30% and a worse prognosis for these patients, whereas *Streptococcus* infection was associated with a lower risk of mortality. *Staphylococcus* may also select a population with more comorbidities (eg, nosocomial acquisition, hemodialysis, chronic skin ulcers). Embolic complications occur in 30% to 40% of left-sided IE cases [13, 17, 22, 23]. In our study, stroke was the only complication associated with poor survival. Our results do not corroborate the association between heart failure and worse prognosis reported in several other studies [16, 17, 24]. The timing of heart failure and surgical intervention in the course of IE may influence the prognostic significance of these variables [25]. Most in-hospital deaths were cardiovascular or related to sepsis, whereas other noncardiovascular deaths (and unknown causes) were more common during follow-up.

Patients with possible IE according to the Duke criteria were included in our study, and these patients by definition did not have echocardiographic lesions. This may explain our results, possibly reflecting less virulent IE with less valvular damage, a lower rate of surgical intervention, fewer complications (heart failure and stroke), and lower mortality rates compared with other

Table 2. Outcome of Patients With Infective Endocarditis and Comparison Between Valve Surgical Treatment and No Valve Surgical Treatment

Variable	Total (n = 616)	No Valve Surgical Treatment (n = 367)	Valve Surgical Treatment (n = 249)	*p* Value[a]
Early complications (≤6 months)	266 (43%)	170 (46%)	96 (39%)	0.06
All embolic events	189 (31%)	115 (31%)	74 (30%)	0.18
Symptomatic embolic event	132 (21%)	82 (22%)	50 (20%)	0.50
Splenic, hepatic, or renal embolic event	49 (8%)	20 (5%)	29 (12%)	0.005
Vascular or coronary embolic event	40 (6%)	19 (5%)	21 (8%)	0.11
Pulmonary embolic event	36 (6%)	31 (8%)	5 (2%)	0.0008
Secondary septic location	82 (13%)	58 (16%)	24 (10%)	0.03
Atrioventricular block	30 (5%)	10 (3%)	20 (8%)	0.003
Heart failure	135 (22%)	81 (22%)	54 (22%)	0.91
Cardiogenic shock	25 (4%)	20 (5%)	5 (2%)	0.03
Neurologic complication[b]	114 (21%)	71 (25%)	43 (17%)	0.03
Stroke	100 (19%)	61 (21%)	39 (16%)	0.06
Brain abscess	8 (2%)	5 (2%)	3 (1%)	0.60
Encephalopathy or meningitis	12 (2%)	8 (3%)	4 (2%)	0.35
Cardiac surgical treatment	249 (40%)	…	249 (100%)	…
≤10 days	37 (6%)	…	37 (15%)	…
10–45 days	96 (16%)	…	96 (39%)	…
45 days to 6 months	59 (10%)	…	59 (24%)	…
≥6 months	51 (8%)	…	51 (20%)	…
Unknown	6 (1%)	…	6 (2%)	…

[a] Comparisons between patients with surgical treatment and those with no surgical treatment by using χ^2 test. [b] In patients with left-sided infective endocarditis only (n = 533).

Table 3. Mode of Death During Follow-Up of 4.8 ± 5.7 Years

Causes of Death	Total (n = 616)	In-Hospital Deaths	Death During Subsequent Follow-Up	Patients With No Valve Surgical Treatment (n = 367)	Patients With Valve Surgical Treatment (n = 249)	Adjusted Hazard Ratio (95% Confidence Interval) for Surgical Treatment Versus No Surgical Treatment	*p* Value[a]
Total death during follow-up	245 (40%)	69 (11%)	176 (29%)	170 (46%)	75 (30%)	0.38 (0.28–0.51)	<0.0001
6-month mortality	92 (15%)	…	…	80 (22%)	12 (5%)	0.19 (0.10–0.36)	<0.0001
In-hospital mortality (≤45 days)	69 (11%)	…	…	60 (16%)	9 (4%)	0.18 (0.09–0.38)	<0.0001
Early mortality (45 days to 6 months)	23 (4%)	…	…	20 (5%)	3 (1%)	0.19 (0.05–0.74)	0.02
Late mortality (≥6 months)	153 (25%)	…	…	89 (24%)	64 (26%)	0.49 (0.33–0.71)	0.0002
Cardiovascular death	100 (41%)	57 (83%)	43 (24%)	70 (41%)	30 (40%)	0.40 (0.25–0.66)	0.0003
Cardiac	42 (17%)	19 (28%)	23 (13%)	24 (14%)	18 (24%)	…	…
Vascular death	17 (7%)	10 (14%)	7 (4%)	16 (9%)	1 (1%)	…	…
Other cardiovascular death	41 (17%)	28 (41%)	13 (7%)	30 (18%)	11 (15%)	…	…
Noncardiovascular death	64 (26%)	8 (11%)	56 (32%)	47 (28%)	17 (23%)	0.29 (0.15–0.56)	0.0002
Cancer	12 (5%)	1 (1%)	11 (6%)	9 (5%)	3 (4%)	…	…
Infection	12 (5%)	0 (0%)	12 (7%)	12 (7%)	0 (0%)	…	…
Trauma	1 (0.4%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	…	…
Other noncardiovascular death	39 (16%)	7 (10%)	32 (18%)	25 (15%)	14 (19%)	…	…
Death of undetermined cause	81 (33%)	4 (6%)	77 (44%)	53 (31%)	28 (37%)	0.40 (0.23–0.69)	0.001

