MAJOR ARTICLE

Influence of the Timing of Cardiac Surgery on the Outcome of Patients With Infective Endocarditis and Stroke

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Background. The timing of cardiac surgery after stroke in infective endocarditis (IE) remains controversial. We examined the relationship between the timing of surgery after stroke and the incidence of in-hospital and 1-year mortalities.

Methods. Data were obtained from the International Collaboration on Endocarditis–Prospective Cohort Study of 4794 patients with definite IE who were admitted to 64 centers from June 2000 through December 2006. Multivariate logistic regression and Cox regression analyses were performed to estimate the impact of early surgery on hospital and 1-year mortality after adjustments for other significant covariates.

Results. Of the 857 patients with IE complicated by ischemic stroke syndromes, 198 who underwent valve replacement surgery poststroke were available for analysis. Overall, 58 (29.3%) patients underwent early surgical treatment vs 140 (70.7%) patients who underwent late surgical treatment. After adjustment for other risk factors, early surgery was not significantly associated with increased in-hospital mortality rates (odds ratio, 2.308; 95% confidence interval [CI], .942–5.652). Overall, probability of death after 1-year follow-up did not differ between 2 treatment groups (27.1% in early surgery and 19.2% in late surgery group, $P = .328$; adjusted hazard ratio, 1.138; 95% CI, .802–1.650).

Conclusions. There is no apparent survival benefit in delaying surgery when indicated in IE patients after ischemic stroke. Further observational analyses that include detailed pre- and postoperative clinical neurologic findings and advanced imaging data (eg, ischemic stroke size), may allow for more refined recommendations on the optimal timing of valvular surgery in patients with IE and recent stroke syndromes.

Keywords. endocarditis; stroke; surgery.

Stroke syndromes remain one of the most common and often devastating complications of infective endocarditis (IE). The published incidence of stroke in IE varies from 10% to 50% [1–8], with an associated mortality that ranges from 20% to 58% [9–11]. The timing of valvular surgery in such patients remains controversial. The high rates of postoperative morbidity and mortality reported in earlier studies [12–14] have resulted in great hesitation in referring patients with IE and recent stroke for immediate valvular surgery. More recent investigations have suggested better outcomes of IE patients with stroke who underwent cardiac valvular surgery, particularly in the presence of ischemic rather than hemorrhagic stroke

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[15–18]. Current recommendations are somewhat ambiguous, but generally favor deferral of surgical intervention for 2–4 weeks after a significant ischemic infarct and at least 4 weeks after intracerebral hemorrhage, unless a delay in surgery puts the patient at immediate risk of death [19–22].

There have been no large, prospective studies to date that definitively guide decision making in terms of the timing of cardiac surgery in IE following acute stroke syndromes. In the present investigation, we utilized a large, prospectively enrolled, multicenter database registry of IE patients to specifically address the outcomes of cardiac surgical intervention following recent stroke. A recent study from The International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), established in 2000, suggested a survival benefit of cardiac surgery at any time during hospitalization after stroke complicating IE [23]. The objective of the current study was to further evaluate the influence of the timing of cardiac surgical interventions on in-hospital and longer-term mortality of patients with IE and recent ischemic stroke.

METHODS

Patient Population

Data from the ICE-PCS were used for this study. From June 2000 to December 2006, 4794 patients with definite IE were enrolled into ICE-PCS from 64 centers in 28 countries. Full details on site criteria for participation and data collection have been presented previously [24].

Patient Selection/Data Collection

Patients were identified prospectively using site-specific procedures to ensure consecutive enrollment. Patients were enrolled in ICE-PCS if they met criteria for "possible" or "definite" IE based upon the modified Duke criteria [25]. A standard case report form was used at all sites to collect data. Analysis included patients with definite IE, ischemic stroke, and known timing of cardiac surgery regarding the onset of stroke. Patients with hemorrhagic stroke were excluded from the study. Study flow is presented in Figure 1.