[a] Comparisons between patients with surgical treatment and those with no surgical treatment by using proportional hazard model. Adjustment with parameters is included in the multivariable analysis and listed in Table 4.

Table 4. Univariate and Multivariable Analysis of Prognostic Factors of Mortality

	Univariate Analysis		Multivariable Analysis	
	Hazard Ratio (95% Confidence Interval)	*p* Value	Hazard Ratio (95% Confidence Interval)	*p* Value
Overall mortality				
Age (per 1-year increase)	1.04 (1.03–1.05)	<0.0001	1.03 (1.02–1.05)	<0.0001
Male	1.12 (0.83–1.49)	0.46	1.38 (1.02–1.87)	0.04
Renal failure	2.12 (1.49–3.00)	<0.0001	1.41 (0.93–2.16)	0.11
Chronic pulmonary disease	1.84 (1.24–2.73)	0.003	1.46 (0.93–2.28)	0.10
Hypertension	1.28 (0.99–1.64)	0.06	0.88 (0.67–1.16)	0.37
Infection in native valve (vs. all patients with infection not located on a native valve)	0.81 (0.61–1.07)	0.14	0.84 (0.50–1.41)	0.52
Infection in mechanical valve (vs. all patients with infection not located on a mechanical valve)	1.72 (0.96–3.08)	0.07	1.97 (1.05–3.70)	0.03
Aortic only location (vs. all other locations of IE)	1.20 (0.92–1.55)	0.18	0.84 (0.59–1.21)	0.36
Mitral only location (vs. all other locations of IE)	0.93 (0.72–120)	0.58	0.64 (0.43–0.96)	0.03
Pacemaker or implantable cardiac defibrillator location (vs. all other locations of IE)	1.35 (0.88–2.08)	0.17	0.66 (0.39–1.11)	0.12
Streptococcus (vs. all other microorganisms)	0.65 (0.50–0.86)	0.002	0.56 (0.39–0.81)	0.002
Staphylococcus (vs. all other microorganisms)	1.29 (0.99–1.69)	0.06	0.36 (0.19–0.69)	0.002
Staphylococcus aureus (vs. all other microorganisms)	1.51 (1.14–2.00)	0.004	2.92 (1.50–5.71)	0.002
Methicillin-resistant *Staphylococcus aureus* (vs. all other microorganisms)	2.58 (1.63–4.10)	<0.0001	1.63 (0.93–2.86)	0.09
Unknown microorganism (vs. known microorganism)	0.83 (0.58–1.18)	0.30	0.84 (0.47–1.47)	0.54
Definite IE (vs. possible IE)	1.40 (1.08–1.81)	0.01	0.98 (0.56–1.70)	0.93
Vegetation (vs. no vegetation)	1.57 (1.21–2.04)	0.0007	1.72 (1.04–2.85)	0.03
Vegetation length ≥15 mm (vs. all other patients with IE)	1.23 (0.81–1.84)	0.33	1.25 (0.80–1.96)	0.32
Embolic event (vs. no embolic event)	1.33 (1.01–1.75)	0.04	0.95 (0.62–1.44)	0.80
Stroke (vs. no stroke)	1.73 (1.25–2.40)	0.001	1.94 (1.19–3.16)	0.01
Atrioventricular block (vs. no atrioventricular block)	1.33 (0.79–2.25)	0.28	1.80 (1.02–3.16)	0.04
Heart failure (vs. no heart failure)	1.10 (0.82–1.48)	0.51	0.91 (0.64–1.28)	0.58
Cardiogenic shock (vs. no cardiogenic shock)	2.67 (1.55–4.61)	0.0004	1.41 (0.74–2.67)	0.29
Valve surgical treatment within 45 days (vs. no surgical treatment)	0.45 (0.32–0.65)	<0.0001	0.38 (0.26–0.56)	<0.0001
Valve surgical treatment between 45 and 180 days (vs. no surgical treatment)	0.35 (0.21–0.57)	<0.0001	0.36 (0.22–0.61)	0.0002
Valve surgical treatment beyond 6 months (vs. no surgical treatment)	0.36 (0.22–0.58)	<0.0001	0.42 (0.25–0.73)	0.002
Cardiovascular mortality				
Age (per 1-year increase)	1.02 (1.01–1.04)	0.003	1.03 (1.01–1.05)	0.00
Male	1.21 (0.75–1.94)	0.44	1.54 (0.93–2.54)	0.09
Renal failure	1.53 (0.85–2.75)	0.15	1.22 (0.62–2.43)	0.57
Chronic pulmonary disease	1.73 (0.94–3.15)	0.08	1.43 (0.72–2.83)	0.31
Hypertension	1.36 (0.92–2.02)	0.12	0.95 (0.61–1.47)	0.81
Infection in native valve (vs. all patients with infection not located on a native valve)	0.83 (0.41–1.68)	0.61	0.95 (0.40–2.25)	0.91
Infection in mechanical valve (vs. all patients with infection not located on a mechanical valve)	0.71 (0.44–1.13)	0.15	1.72 (0.67–4.46)	0.26
Aortic only location (vs. all other locations of IE)	1.16 (0.79–1.72)	0.45	1.04 (0.58–1.86)	0.91
Mitral only location (vs. all other locations of IE)	0.71 (0.44–1.13)	0.14	0.69 (0.35–1.36)	0.29
Pacemaker or implantable cardiac defibrillator location (vs. all other locations of IE)	1.28 (0.67–2.46)	0.46	0.98 (0.41–2.34)	0.97
Streptococcus (vs. all other microorganisms)	0.65 (0.42–1.01)	0.05	0.65 (0.35–1.20)	0.17
Staphylococcus (vs. all other microorganisms)	1.56 (1.04–2.33)	0.03	0.31 (0.10–0.95)	0.04
Staphylococcus aureus (vs. all other microorganisms)	1.84 (1.22–2.78)	0.004	4.41 (1.45–13.33)	0.01
Methicillin-resistant *Staphylococcus aureus* (vs. all other microorganisms)	3.09 (1.65–5.78)	0.0004	1.93 (0.89–4.18)	0.09

(*Continued*)

Table 4. Continued

	Univariate Analysis		Multivariable Analysis	
	Hazard Ratio (95% Confidence Interval)	*p* Value	Hazard Ratio (95% Confidence Interval)	*p* Value
Unknown microorganism (vs. known microorganism)	0.72 (0.39–1.33)	0.29	0.76 (0.26–2.23)	0.62
Definite IE (vs. possible IE)	1.93 (1.26–2.96)	0.003	0.92 (0.35–2.40)	0.86
Vegetation (vs. no vegetation)	2.33 (1.50–3.62)	0.0002	2.79 (1.17–6.67)	0.02
Vegetation length ≥15 mm (vs. all other patients with IE)	1.50 (0.85–2.64)	0.16	1.54 (0.82–2.91)	0.18
Embolic event (vs. no embolic event)	1.93 (1.29–2.87)	0.001	0.84 (0.41–1.72)	0.64
Stroke (vs. no stroke)	2.84 (1.87–4.33)	<0.0001	3.53 (1.67–7.46)	0.00
Atrioventricular block (vs. no atrioventricular block	2.36 (1.23–4.55)	0.01	4.10 (1.91–8.77)	0.00
Heart failure (vs. no heart failure)	1.12 (0.70–1.77)	0.64	0.81 (0.45–1.43)	0.46
Cardiogenic shock (vs. no cardiogenic shock)	2.09 (0.91–4.78)	0.08	1.04 (0.39–2.77)	0.94
Valve surgical treatment within 45 days (vs. no surgical treatment)	0.52 (0.31–0.88)	0.02	0.38 (0.21–0.68)	0.001
Valve surgical treatment between 45 and 180 days (vs. no surgical treatment)	0.23 (0.08–0.64)	0.005	0.24 (0.09–0.69)	0.008
Valve surgical treatment beyond 6 months (vs. no surgical treatment)	0.59 (0.29–1.20)	0.14	0.83 (0.38–1.81)	0.630

IE = infective endocarditis.

studies [4–6, 9,14, 16, 26]. Some biases may also exist in the other studies based on declarative records and including the most serious forms of definite IE.