Definitions

"Stroke" was defined as an acute neurological deficit of vascular etiology lasting >24 hours, and was further characterized as ischemic or hemorrhagic using neuroimaging results. Patients with other neurologic manifestations associated with IE (eg, meningitis, brain abscess, septic encephalopathy, intracranial mycotic aneurysm, transient ischemic attack) were excluded.

On the basis of the time between stroke and cardiac surgery, patients were divided into 2 groups: early (surgery performed 1–7 days after ischemic stroke) and late (surgery >7 days after ischemic stroke). Survival duration was defined as the time of admission into referral center to time of death or last contact.

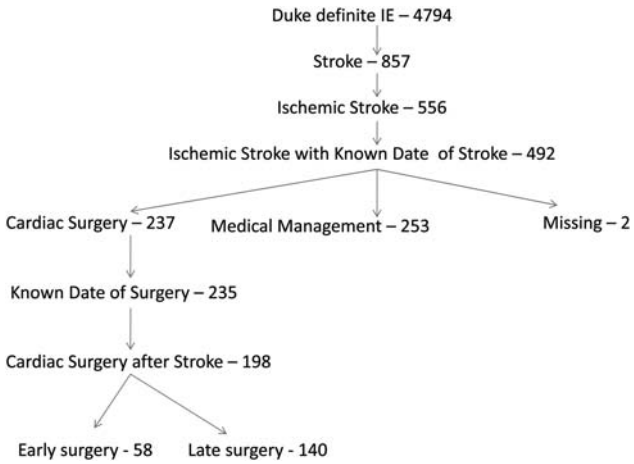

Figure 1. Flow diagram of the International Collaboration on Endocarditis–Prospective Cohort Study study.

Statistical Analyses

Categorical variables are reported as frequency and percentage. Continuous variables are reported as median and 25th and 75th percentiles. Simple comparisons were done for categorical variables using the χ^2 test or Fisher exact test as appropriate. If the number of patients within the cell was <10 patients, we used Freeman-Halton extension of the Fisher exact test as a more conservative approach. The Wilcoxon rank sum test was used for continuous variables.

A multivariate logistic model was applied to assess the strongest independent risk factor for in-hospital death after adjustment for possible confounding factors. All variables that were statistically significant ($\alpha = .05$) in the bivariable analyses were included in the initial (full) multivariable logistic regression model. Regression diagnostics and overall model fit were performed according to standard procedures. In multivariable analysis, variables not significantly associated ($\alpha > .05$) with the outcome were removed from the model to avoid overfitting the model. Each of the removed variables was then individually reinserted into the model to assess if its presence altered the regression coefficient by ≥20%. If so, this confounding variable was included in the final model. The resulting multivariable logistic regression model was considered the final model and was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the remaining risk factors [26]. Coefficients were computed by the method of maximum likelihood.

To assess the impact of early surgery on long-term survival, the probability of survival was estimated by use of the Kaplan-

Meier method and the log-rank test for patients undergoing cardiac surgery who were in the early vs late groups. Multivariable Cox proportional hazard regression model was used to determine the impact of early surgery on long-term survival after adjustment for clinical covariates found to be associated with survival.

For all statistical tests, significance was determined at an α level of .05. All analyses were performed using SAS software (version 9.3, SAS Institute, Cary, North Carolina).

RESULTS

Among 4794 patients with IE, there were 857 (18%) whose course was complicated by stroke, at a median of 4 days (25th and 75th percentile: 0 and 17 days) from the onset of symptoms (Figure 1). Overall, in the majority of these IE patients presenting with stroke syndromes, neuroimaging confirmed ischemic (556 patients, 64.9%) rather than hemorrhagic events. These patients with ischemic strokes formed the basis for all our further investigations. Among the 556 patients with ischemic stroke, the percentage of patients undergoing cardiac surgery was significantly lower than for 3937 patients without stroke (237 [42.6%] vs 2016 [51.2%], respectively, $P < .001$; OR = 0.709 [95% CI, .593 vs .849]). The median time from admission to referral center to cardiac surgery in patients with IE and stroke was 8 days (25th and 75th percentile: 3 and 20 days), which was not different than in patients without stroke (median 8 days, 25th and 75th percentile: 2 and 19 days). Of 237 patients who underwent surgical treatment, 198 underwent surgery after their stroke. Cardiac surgery was performed 1–7 days after stroke (early group) in 58 (29.3%), and 140 (70.7%) after 7 days (late group).

Demographic characteristics and baseline clinical data were compared between the 2 groups (Table 1). There were no differences regarding baseline characteristics except for causative microorganism. When compared to all other pathogens or culture-negative cases, *Staphylococcus aureus* IE was more commonly associated with valve surgery within the first week after onset of neurologic symptoms (28 [48%] vs 45 [32.1%], $P = .036$). Time to admission into the referral center was also shorter in the early surgery group. No differences between groups in the terms of presence or frequencies of chronic underlying diseases, predisposing factors for IE, or clinical manifestations of IE were found.

Complications of IE that might be associated with a greater likelihood of cardiac surgery and in-hospital mortality are presented in Table 2. The incidence of IE complications was similar between the 2 groups, except for a tendency toward a higher frequency of congestive heart failure in patients in the late surgery group ($P = .061$). Differences in in-hospital mortality are also presented in Table 2. There was a nonsignificant trend toward higher in-hospital mortality in the early group.

Table 1. Demographic Data and Clinical Characteristics of Infective Endocarditis in 198 Patients With Stroke Who Underwent Cardiac Surgery

	Time to Surgery Poststroke		
	1–7 d (n = 58)	>7 d (n = 140)	*P* Value
Age			
Median, y	53.1	57.0	.210
25th–75th percentile	40.7–61.3	44.2–67.0	
Sex			
Female	18 (31.0)	45 (32.1)	.879
Region			
North America	15 (25.9)	24 (17.1)	.292
South America	5 (8.6)	9 (6.4)	
Australia/New Zealand/Asia	15 (25.9)	29 (20.7)	
Northern and Central Europe	13 (25.9)	38 (27.1)	
South Europe/Mid East/Africa	10 (13.8)	40 (28.6)	
Most common underlying diseases			
Diabetes mellitus	14 (24.1)	24 (17.1)	.323
Moderate or severe renal disease	5 (8.6)	7 (5.0)	.748
On hemodialysis	5 (8.6)	6 (4.3)	.306
Type of IE			
Native valve	44 (75.9)	100 (71.4)	.797
Prosthetic	13 (22.4)	32 (22.9)	
Other or data missing	1 (1.7)	1 (0.7)	
Presence of vegetation			
Mitral vegetation	35 (60.3)	81 (57.9)	.874
Aortic vegetation	25 (43.1)	68 (48.6)	.637
Location of vegetation			
Aortic and/or mitral valve	55 (94.8)	131 (93.6)	.781
Both left and right side involvement	0 (0.0)	6 (4.3)	.183
Time of admission after onset of IE			
<1 mo	45 (77.6)	90 (64.3)	.005
>1 mo	9 (15.5)	48 (34.3)	
IE onset after admission or data missing	4 (6.9)	2 (1.4)	
Transfer from another hospital	33 (56.9)	88 (62.9)	.519
Healthcare-associated infection	17 (29.3)	28 (20.0)	.192
Microbial etiology			
Staphylococcus aureus	28 (48.3)	45 (32.1)	.061
Viridans group streptococci	4 (6.9)	17 (12.1)	
Enterococcus species	6 (10.3)	8 (5.7)	
Other	20 (34.5)	70 (50.0)	

Data are presented as No. (%) unless otherwise specified.

Abbreviation: IE, infective endocarditis.