The surgical rate in our study was at the lower end of the range reported in the literature (26% during the in-hospital phase compared with 50% in some other studies) [1, 5, 6, 15, 27]. Our results may confirm the apparent benefit of valve surgical treatment on mortality, as also suggested in recent studies [6, 28–30]. Surgical treatment was associated with a decrease in mortality rates. A benefit of early valve surgical treatment has been found in selected patients (young and with low operative risk) [28]. We indeed found a better prognosis in patients in whom the surgical treatment was performed earliest. Bannay and colleagues [6] suggested that the protective effect of valve surgical treatment on mortality may be restricted to patients with native valve IE. Tleyjeh and associates [26] observed, in a subgroup analysis, an

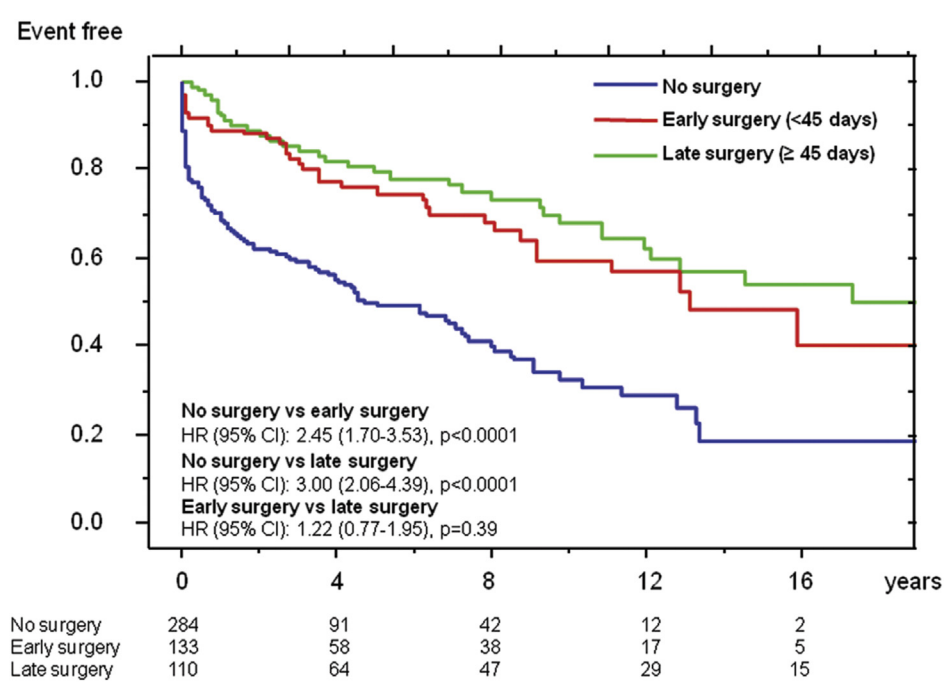

Fig 2. All-cause death in patients with surgical treatment or no surgical treatment in left-sided infective endocarditis. (FU = follow-up.)

increased mortality rate with surgical treatment for patients with prosthetic valve IE. Whether the subgroup of patients with a prosthetic valve benefits from valve surgical treatment is an important issue that should be analyzed in a future study.

Our study was limited by its retrospective design and single-centre experience. However, registry data from a large cohort of consecutive patients are complementary to those from multicentre and declarative studies. There was also a time-dependent effect, which makes it difficult to evaluate benefits of valve surgical treatment. We used different periods to identify early and late surgical treatment in our analysis. Such an analysis may in part remove bias that reflects the time-dependant nature of the data. Patients were included in an academic tertiary referral centre, so the percentage of severe cases may have been overestimated. However, this possible bias is likely to be limited because IE should be managed in hospitals with a cardiac or surgical platform. The in-hospital mortality rate was lower than in other studies, perhaps because of the inclusion of "possible" cases of IE. The opposite may also be true if cases with fatal outcome have been not recognized as IE, a common drawback of studies of IE. Finally, we did not have echocardiographic data for all patients, and quantification of valvular regurgitation is crucial for the decision to perform surgical treatment.