Table 2. Indications for Surgery and Outcome of Infective Endocarditis Complicated With Stroke Regarding Time to Surgery

Indications for Surgery	Time to Surgery Poststroke 1–7 d (n = 58)	Time to Surgery Poststroke >7 d (n = 140)	*P* Value
Other systemic embolization (excluding stroke)	26 (44.8)	57 (40.7)	.637
Intracardiac abscess	14 (24.1)	46 (32.9)	.240
Congestive heart failure	20 (34.5)	69 (49.3)	.061
Persistent positive blood cultures	8 (13.8)	10 (7.1)	.174
Mycotic aneurism	1 (1.7)	0 (0.0)	.293
Valve perforation	11 (19.0)	22 (15.7)	.676
Intracardiac fistula formation	1 (1.7)	3 (2.2)	1.000
Hospital mortality	13 (22.4)	17 (12.1)	.082

All data are presented as No. (%).

Multivariable logistic regression modeling was utilized to determine characteristics associated with in-hospital death and to estimate the impact of early surgery. Univariate analysis identified age, diabetes mellitus, healthcare-associated infection, and intracardiac abscess as possible risk factors associated with in-hospital mortality (Table 3). These covariates were entered into the model along with early surgery. Because age and diabetes were not any more significantly associated with in-hospital mortality in the multivariable model and were not identified as significant confounders, they were excluded from the final model to enhance the accuracy of the model. Goodness-of-fit (Hosmer-Lemeshow test, $P = .817$) and accuracy (concordance = 0.773) indexes of the regression models were satisfactory. The analysis confirmed that intracardiac abscess and healthcare acquisition were independent covariates associated with in-hospital mortality, but timing of surgery did not significantly influence patients' outcome (Table 4).

To evaluate the potential influence of early surgery on 1-year mortality, 1-year survival was calculated according to the Kaplan-Meier method (Figure 2). There was no difference in 1-year mortality between 2 surgical treatment groups. The probability of survival 1 year after admission to referral center was 72.9% in the early group vs 80.8% in the late group ($P = .328$, log-rank test). Cox regression analysis confirmed that after an adjustment for other previously identified significant covariates (intracardiac abscess and healthcare-associated IE), timing of cardiac surgery had no significant impact on long-term survival (Table 4). Healthcare-associated IE was still associated with a greater probability of death within 1 year of admission, although the result was not any more statistically significant. After repeating the analysis with stratification by the type of IE (native or

Table 3. Demographic Data and Clinical Characteristics of In-Hospital Survivors and Nonsurvivors

	Time to Surgery Poststroke (d) Survivors (n = 168)	Time to Surgery Poststroke (d) Nonsurvivors (n = 30)	*P* Value
Age			
Median, y	54.4	62.5	.010
25th–75th percentile	41.9–64.0	53.8–73.6	
Sex			
Female	50 (29.8)	13 (43.3)	.201
Region			
North America	36 (21.4)	3 (10.0)	.196
South America	9 (5.4)	5 (16.7)	
Australia/New Zealand/Asia	38 (22.6)	6 (20.0)	
Northern and Central Europe	43 (25.6)	8 (26.7)	
South Europe/Mid East/ Africa	42 (25.0)	8 (26.7)	
Most common underlying diseases			
Diabetes mellitus	28 (16.9)	10 (33.3)	.045
Moderate or severe renal disease	9 (5.4)	3 (10.0)	.397
On hemodialysis	8 (4.8)	3 (10.0)	.222
Type of IE			
Native valve	123 (76.4)	21 (70.0)	.633
Prosthetic	36 (22.4)	9 (30.0)	
Other or data missing	2 (1.2)	0 (0.00)	
Presence of vegetation			
Mitral vegetation	96 (57.1)	20 (66.7)	.422
Aortic vegetation	80 (47.6)	13 (43.3)	.735
Location of vegetation			
Aortic and/or mitral valve	157 (93.5)	29 (96.7)	.697
Both left and right side involvement	6 (3.6)	0 (0.00)	.594
Time of admission after onset of IE			
<1 mo	110 (65.5)	25 (83.3)	.104
>1 mo	53 (31.6)	4 (13.3)	
IE onset after admission or data missing	5 (3.0)	1 (3.3)	
Transfer from another hospital	104 (61.9)	17 (56.7)	.773
Healthcare-associated infection	30 (17.9)	15 (50.0)	<.001
S. aureus infection	58 (34.5)	15 (50.0)	.149
Systemic embolization	70 (41.7)	13 (43.3)	1.000
Intracardiac abscess	43 (25.6)	17 (56.7)	.001
Congestive heart failure	73 (43.5)	16 (53.3)	.327
Persistent positive blood cultures	13 (7.7)	5 (16.7)	.159
Mycotic aneurysm	1 (0.6)	0 (0.0)	1.000
Valve perforation	26 (15.5)	7 (23.3)	.293
Intracardiac fistula formation	3 (1.8)	1 (3.3)	.485
Early surgery	45 (26.8)	13 (43.3)	.082

Data are presented as No. (%) unless otherwise specified.

Abbreviation: IE, infective endocarditis.

Table 4. Risk Factors for In-Hospital Death and 1-Year Mortality by Multivariate Regression Analysis

	In-Hospital Mortality Logistic Regression Analysis			One-Year Mortality Cox Regression Analysis		
Variable	Adjusted OR	95% CI	*P* Value	Adjusted HR	95% HR Confidence Limits	*P* Value
Early surgery	2.308	.942–5.652	.065	1.138	.802–1.650	.481
Intracardiac abscess	4.529	1.921–11.152	.001	0.990	.688–1.455	.957
Healthcare- associated infection	4.574	1.919–11.093	.001	1.533	.995–2.481	.066

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

prosthetic valve), there was still no difference in survival according to the type of affected valves (data not presented).

DISCUSSION

The appropriateness and timing of cardiac surgery after stroke in IE remains controversial owing to numerous limitations of previous studies including, small statistical sample sizes, retrospective data collection, and nonrandomized trial designs. The present study is the first to our knowledge to evaluate timing of surgery after stroke in IE with risk adjustment for differences in patient characteristics. Early surgery was found to be associated with a nonsignificant increase in-hospital mortality when compared with patients operated on later (>7 days) after stroke, but this finding may have been related to adverse clinical characteristics in the early surgery group. Importantly, 1-year mortality rates were similar for early vs late surgery, and the in-hospital and 1-year mortality rates in our early surgery group compares favorably with overall cited mortality rates described in recent literature of patients with IE in general [27]; all patients with IE undergoing cardiac surgery [28]; all patients with IE who experience stroke [9, 29]; and all patients with IE, stroke, and surgery [15, 16].

Our findings add credence to a growing body of literature suggesting that early cardiac surgery after ischemic stroke is not contraindicated and can be performed without delay with acceptable operative and longer-term survival when indications for surgery are present. A recently published study by Gaca et al confirms the safety of surgery after stroke, although they showed that postoperative length of stay was longer in patients with a recent stroke than those with a more remote stroke event [30]. In the context of other recent studies demonstrating the relative safety of early surgery from a neurologic perspective [15, 20, 26], it appears that early surgery for IE when otherwise indicated should not be delayed for the presence of stroke alone. As recently reported in the Early Surgery