In conclusion, we found high mortality rates in a contemporary community study of consecutive patients with IE with a long follow-up. Prognostic factors for mortality were consistent with those identified in previous studies for short-term mortality. Our results confirm the apparent benefit of valve surgical treatment on long-term mortality.

The authors wish to thank Sophie Rushton-Smith, PhD, who provided editorial support on the final version of the manuscript and was funded by the authors.

References

1. Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. J Am Coll Cardiol 2012;59:1968–76.
2. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA 2002;288:75–81.
3. Chu VH, Cabell CH, Benjamin DK, et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004;109:1745–9.
4. Fedeli U, Schievano E, Buonfrate D, Pellizzer G, Spolaore P. Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system. BMC Infect Dis 2011;11:48.
5. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463–73.
6. 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 Heart J 2011;32:2003–15.
7. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994;96:200–9.
8. Horstkotte D, Follath F, Gutschik E, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary: the Task Force on Infective Endocarditis of the European Society of Cardiology. Eur Heart J 2004;25:267–76.
9. Correa de Sa DD, Tleyjeh IM, Anavekar NS, et al. Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota. Mayo Clin Proc 2010;85:422–6.
10. Sy RW, Kritharides L. Health care exposure and age in infective endocarditis: results of a contemporary population-based profile of 1536 patients in Australia. Eur Heart J 2010;31:1890–7.
11. Mouly S, Ruimy R, Launay O, et al. The changing clinical aspects of infective endocarditis: descriptive review of 90 episodes in a French teaching hospital and risk factors for death. J Infect 2002;45:246–56.
12. Tleyjeh IM, Abdel-Latif A, Rahbi H, et al. A systematic review of population-based studies of infective endocarditis. Chest 2007;132:1025–35.
13. Thuny F, Di Salvo G, Disalvo G, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005;112:69–75. http://dx.doi.org/10.1161/CIRCULATIONAHA.104.493155.
14. Bishara J, Leibovici L, Gartman-Israel D, et al. Long-term outcome of infective endocarditis: the impact of early surgical intervention. Clin Infect Dis 2001;33:1636–43.
15. Netzer ROM, Altwegg SC, Zollinger E, Täuber M, Carrel T, Seiler C. Infective endocarditis: determinants of long term outcome. Heart Br Card Soc 2002;88:61–6.
16. Heiro M, Helenius H, Hurme S, et al. Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980-2004. BMC Infect Dis 2007;7:78.
17. Gálvez-Acebal J, Rodríguez-Baño J, Martínez-Marcos FJ, et al. Prognostic factors in left-sided endocarditis: results from the Andalusian multicenter cohort. BMC Infect Dis 2010;10:17.
18. Aksoy O, Sexton DJ, Wang A, et al. Early surgery in patients with infective endocarditis: a propensity score analysis. Clin Infect Dis 2007;44:364–72.
19. 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.
20. Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. JAMA 2003;289:1933–40.
21. San Román JA, López J, Vilacosta I, et al. Prognostic stratification of patients with left-sided endocarditis determined at admission. Am J Med 2007;120:369.e1–e7.
22. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation 2013;127:2272–84.
23. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis 2008;47:23–30.
24. Nadji G, Rusinaru D, Rémadi J-P, Jeu A, Sorel C, Tribouilloy C. Heart failure in left-sided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment. Eur J Heart Fail 2009;11:668–75.

25. Røder BL, Wandall DA, Frimodt-Møller N, Espersen F, Skinhøj P, Rosdahl VT. Clinical features of *Staphylococcus aureus* endocarditis: a 10-year experience in Denmark. Arch Intern Med 1999;159:462–9.
26. Tleyjeh IM, Ghomrawi HMK, Steckelberg JM, et al. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. Circulation 2007;115:1721–8.
27. Cabell CH, Abrutyn E, Fowler VG, et al. Use of surgery in patients with native valve infective endocarditis: results from the International Collaboration on Endocarditis Merged Database. Am Heart J 2005;150:1092–8.
28. 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.
29. Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA 2003;290:3207–14.
30. Kiefer T, Park L, Tribouilloy C, et al. Association between valvular surgery and mortality among patients with infective endocarditis complicated by heart failure. JAMA 2011;306:2239–47.