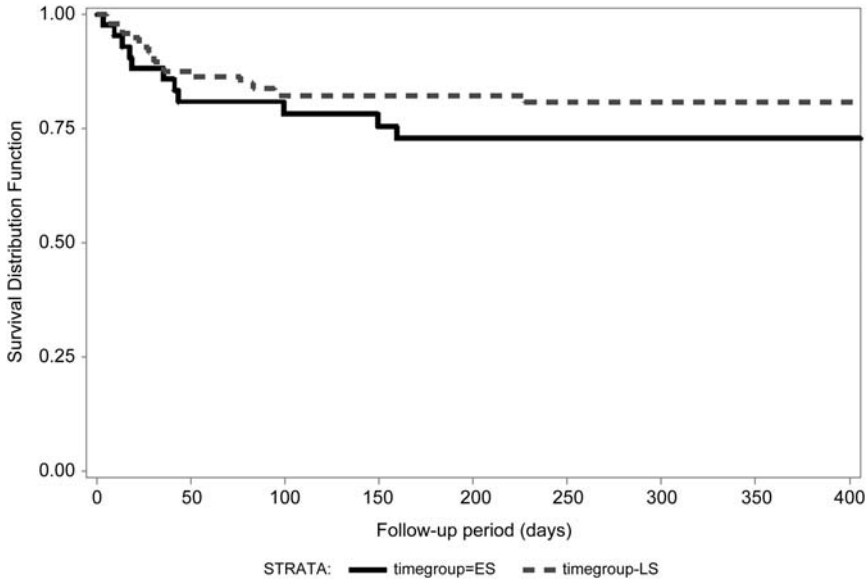

Figure 2. One-year survival for 198 patients undergoing surgery after ischemic stroke. Solid line, early surgery group; dashed line, late surgery group; *P* = .328. Abbreviations: ES, early surgery; LS, late surgery.

Versus Conventional Treatment for Infective Endocarditis randomized study, delayed surgery may be associated with additional embolic events, and delayed surgery was not associated with a higher mortality [31].

This study has several limitations. The ICE-PCS cohort may be influenced by referral bias, because many centers are tertiary care facilities with voluntary participation. Selection bias for both surgical intervention and its timing after hospitalization may influence the results of this study, and the basis for surgical timing may be arbitrary rather than based on specific clinical reasons. The ICE-PCS case report form does not record data on the severity of neurologic deficit with stroke, the size, number and location of embolic lesions, or information on the presence of septic shock; in addition, patients with adverse clinical status may have had delayed or no surgery performed. Among the patients with ischemic stroke who underwent cardiac surgery for IE, data on the severity of stroke or neurologic impairment before and after surgery (eg, Glasgow Coma Scale or NIH stroke scale) were not collected to determine whether this influenced timing of surgery or outcome. Furthermore, data on the time of stroke were missing in 11% percent of patients with ischemic stroke. Finally, data regarding vegetation size after stroke were not collected; it is conceivable that larger vegetation sizes may have influenced earlier timing of surgery.

In summary, there seems to be no apparent survival benefit in delaying otherwise indicated valvular surgery in IE patients after ischemic stroke. However, it is unlikely in the near future that randomized studies regarding surgery in IE patients, if performed, will enroll enough patients with stroke and subsequent surgery to allow for more meaningful statistical analysis in this area. Further observational analyses that include pre- and postoperative clinical and neuroimaging data, however, may allow for more refined recommendations on the precise role of early valvular surgery in patients with IE and recent ischemic stroke.

Notes

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Potential conflicts of interest. B. B. is a consultant for Pfizer and Pliva Pharmaceuticals and has also participated as a speaker for MSD, Pfizer, and Pliva. A. S. B. has received grants from Cubist, Astellas, Polymedix Inc, and Trius, and is receiving payments for lectures from Duke University Center (ID Grand Rounds). A. W. has provided expert testimony for Young Moore and Henderson, has received grants from Gilead Sciences, Edward Lifesciences, and Abbott Vascular, and has received honoraria from American Physician, Springer, and the American College of Cardiology Foundation. 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.

References

1. Roy P, Tajik AJ, Giuliani ER, et al. Spectrum of echocardiographic findings in bacterial endocarditis. Circulation **1976**; 57:474–82.
2. Stewart JA, Silimperi D, Harris P, et al. Echocardiographic documentation of vegetative lesions in infective endocarditis: clinical implications. Circulation **1980**; 61:374–80.
3. Lutas EM, Roberts RB, Devereux RB, et al. Relation between the presence of echocardiographic vegetations and the complication rate in infective endocarditis. Am Heart J **1986**; 112:107–13.
4. Bain RJ, Geddes AM, Littler WA, et al. The clinical and echocardiographic diagnosis of infective endocarditis. J Antimicrob Chemother **1987**; 20(suppl A):17–24.
5. Steckelberg JM, Murphy JG, Ballard D, et al. Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med **1991**; 114:635–40.
6. DeCastro S, Magni G, Beni S, et al. Role of transthoracic and transesophageal echocardiography in predicating embolic events with active endocarditis involving native cardiac valves. Am J Cardiol **1997**; 80:1030–4.
7. DiSalvo G, Habib G, Pergola V, et al. Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol **2001**; 37:1067–76.
8. Thuny F, DiSalvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography. Circulation **2005**; 112:69–75.
9. Heiro M, Nikoskelainen J, Engblom E, et al. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med **2000**; 160:2781–7.
10. Pruitt AA, Rubin RH, Karchmer AW, et al. Neurologic complications of endocarditis. Medicine **1978**; 57:329–43.
11. Salgado AV, Furlan AJ, Keys TF, et al. Neurologic complications of endocarditis: a 12 year experience. Neurology **1989**; 39:173–8.
12. Maruyama M, Kuriama Y, Sawada T, et al. Brain damage after open heart surgery in patients with acute cardioembolic stroke. Stroke **1989**; 20:1305–10.
13. Gillinov AM, Shah RV, Curtis WE, et al. Valve replacement in patients with endocarditis and acute neurologic deficit. Ann Thorac Surg **1996**; 61:1125–29.
14. Eishi K, Kawazoe K, Kuriyama Y, et al. Surgical management of infective endocarditis associated with cerebral complications. J Thorac Cardiovasc Surg **1995**; 110:1745–55.
15. Ruttmann E, Willeit J, Ulmer H, et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke **2006**; 37:2094–99.
16. Thuny F, Avierinos JF, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J **2007**; 28:1155–61.
17. Snygg-Martin U, Gustafson L, Rosengen 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.
18. Cooper HA, Thompson EC, Laureno R, et al. Subclinical brain embolization in left-sided infective endocarditis. Circulation **2009**; 120:585–91.
19. Braunwald's heart disease: a textbook of cardiovascular medicine, 8th ed. Philadelphia: Saunders Elsevier, **2008**.
20. Angstwurm K, Borges AC, Halle E, et al. Timing the valve replacement in infective endocarditis involving the brain. J Neurol **2004**; 251:1220–26.
21. 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). Endorsed by the European Society of Clinical Microbiology and Infectious

Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J **2009**; 30:2369–413.
22. 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, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation **2005**; 111:e394–434.
23. Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis. Circulation **2010**; 121:1005–13.
24. 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**; 169:1720–3.
25. 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.
26. Furuno JP, Johnson JK, Schweizer ML, et al. Community-associated methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis among HIV patients: a cohort study. BMC Infect Dis **2011**; 11:298.
27. Fedeli U, Schievano E, Buonfrate D, et al. Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system (1863 pts). BMC Infect Dis **2011**; 11:48.
28. Mokhles MM, Ciampichetti I, Head SJ, et al. Survival of surgically treated infective endocarditis: a comparison with the general Dutch population. Ann Thorac Surg **2011**; 91:1407–12.
29. Chen CH, Lo MC, Hwang KL, et al. Infective endocarditis with neurologic complications: 10-year experience. J Microbiol Immunol Infect **2001**; 34:119–24.
30. Gaca JG, Sheng S, Daneshmand MA, et al. Outcomes for endocarditis surgery in North America: a simplified scoring system. J Thorac Cardiovasc Surg **2011**; 141:98–106.
31. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med **2012**; 366:2466–73.

Appendix

ICE Authorship Index 2012 (updated 28 August 2012)

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